Plastic Surgery International

Cleft Lip and Palate Treatment

Guest Editors: Nivaldo Alonso, David M. Fisher,
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Editorial Board

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Hindawi Publishing Corporation
Plastic Surgery International
Volume 2013, Article ID 372751, 1 page
http://dx.doi.org/10.1155/2013/372751

Editorial

Cleft Lip and Palate Treatment

Nivaldo Alonso,[1] David M. Fisher,[2] Luiz Bermudez,[3] and Renato da Silva Freitas[4]

[1] *Craniofacial Unit, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, 04516-010 São Paulo, SP, Brazil*
[2] *Cleft Palate and Lip Program, Hospital for Sick Children, Toronto, ON, Canada*
[3] *Operation Smile International, Bogota, Colombia*
[4] *Universidade Federal do Paraná, Curitiba, PR, Brazil*

Correspondence should be addressed to Nivaldo Alonso; nivalonso@gmail.com

Received 12 May 2013; Accepted 12 May 2013

Cleft lip and palate is still a very challenging facial deformity, and this special issue has shown this very clearly. Many papers came from all around the world, and the topics were very up to date and have raised very interesting points. The topics about humanitarian mission and its role and the benefits are elucidated in these articles, but the conclusion is that the world still does not have the solutions for the developing country, and there are benefits but no final and definitive answer for the problem. The balance between comprehensive cleft care and financial support is still unsolved. The genetic and the management of these patients with orocleft cleft palates raised a very interesting point about the future for prevention of these deformities. The knowledge of the genes involved in nonsyndromic cleft patients, even though the etiology is still poorly understood, could be the key for treatment. This issue reviewed all the most recent important genetic topics in cleft lip and palate. Some very interesting topics on techniques for lip repair have shown us that still some modification could improve the final cosmetic results. Some criterion on the evaluation of alveolar bone grafting could help in the final evaluation of the dental rehabilitation. At least we still have a long journey in the future when we look at protocols in cleft lip and palate; the literature is still missing a large number of papers based in real medical evidences. Only a few subjects have high level evidence supporting like the no use of infant orthopedics appliance for early palate surgery. Some points like age and technique for palatal repair are still unclear, showing that randomized controlled trials are needed. Multicentric collaborations and uniform protocols are strongly recommended.

This issue was a very pleasing work and has shown us that so many new ideas and thoughts are very helpful to keep on the big challenge to solve this facial malformation in the future.

Nivaldo Alonso
David M. Fisher
Luiz Bermudez
Renato da Silva Freitas

Hindawi Publishing Corporation
Plastic Surgery International
Volume 2013, Article ID 641570, 10 pages
http://dx.doi.org/10.1155/2013/641570

Research Article

Implementing the Brazilian Database on Orofacial Clefts

Isabella Lopes Monlleó,[1,2] Marshall Ítalo Barros Fontes,[1] Erlane Marques Ribeiro,[3] Josiane de Souza,[4] Gabriela Ferraz Leal,[5] Têmis Maria Félix,[6] Agnes Cristina Fett-Conte,[7] Bruna Henrique Bueno,[8] Luis Alberto Magna,[8] Peter Anthony Mossey,[9] and Vera Gil-da Silva-Lopes[8]

[1] *Medical Genetics Sector, State University of Alagoas (UNCISAL), Brazil*
[2] *Clinical Genetics Service, Federal University of Alagoas (UFAL), Brazil*
[3] *Medical Genetics Sector, Hospital Infantil Albert Sabin (HIAS), Brazil*
[4] *Medical Genetics Sector, Assistance Center for Cleft Lip and Palate (CAIF), Brazil*
[5] *Medical Genetics Sector, Facial Deformity Care Center (CADEFI), Brazil*
[6] *Medical Genetics Service, Hospital de Clínicas de Porto Alegre (HCPA), Brazil*
[7] *Molecular Biology Department, Medicine School of São José do Rio Preto (FAMERP/FUNFARME), Brazil*
[8] *Department of Medical Genetics, Faculty of Medical Sciences, University of Campinas, 13083-887, Brazil*
[9] *Dundee University Dental School, UK*

Correspondence should be addressed to Vera Gil-da Silva-Lopes; vlopes@fcm.unicamp.br

Received 28 July 2012; Accepted 7 February 2013

Academic Editor: Renato Da Silva Freitas

Background. High-quality clinical and genetic descriptions are crucial to improve knowledge of orofacial clefts and support specific healthcare polices. The objective of this study is to discuss the potential and perspectives of the Brazilian Database on Orofacial Clefts. *Methods*. From 2008 to 2010, clinical and familial information on 370 subjects was collected by geneticists in eight different services. Data was centrally processed using an international system for case classification and coding. *Results*. Cleft lip with cleft palate amounted to 198 (53.5%), cleft palate to 99 (26.8%), and cleft lip to 73 (19.7%) cases. Parental consanguinity was present in 5.7% and familial history of cleft was present in 26.3% subjects. Rate of associated major plus minor defects was 48% and syndromic cases amounted to 25% of the samples. *Conclusions*. Overall results corroborate the literature. Adopted tools are user friendly and could be incorporated into routine patient care. The BDOC exemplifies a network for clinical and genetic research. The data may be useful to develop and improve personalized treatment, family planning, and healthcare policies. This experience should be of interest for geneticists, laboratory-based researchers, and clinicians entrusted with OC worldwide.

1. Introduction

Accurate and detailed phenotype description of orofacial clefts (OC) is crucial to produce good etiological and epidemiological studies. In this regard, attention should be given to subphenotypic features of the lip (completeness of the cleft, presence of pits/prints, dental and orbicularis oris muscle anomalies), and palate (completeness of the cleft, submucous defects, bifid uvula, and ankyloglossia). Similarly important is the screening of minor and major associated defects which has prevalence rate that ranges from 8% to 75%. Although there are true population differences, methodological factors such as sample source and size, method of ascertainment, case definitions, inclusion criteria, coding system, and case classification account for much of this wide variation [1–13].

In the postgenomic era capturing and processing information on human genetic variation, gene-environment interactions, and genotype-phenotype correlations are essential to develop personalized interventions. This has been reinforced by the Human Variome Project (HVP), an international effort launched in 2006. The HVP aim is to develop and make knowledge housed within linked databases on genes,

mutations, and variants accessible to the research and medical communities [14, 15].

Databases may also serve as tools in educating health professionals, policymakers, and the general public towards prevention of unnecessary suffering, improvement of healthcare, and elimination of erroneous beliefs that still remain in some cultures. On humanitarian and ethical grounds, these should be ultimate reasons for birth defects research [16–19].

Recognizing the impact of OC, the World Health Organization assigned the coordination of the International Perinatal Database of Typical Orofacial Clefts (IPDTOC) to the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), in 2002 [18–20].

As stated in the report *Global Registry and Database on Craniofacial Anomalies* [18], the quality of recorded data should be of more concern than completeness of ascertainment in this kind of system. The IPDTOC was launched in 2003 and has collected and analysed case-by-case clinical and epidemiological information OC from birth defects registries worldwide using a standard definition and system for case classification [12].

Care for people with OC in Brazil has been funded by the government through the Unified Health System (Sistema Único de Saúde, SUS) since 1993. In 1998, the National Health Ministry (NHM) created the Brazilian Reference Network for Craniofacial Treatment (RRTDCF). These measures, however, were not preceded or followed by assessment of specific characteristics and impact of OC on the Brazilian population. Currently the RRTDCF numbers 21 units, but just five of them count with geneticist/dysmorphologist in the team [17, 21, 22].

Brazil is a continental country of more than 180 million inhabitants with diverse genetic background and multicultural profile. There is still a shortfall in epidemiological data on overall birth defects in the country. Similar to other parts of the world, data recorded through birth certificates has been criticized on the grounds of ascertainment, sensitivity, reliability, completeness, and consistence of the reports [23–25].

According to the Latin-American Collaborative Study of Congenital Malformations (ECLAMC), the Brazil's birth prevalence of cleft lip (CL) is 49/10,000, cleft lip with cleft palate (CLP) is 116/10,000, and cleft palate (CP) is 58/10,000 [26]. ECLAMC is a hospital-based register which covers only 2% of all Brazilian births [25]. Despite this limitation, the high quality of ECLAMC's data and the fact that OC are among the best ascertained birth defects probably make these figures representative of Brazil's prevalence.

Besides ECLAMC, some cleft services and hospitals linked or not to the RRTDCF record data according to their research field of interest. Therefore, they may include epidemiological, morbidity, mortality, clinical, genetic, and outcome issues. Information gathered, however, is not standardized [17].

High quality of clinical and genetic descriptions is crucial to improve knowledge on OC and support specific healthcare polices. The development and implementation of the Brazilian Database on Orofacial Clefts (BDOC) reported here is a pioneer nationwide initiative to fill in the gap on clinical and genetic information on OC in the Brazilian population.

2. Aim

The aims of this study are to report the implementation, to describe preliminary clinical and familial characteristics and to discuss the potential, and perspectives of the BDOC.

3. Methods

3.1. Database Design. BDOC is a nationwide, hospital-based, voluntary and primary database. Initially, a 10-year schedule was planned to run as a continuous and flexible system in which new aims and tools can be aggregated according to the experience gained. General planning of activities started in 2006 and the validation of the tools started in 2008 in voluntary hospitals with clinical geneticists. According to the strategy originally proposed, after this phase, other hospitals without geneticists could be invited to participate. Clinical and laboratory data are updated during the followup of each subject. The database was approved by the local Institutional Review Boards and the National Research Ethics Committee (CONEP # 14733). All subjects provided informed consent.

Standardized individual and familial information forms the core database. It is complemented by other five satellite protocols designed to cover the following issues: (1) genetic (Biobank of DNA); (2) morbidity and mortality; (3) services' structure and dynamics; (4) professionals' educating characteristics and protocols; and (5) subject/parent satisfaction.

Core database was initiated in eight sites comprising three units of the RRTDCF, two multiprofessional non-RRTDCF centres, and three genetic services. These sites were invited because they all have geneticists with clinical experience in dysmorphology. All of them were personally visited by the coordinators (ILM and VLGSL) before starting the collection of data.

3.2. Target Population, Inclusion Criteria, and Work Definitions. Individuals with typical OC and Pierre-Robin sequence in isolated and nonisolated presentation were included. Data on abortuses, stillbirths, cleft uvula, median, oblique, and submucous clefts were not included.

Typical OC (CL, CLP, and CP) and Pierre-Robin sequence were defined according to the International Classification of Diseases 10th Edition. Terms *isolated* and *associated* were used to refer to additional minor or major defects regardless of the cause or mechanism involved while *syndromic* and *nonsyndromic*, to refer to the underlying aetiology [13].

Case classification was based on the definitions of the IPDTOC Working Group (2011) which defines three phenotype categories: isolated clefts, recognized syndrome, and multimalformed cases (MMC). Accordingly, cases of known nonrandom association (e.g., VACTERL) are included into the category of recognized syndromes. Cases with random combination of major unrelated defects with evidence of distinct aetiological factors are included in the group of MMC. Deformities were considered minor defects [12]. A list of minor defects was reviewed along with ICBDSR in May 2007 and is available at http://www.icbdsr.org/.

Table 1: Distribution of subjects according to participant site, geographic origin, age, and birth weight.

	RRTDCF	Multidisciplinary non-RRTDCF	Genetic service	Total
Number of cases *n* (%)	141 (38)	107 (29)	122 (33)	370 (100)
Geographic origin				
Northeast *n* (%)	62 (44)	86 (80)	86 (70)	234 (63.2)
South *n* (%)	79 (56)	21 (20)	—	100 (27)
Southeast *n* (%)	—	—	36 (30)	36 (9.7)
Age (years, mean)[#]	2.7	1.5	8.5	4.3[*]
Birth weight (grams, mean)[†]	3,057	3,152	2,932	3,055[**]

[#]Mann-Whitney test: RRTDCF × non-RRTDCF, $P = 0.049$; RRTDCF × genetic services, $P < 0.0001$; non-RRTDCF × genetic services, $P < 0.001$; [*]Kruskal-Wallis test, $P = .000$; [†]LSD test: RRTDCF × non-RRTDCF, $P = 0.230$; RRTDCF × genetic services, $P = 0.136$; non-RRTDCF × genetic services, $P = 0.014$; [**]ANOVA, $P = 0.047$.

3.3. Collection, Storage, and Processing of Data. Data were collected using a paper-based record form specifically designed for this database according to the operating manual. These tools were based on the "US National Birth Defects Prevention Study" and ESF "common core protocols" for cleft research and developed as part of a previous study [27].

The record form comprises 80 questions which cover the following information: (1) obstetric, birth, neonatal, and medical history; (2) socioeconomic status; (3) family history where possible (1st-, 2nd-, and 3rd-degree relatives); (3) type of cleft according to topography (lip, alveolus, hard, and soft palate), severity (unilateral or bilateral) and laterality (left and right sided), (4) morphological assessment (including verbatim description of dysmorphic features); (5) laboratory tests (standard cytogenetics, fluorescence in situ hybridization—FISH) and/or molecular analysis, biochemical tests, ultrasound, X-ray images, and so forth; and (5) diagnosis and its evidences.

Operating manual includes the following content: (1) diagram for phenotype categorization, (2) operating definitions, (3) clinical descriptors, (4) list of related defects, (5) list of minor defects, (6) examples of twinning, (7) examples of toxic and occupation-related substances, (8) examples of consanguineous relationships, (9) instructions for taking standard photographs, and (10) examples on how to fill the form.

All subjects were personally interviewed and examined by the participant geneticist during routine genetic evaluation from November 2008 to December 2010. As the major proposal of this database is to collect clinical and familial information, there were no restrictions regarding age and existence of previous cleft surgery at the time of enrolment.

Forms were sent by post or delivered in person for data reviewing and coding at Unicamp where the BDOC is seeded. The data manager checked all the information received and sought for clarifications when needed. Before entering data into the electronic database, all record forms were manually reviewed and coded by the coordinators.

3.4. Pretest of the BDOC Tools and Strategy for Group Management. Record form and operating manual were pretested by seven geneticists throughout a six-month period. A total of 143 record forms and 10 assessment questionnaires were included. Mean time spent to complete the record form at the end of this phase was 20 minutes (SD = 4.57) [28].

All geneticists asked for revision of wording, spacing, and ordering of some questions. Coordinator centre asked for further information and clarification of some responses in 28 record forms. Despite this, record form and operating manual were assessed as useful and reliable tools [28].

At the end of this phase a unit of the RRTDCF ceased its participation and, a new site, a genetic service, was included. All participants attended biannual meetings to exchange experience, discuss data, and plan the next stages.

3.5. Statistical Methods. The electronic database was built using Microsoft Access version 2007. Data processing and analysis were performed using two statistical packages (SPSS for Windows version 15.0 and EpiInfo versions 3.5.1 and 3.04d). Categorical variables were analysed using chi-square test. Numerical variables were tested for normality using one-sample Kolmogorov-Smirnov test. Variables with normal distribution were tested using ANOVA and Student's *t*-test, while variables with nonnormal distribution were tested using Kruskal-Wallis and Mann-Whitney tests. The significance level of 5% ($P < 0.05$) was adopted for all tests.

4. Results

Demographic, clinical, and familial information of 370 individuals with OC was prospective and systematically recorded in the sites identified in Figure 1. As only minor amendments were recommended after the testing phase, respective record forms were included into the sample. Figure 2 summarizes how the BDOC worked throughout the studied period.

Majority of subjects (63.2%) were living in the northeast of Brazil. Males amounted to 219 (59.2%) while females to 151 (40.8%). Birth weight was available in 324 cases. It ranged from 1195 g to 4900 g (mean = 3100; mode = 2800; median = 3100; and SD = 606.6). Age ranged from 0 to 50 years (mean = 4.3; mode = 0; median = 0.5; and SD = 7.3).

Table 1 shows the distribution of patients according to participant site, geographic origin, age, and birth weight at the time of enrolment in the database. Ratio of patients seen at units of the RRTDCF, cleft multidisciplinary non-RRTDCF centres, and genetic services was 1.3 : 1.0 : 1.1. Patients seen at genetic services were significantly older ($P < 0.001$) and had lower birth weight ($P = 0.047$) than those seen elsewhere.

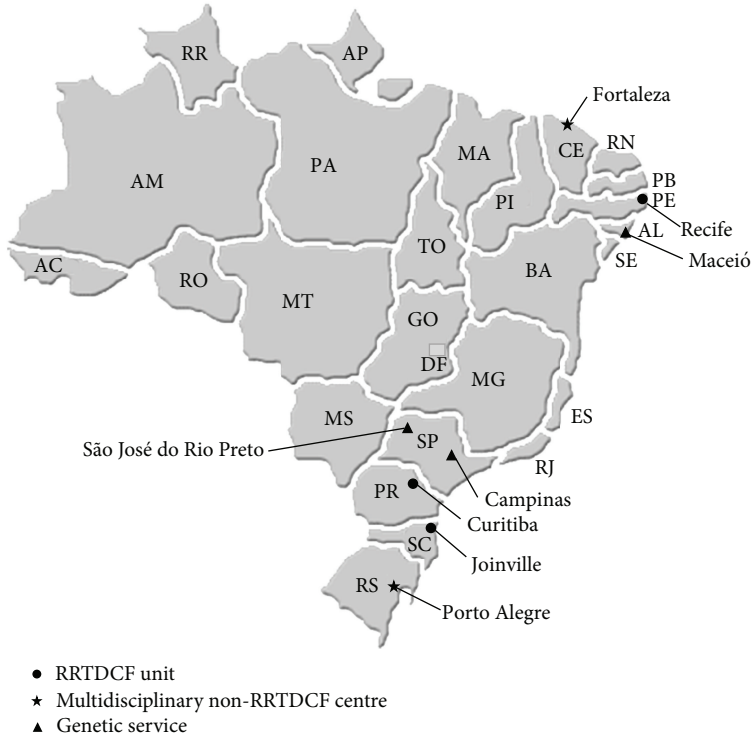

Figure 1: Map of Brazil showing localization of cities and sites participating in the Brazilian database on orofacial clefts (BDOC).

Table 2: Distribution of subjects according to type of clefts with regard to gender, cleft's severity and laterality, and presence of additional defects.

Variable	CLP	CL	CP	Total	$P^{\#}$
Number of cases (%)	198 (53.5)	73 (19.7)	99 (26.8)	370 (100)	
Gender					0.0001
Male	137 (69)	39 (53)	43 (43)	219 (59)	
Female	61 (31)	34 (47)	56 (57)	151 (41)	
Severity					0.0002
Unilateral	120 (60)	62 (85)	—	182 (67)	
Bilateral	78 (40)	11 (15)	—	89 (33)	
Laterality					0.0001
Unilateral left	85 (70)	41 (66)	—	126 (69)	
Unilateral right	35 (30)	21 (34)	—	56 (31)	
Additional minor defects					0.193
Yes	87 (44)	26 (36)	49 (49)	162 (44)	
No	111 (56)	47 (64)	50 (51)	208 (56)	
Additional major defects					0.003
Yes	41 (21)	6 (8)	29 (29)	76 (21)	
No	157 (79)	67 (92)	70 (71)	294 (79)	

$^{\#}$Chi square.

Distribution of subjects according to type of cleft (CL, CLP, and CP) with regard to gender, severity, laterality, and presence of additional defects is shown in Table 2. CLP prevailed over CP and CL, unilateral over bilateral, and left-over right-sided clefts.

Chi-squared contingency table revealed significant differences among all groups of clefts. There was an excess of males among individuals with CLP + CL (male : female ratio = 1.85, $P = 0.0001$) and of females among those with CP (female : male ratio = 1.30, $P = 0.0001$). Bilateral clefts were

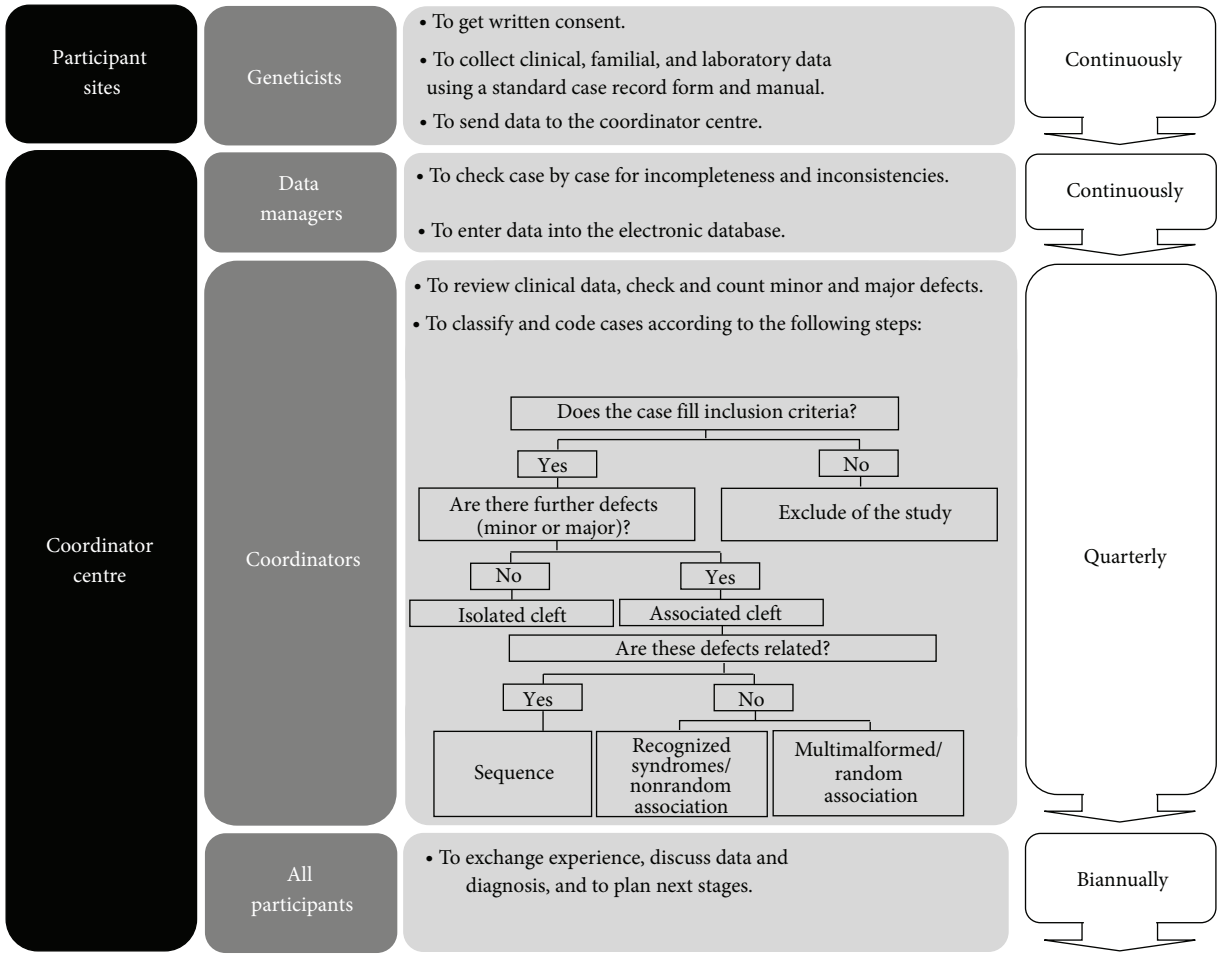

Figure 2: A summary of the process of recording cases through the Brazilian database on orofacial clefts (BDOC). Please refer to text for details.

more frequent for subjects with CLP than for those with CL ($P = 0.0002$).

Parental consanguinity was present in 21/368 (5.7%) cases, 10 of which were first cousins. Consanguineous marriages were not statistically associated with geographic origin ($P = 0.425$), type of cleft ($P = 0.451$), and phenotype category (i.e., if isolated versus syndromes and MMC) ($P = 0.381$).

Excluding 12 individuals from whom familial data were not available, familial history of cleft was found in 94/358 (26.3%) cases. First-degree relatives were affected in 18 (19.4%), second degree in 12 (12.9%), and third degree and above in 63 (67.7%) families. There was an excess of affected relatives in the CLP subgroup in comparison with CP ($P = 0.005$) but not with CL ($P = 0.183$).

Global rate of associated defects (minor plus major) was 179 (48.4%). Fifty-nine (15.9%) subjects showed both minor and major, 103 (27.8%) had only minor and 17 (4.6%) had only major-associated defects. As shown in Table 2, there was no statistically significant difference among subgroups of cleft with regard to rate of minor defects ($P = 0.193$). On the other hand, major defects were more likely to be found in the groups of CLP and CP and unlikely in the group of CL ($P = 0.003$).

Ninety-three (25%) subjects were classified as having syndromic clefts. Comparisons between nonsyndromic and syndromic cases are presented in Table 3. There were no statistically significant differences between these groups with regard to gender and severity of the cleft.

Syndromic cases were more likely to be found at genetic services ($P = 0.006$) and statistically more associated with CP ($P = 0.000$). These cases also showed lower birth weight in both categorical ($P = 0.001$) and quantitative analyses ($P = 0.000$) and higher mean of *minor* defects ($P = 0.000$).

Subjects were regrouped according to the number of minor defects into two categories (1–3 and ≥4 defects). There was a predominance of syndromic cases in the subgroup with four and above *minor* defects ($P = 0.000$). Anatomic distribution of *minor* and *major* defects is shown in Figures 3 and 4, respectively.

Based on verbatim description, the following phenotype categories were identified: 277 (75%) isolated clefts, 47 (12%) recognized syndromes or associations, and 46 (13%) multiple

Table 3: Distribution of syndromic and nonsyndromic cases according to several variables.

Variables	Nonsyndromic	Syndromic	Total	$P^{\#}$
Number of cases (%)	277 (75)	93 (25)	370 (100)	
Category of site				0.006
RRTDCF unit	111 (40)	30 (33)	141 (38)	
Non-RRTDCF centre	87 (31)	20 (21)	107 (29)	
Genetic services	79 (29)	43 (46)	122 (33)	
Gender				0.324
Male	168 (61)	51 (55)	219 (59)	
Female	109 (39)	42 (45)	151(41)	
Birth weight (grams)				
≤2500	27 (11)	22 (26)	49 (21)	0.001
>2500	212 (89)	63 (74)	275 (79)	
Mean	3,145	2,800	3,055	0.000
Type of cleft				0.000
CLP	152 (55)	46 (49)	198 (53)	
CL	65 (23)	8 (9)	73 (20)	
CP	60 (22)	39 (42)	99 (27)	
Severity				0.167
Unilateral	150 (69)	32 (59)	182 (67)	
Bilateral	67 (31)	22 (41)	89 (33)	
Minor defects				0.000
0	192 (69)	16 (17)	208 (56)	
1–3	57 (21)	31 (34)	88 (24)	0.141
≥4	28 (10)	46 (49)	74 (20)	0.000
Mean	2.97	5.09	3.98	.000
Major defects (OC excluded)				
0	277 (100)	19 (20)	296 (80)	—
1–3	—	69 (74)	69 (19)	—
≥4	—	5 (6)	5 (1)	—
Mean	—	1.59	—	—
Phenotype category				
Isolated cleft	277 (100)	—	277 (75)	—
Syndrome and association	—	47 (51)	47 (13)	—
Multimalformed case	—	46 (49)	46 (12)	—

$^{\#}$Chi square.

malformed cases (Table 3). Eighteen (40%) individuals with recognized syndromes had not additional *major* defects.

The 47 clinical recognized syndromes and associations were categorized according to aetiology. Mendelian syndromes were in the lead (n = 21; 45%), followed by chromosomal (n = 18; 38%), heterogeneous (n = 6; 13%), and teratogenic categories (n = 2; 4%).

5. Discussion

The BDOC was designed to gather detailed, high-quality, and continuing updated information on clinical and familial characteristics of OC in the Brazilian population. This is crucial to set a solid basis for future genotype-phenotype studies in which accuracy and consistency of the collected data are issues of much concern than level of ascertainment [18, 19].

In this study, information was prospectively collected by experienced geneticists during their ordinary activities. Data was recorded and processed following a standard method and a strictly defined protocol.

The database was regularly updated with new clinical or laboratory data of patients registered. If on one hand these are strengths of our database, on the other hand they make the process of record taking lengthy. Moreover, complementary investigation and genetic tests are not equally available in different regions of Brazil. These issues have direct implications on the number of cases we are able to record and follow per year and should be borne in mind when interpreting our results.

More than 84.3% of the Brazilian population lives in the three regions from which our data were collected. Among them, southeast is the most densely inhabited area followed by northeast and south [29]. These regions host 17 out of 21

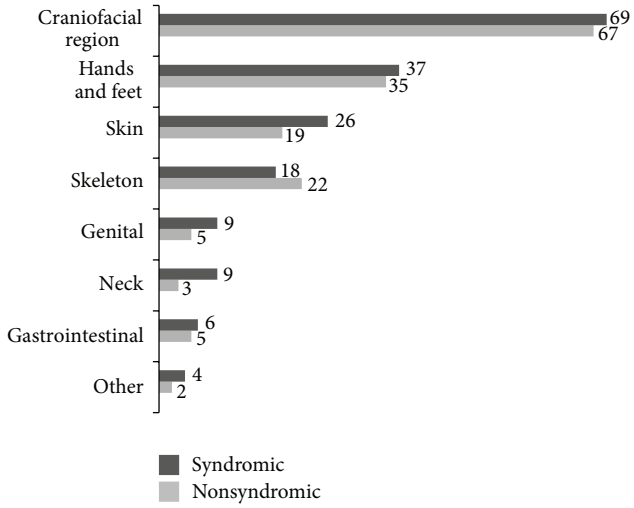

Figure 3: Distribution of minor defects according to anatomic region between nonsyndromic and syndromic cases.

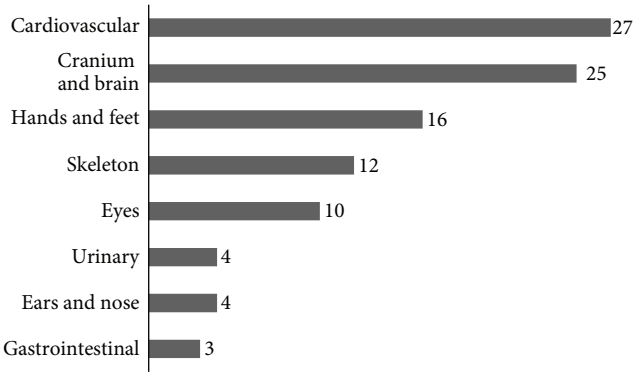

Figure 4: Distribution of major defects according to anatomic region among syndromic cases.

units of the RRTDCF, 18 out of 22 multidisciplinary non-RRTDCF sites [17], and 47 out of 56 clinical genetic services [30] of the country.

Subjects of this study were predominantly from northeast, followed by south and southeast. This result does not reflect differential prevalence of OC but specificities of the participant sites. Southeast region is represented by two genetic services in which individuals attend with various birth defects, OC included. South is represented by three sites specifically dedicated to cleft care (two RRTDCF units plus a multidisciplinary non-RRTDCF site). The northeast region counts with a site of each category of service (genetic, RRTDCF, and multidisciplinary non-RRTDCF). The genetic service from the last-mentioned region was conducting a parallel study on OC which justifies its high amount of subjects [31]. Taking these specificities into account, participant sites were proportionally represented in the study.

Study design allowed a wide range of subjects' age at enrolment. Younger individuals were preferentially seen in multidisciplinary non-RRTDCF and RRTDCF sites. Subjects enrolled at genetic units were among the oldest, suggesting that the subjects primarily refer to surgery treatment instead of genetic evaluation. In addition, previous studies [22, 31] have showed that there is high level of inequality to access genetic evaluation and counselling in Brazil.

The overall results on type of cleft, gender ratio differences, severity (unilateral and bilateral) and laterality (left and right sided) of the lip defects corroborate the literature [2, 11, 13, 32, 33].

Prevalence of consanguinity in this sample was higher than that reported for the Brazilian population [34–36] and did not show preferential geographic distribution. It has been suggested that there is a greater genetic component in the aetiology of CL based on the observation of an excess of individuals with CL over CLP in the offspring of consanguineous parents [37]. We did not find statistically significant association between type of cleft and parental consanguinity. This result, however, should be confirmed in the future using a larger sample.

In the present study, more than one in four subjects showed family history of OC and almost one in five had an affected individual among their first degree relatives. In this subgroup, CLP was the most prevalent followed by CL and CP. A population-based study conducted in Denmark showed that anatomical severity does have an effect on recurrence in first-degree relatives and the type of cleft is predictive of the recurrence type. Third-degree relatives also have an increased recurrence risk compared to the background population [38].

In our sample, global rate of associated defects was around 48% and predominated among subjects with CP. Minor defects were more prevalent in craniofacial region, while cardiovascular and central nervous systems were mainly and almost equally affected by major defects. One out of four individuals was assigned as a syndromic case. Proportion of syndromic cases was higher among individuals with CP and lower among those with CL.

Methodological differences regarding case definition, inclusion or exclusion of minor defects, and anomalies/syndromes grouping-system hinder comparisons with many published data. Despite this, our results on global rate of associated defects and anatomic regions involved are similar to those reported by previous studies [9, 13, 32].

Among more than 20 investigated genes, *IRF6*, *VAX1,* and 8q24 *locus* have a confirmed role in nonsyndromic OC. Environmental factors, lifestyle, and the preventive role of vitamin supplements have been also investigated. Maternal smoking during pregnancy is consistently linked with increased risk of OC. Findings on the other risk factors and gene-environment interactions, including folic acid, have been inconclusive due to methodological issues [1–4, 39]. Besides these factors, a meta-analysis approach showed that parents of 40 years or older have higher probability of having a child with OC [40].

Despite important advances in the understanding of nonsyndromic OC, around 50% of patients with syndromic pictures remain as cases of multiple congenital anomalies without an identifiable aetiological factor. Laboratory facilities have improved the rate of specific diagnosis so that

more than 600 syndromes involving OC have been already recognized. Chromosomal aberrations are the most frequent aetiological group, followed by Mendelian/heterogeneous abnormalities and teratogenic factors [8, 13, 32, 41, 42].

Numeric and structural chromosomal abnormalities, including 22q11 deletion, were detected in 13 cases. Mendelian, heterogeneous, and teratogenic conditions were diagnosed on the basis of clinical evidences.

Limited laboratory facilities are challengeable and the Brazilian database may be helpful to define which tests are critical to our population. Collaboration to make these tests available into the network would be economically advantageous. This is an important strategy for healthcare planning [15, 43–45].

As knowledge of genetics and of gene-environment interaction in the aetiology of OC improves, clinical genetics is becoming increasingly important specialty to ensure accurate diagnosis and allow appropriate genetic counselling [3]. Therefore, clinical genetic approach improves accuracy, consistency, and reliability of clinical descriptions and aetiological assessment which are critical to genotype-phenotype correlations. Understanding these imbricate mechanisms using modern technologies is important to improve therapy and prevention.

The process of interpreting clinical data to determine whether an individual has the defect of interest as syndromic or nonsyndromic defect is complex and involves some degree of subjectivity [4, 46]. Methods and terminology should be as well-defined as possible in order to make process uniform. In this regard, adoption of a stepwise approach is much advantageous [4].

The experience reported here shows how a group of geneticists has developed, implemented, and maintained a network suitable for clinical and genetic research on OC. Strengths of this study are that (1) information is prospectively collected by geneticists experienced in dysmorphology following a standard method and strictly defined protocol; (2) data is centrally storage and processed following a defined stepwise approach which uses IPDTOC/ICBDMS definitions, descriptors, and code system; (3) case record form and operating manual are user-friendly tools and may be incorporated in the routine in other cleft centres, these tools are available to interested researchers through contact with the Cranio-Face Brazil Project (cranface@fcm.unicamp.br); (4) experience gained throughout the process is shared among participants in face-to-face biannual meetings which improve enthusiasm and cohesiveness of the group.

Approaches with new technologies such as Genome Wide Association Studies (GWAS) and open array using accurate clinical data probably would bring interesting results to improve knowledge on the aetiology of OC. Besides research applications, information gathered in the BDOC may be useful to develop and improve personalized treatment, family planning, and public health policies on clinical and laboratory genetic investigation. This should be of interest not only for geneticists and laboratory-based scientists but also—and perhaps especially—for policymakers and clinicians entrusted with OC worldwide.

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgments

The authors thank Professor Pierpaolo Mastroiacovo, Director of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), Rome, Italy, Professor Eduardo Enrique Castilla, Director of the Estudio Colaborativo Latinoamericano de Malformaciones Congénitas (ECLAMC), Professor John Clark, Lead Clinician of the National Managed Clinical Network for Cleft Service in Scotland (CleftSis), for their expert opinion on the design of the BDOC, Romulo Mombach, Clinical Geneticist, for his collaboration during the test stage of the BDOC, and Mailme de Souza Oliveira and Renata Barbosa, Cranio-Face Brazil Project grantees, for technical assistance. This study was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES no. 2854/06-6); Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq nos. 408820/2006-3, 502438/2010-0, and 471422/2011-8); Fundação de Amparo a Pesquisa do Estado de Alagoas (FAPEAL no. 809 60030-700/2009), Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP nos. 2008/50421-4 and 2008/09657-4; 2009/08756-1). V. G. Silva-Lopes is supported by CNPq 304455/2012-1.

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Hindawi Publishing Corporation
Plastic Surgery International
Volume 2013, Article ID 247908, 4 pages
http://dx.doi.org/10.1155/2013/247908

Clinical Study

Prevalence of Oral Habits in Children with Cleft Lip and Palate

Paula Caroline Barsi, Thaieny Ribeiro da Silva, Beatriz Costa, and Gisele da Silva Dalben

Pediatric Dentistry, Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo (HRAC/USP), R. Silvio Marchione, 3-20-Vila Universitária, 17012-900 Bauru, SP, Brazil

Correspondence should be addressed to Gisele da Silva Dalben; gsdalben@usp.br

Received 3 August 2012; Accepted 3 February 2013

Academic Editor: Renato Da Silva Freitas

This study investigated the prevalence of oral habits in children with clefts aged three to six years, compared to a control group of children without clefts in the same age range, and compared the oral habits between children with clefts with and without palatal fistulae. The sample was composed of 110 children aged 3 to 6 years with complete unilateral cleft lip and palate and 110 children without alterations. The prevalence of oral habits and the correlation between habits and presence of fistulae (for children with clefts) were analyzed by questionnaires applied to the children caretakers. The cleft influenced the prevalence of oral habits, with lower prevalence of pacifier sucking for children with cleft lip and palate and higher prevalence for all other habits, with significant association ($P < 0.05$). There was no significant association between oral habits and presence of fistulae ($P > 0.05$). The lower prevalence of pacifier sucking and higher prevalence of other oral habits agreed with the postoperative counseling to remove the pacifier sucking habit when the child is submitted to palatoplasty, possibly representing a substitution of habits. There was no causal relationship between habits and presence of palatal fistulae.

1. Introduction

The manner how children are raised is very important for their full development, general health, and inclusion or exclusion of costumes and habits.

Habit is a behavior acquired by the frequent repetition or physiologic exposure with regularity [1]. Related to the mouth, it is commonly observed in children and may be harmful when excessively repeated or in more vulnerable ages. They often involve patterns of muscle contraction and may contribute to the etiology of malocclusion, because they affect the entire orofacial region.

In the presence of habits, the duration of the applied force is the most critical variable to be analyzed, because the longer the duration, the greater will be the impact on the dentition, musculature, and bone structure [2].

Considerable differences are observed in the prevalence of habits throughout the world. Traditions, cultural influences, and child raising are possible factors that influence their prevalence. The prevalence of sucking habits in Brazil seems to vary between states because of differences in culture, ethnicity, and lifestyle [3].

The period of breastfeeding has been indicated as a possible cause of nonnutritive sucking habits [3]. Holanda et al. [4] stated that breastfeeding for longer than six months is considered a protective factor against the persistence of pacifier use but highlighted that the affective relationship between mother and child during breastfeeding and after this period should be further investigated to better understand the etiology of nonnutritive sucking habits. The extended breastfeeding seems to have a healthy psychological impact and possibly provide a greater sensation of confidence and safety during child development. The higher income and educational level of parents are also associated with sucking habits, such as pacifier sucking at the age range from 3 to 5 years [4].

Nonnutritive sucking habits are risk factors for the occurrence of anterior open bite and posterior crossbite. Heimer et al. [5] observed a significant reduction in the prevalence of anterior open bite with age, suggesting the self-correction of this malocclusion when the habit is discontinued.

Anxiety, stress, and loneliness may also trigger habits as nail biting, commonly observed in children, which may be originated from the thumb-sucking habit that is transferred

to the nails. The clinical examination of these patients reveals tooth crowding, rotation and wear of edges of mandibular incisors, and protrusion of maxillary incisors [6].

The recognition and elimination of oral habits are extremely important also for the prognosis of periodontal diseases. Some oral habits are considered cofactors in the development of gingival recessions [7].

The sucking process is observed early at 29 weeks of intrauterine life and is the first muscle coordination activity of the child [8]. Even though the sucking habit is very common during childhood and continued up to the second year of life, immediate intervention is necessary in children with operated clefts, because the habits have a great influence on the treatment outcome of cleft lip and palate. The pressure applied on the oral cavity muscles during sucking habits interferes with the repair of cleft lip and palate [8].

The literature on oral habits in children with cleft lip and palate is scarce. The objective of this study was to investigate the oral habits among individuals with operated cleft with and without palatal fistulae, compared to individuals without clefts.

2. Material and Methods

The project was approved by the Institutional Review Board (protocol number 286/2011). The study was conducted on 110 children with complete unilateral cleft lip and palate aged three to six years, with or without palatal fistulae, attending a reference craniofacial center in Brazil. Children were included regardless of ethnicity and gender. Children with associated anomalies, syndromes, and/or neuropsychomotor developmental disorders were excluded.

Data were collected by a questionnaire responded by the caretakers. Before onset, this questionnaire was applied to ten individuals (not participating in the study) to check if the caretakers might have any doubt in indicating their responses. The questionnaire consisted of a form indicating the several types of oral habits in which the caretakers had to choose between "yes" or "no" and indicate the duration and frequency of the habit (since when/how often).

These questionnaires were applied to caretakers of two groups of children. The first (study) group comprised children attending the pediatric dental clinic of the craniofacial center during the study period. This group was further divided in two subgroups, namely, with or without palatal fistulae. To evaluate the presence of these fistulae, children were submitted to clinical examination using a dental mirror and tongue depressor, under artificial light, by a single examiner. Palatal fistulae were considered as present regardless of their size and location, either in the hard, intermediate or soft palate.

The second (control) group was composed of children without clefts aged three to six years, attending a nursery center in the city of Bauru, for comparison of results between children with and without clefts.

The prevalence of oral habits between children with and without clefts was compared by the Fisher test. The presence of oral habits between children with clefts with or without fistulae was assessed by the Fisher test followed by the Chi-square test. All statistical tests were applied at a significance level of $P < 0.05$.

3. Results

All children with clefts had already been submitted to surgical repair. In this group, 65.5% of clefts affected the left side and fistulae were observed in 42.72%, primarily affecting the hard palate (74.5%), followed by the intermediate palate (17.1%), soft palate (4.2%), and intermediate and hard palate (4.2%). No significant association was observed between oral habits and the presence of palatal fistulae according to the Fisher test ($P > 0.05$).

The results for both groups are presented in Figure 1. When compared to the control group, children with clefts presented significant association with tongue thrusting at rest, in speech and in swallowing, tongue sucking, object sucking and interposition, lip sucking, cheek sucking, and nail biting. Conversely, there was significant association between the presence of cleft and lack of pacifier sucking habit. There was no significant association ($P > 0.05$) with thumb and finger sucking.

4. Discussion

This study analyzed the prevalence of oral habits in children with cleft lip and palate compared to children without clefts, correlating possible causes and interferences. Data were collected by a questionnaire applied to the caretakers and relied on their responses; thus, the following discussions should be considered under the light of caretakers' reports. Mainly, the findings revealed lower prevalence of pacifier sucking and higher prevalence of other habits in children with clefts compared to children without clefts.

Silva Filho et al. [9] analyzed the most common habits in children without clefts and reported pacifier sucking among the most frequent (28.95%). In the present study, the prevalence of pacifier sucking was higher in children without clefts compared to children with clefts. In general, the prevalence of sucking habits in children has been associated with several factors including age, gender, ethnicity, number of siblings, and socioeconomic status [10]. This study further suggests that lip and palate repair surgeries performed early may also interfere with the prevalence of oral habits as pacifier sucking.

Satyaprasad [8] reported that even though some oral habits are very common during childhood and persist up to the second year of life, immediate intervention is necessary in children with clefts because they may have a harmful influence on the treatment outcome of cleft lip and palate. The results of their electromyography study of several orofacial muscles revealed that they remain active during sucking habits, thus possibly altering the outcome of cleft treatment.

Patients submitted to surgeries for lip and palate repair also present alterations in muscle functions in the orofacial region. Due to the difference in the adaptability and functions of muscles in the postoperative period, interventions and

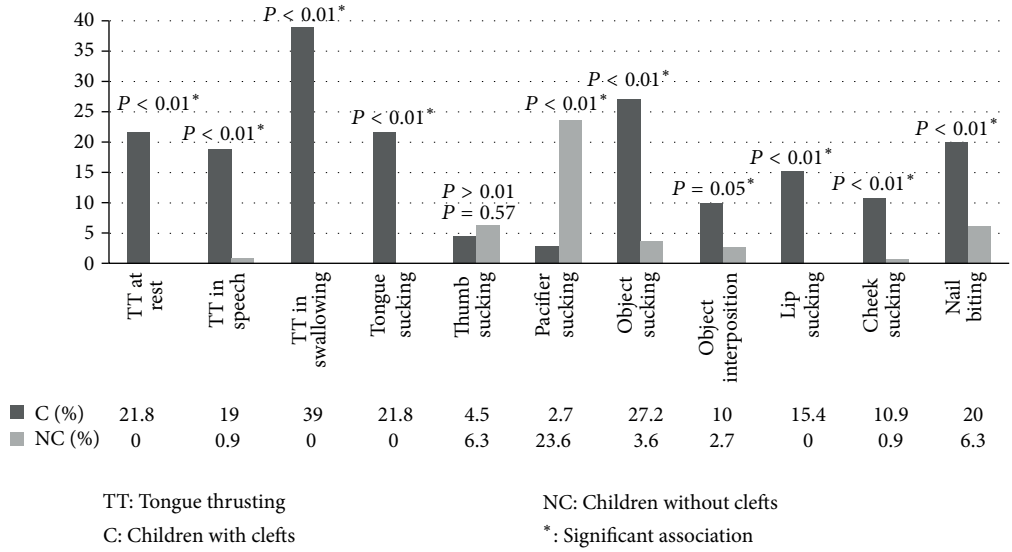

Figure 1: Prevalence of oral habits in children with cleft lip and palate compared to the control group.

additional care are necessary [8]. Therefore, the parents are commonly advised by medical doctors, especially plastic surgeons, to remove the pacifier sucking habit of their children after the repair surgeries.

Mothers routinely report that they do not even offer the pacifier to the child to avoid the establishment of the habit. Almeida et al. [11] reported that finger or pacifier sucking is normal in the onset of child development, and the opposition of parents to these habits may cause negative psychological consequences to the child. Franco et al. [12] suggests knowledge on the etiology of acquisition of sucking habits and how they may be harmful to allow their prevention by follow-up and counseling to the parents.

Holanda et al. [4] highlighted that the pacifier-sucking habit is significantly associated with age (3–5 years), with greater association at the age of 3 years. The present study included children aged 3 to 6 years to investigate the prevalence of oral habits and revealed that, in the case of children with clefts, pacifier sucking is interrupted early by the parents because of the lip and palate surgery, thus being uncommon in this group of children.

Franco et al. [12] confirmed that, in children with clefts, the acquisition of sucking habits may be influenced by the repair surgeries at early ages, because they use arm retainers in the first month after surgery, which precludes placement of the hand and objects in the mouth, to avoid trauma and infection. Interruption of pacifier sucking is also recommended, making children to abandon the sucking habit often present in earlier periods.

Considering the age range included in the study, all children in the sample had already been operated, since lip repair in the institution is usually performed at three months of age. The higher prevalence of other habits than pacifier sucking, such as tongue thrusting at rest, in speech and swallowing, tongue sucking, interposition and sucking of other objects, and lips, cheeks, and nail biting in the group of children with clefts probably represents a substitution of habits by the children, who are restrained from using the pacifier in the postoperative period. It should be highlighted that such other habits may also be harmful to the development of dental occlusion. Habits as tongue thrusting and sucking may be difficult to manage because of the prompt availability of the involved structure, that is, the tongue rather than a foreign object. Therefore, these children should be followed and their caretakers properly counseled concerning the possible occurrence of such habits to avoid their establishment or allow early intervention.

This study did not demonstrate correlation between oral habits and presence of fistulae. Passos et al. [13] conducted a study in the same institution as the present investigation and observed that 27% of subjects in their study presented palatal fistulae, reporting that the occurrence of palatal fistulae after primary palatoplasty is not uncommon.

Passos et al. [13] further reported that, after discharge, the caretakers of patients are advised by the nursing team and receive a handout with information on the postoperative care that must be followed until complete healing of the palate. However, doubts may arise on the compliance with this care and how this might significantly influence the formation of fistulae, considering that many individuals assisted at the institution present low socioeconomic cultural level, in addition to the overindulgence observed in families of children with clefts.

Investigation of the prevalence of oral habits and correlation between fistula and oral habits in children with cleft lip and palate is fundamental to allow better knowledge and confidence of professionals treating these patients, who may then offer better counseling for the patients' parents or caretakers.

In conclusion, considering the medical orientation on the need to remove the pacifier-sucking habit when the child is submitted to palatoplasty, due to the difference of

adaptability and muscular functions in the postoperative period, the present findings reflect such advice, revealing lower prevalence of pacifier sucking and higher prevalence of other oral habits, supposedly a substitution of habits. No relationship was observed between habits and presence of palatal fistulae or dehiscences. Of course, the occurrence of palatal fistulae may also be influenced by other factors such as surgeon's skill, postoperative infection, and care, besides others [13]. However, the present findings suggest the need of a prospective, randomized study to assess the actual influence of oral habits on the postoperative outcome, considering the possibility of substitution by other habits and their long-term consequences in the children's lives.

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Hindawi Publishing Corporation
Plastic Surgery International
Volume 2013, Article ID 671786, 6 pages
http://dx.doi.org/10.1155/2013/671786

Review Article

Investing in a Surgical Outcomes Auditing System

Luis Bermudez, Kristen Trost, and Ruben Ayala

Research and Outcomes Department, Operation Smile, Inc., Norfolk, VA 23509, USA

Correspondence should be addressed to Kristen Trost; kristen.trost@gmail.com

Received 31 August 2012; Accepted 19 October 2012

Academic Editor: Nivaldo Alonso

Background. Humanitarian surgical organizations consider both quantity of patients receiving care and quality of the care provided as a measure of success. However, organizational efficacy is often judged by the percent of resources spent towards direct intervention/surgery, which may discourage investment in an outcomes monitoring system. Operation Smile's established Global Standards of Care mandate minimum patient followup and quality of care. *Purpose*. To determine whether investment of resources in an outcomes monitoring system is necessary and effectively measures success. *Methods*. This paper analyzes the quantity and completeness of data collected over the past four years and compares it against changes in personnel and resources assigned to the program. Operation Smile began investing in multiple resources to obtain the missing data necessary to potentially implement a global Surgical Outcomes Auditing System. Existing personnel resources were restructured to focus on postoperative program implementation, data acquisition and compilation, and training materials used to educate local foundation and international employees. *Results*. An increase in the number of postoperative forms and amount of data being submitted to headquarters occurred. *Conclusions*. Humanitarian surgical organizations would benefit from investment in a surgical outcomes monitoring system in order to demonstrate success and to ameliorate quality of care.

1. Introduction

A strong argument can be made that the success of humanitarian surgical organizations must consider both quantity of patients receiving care and the quality of the care provided. However, the efficacy of a nonprofit organization is often judged by asking what percentage of an organization's resources is spent towards direct intervention; in this case, the percentage that goes directly towards providing surgery. Such scrutiny might discourage humanitarian organizations from investing in adequate review of their outcomes, to the detriment of the patients being served. In order for surgical outcomes to be effectively monitored for both patient followup and measuring success, adequate resources need to be allotted towards the establishment of effective systems.

Operation Smile, an international medical nonprofit providing free surgical care for children with clefts, is striving towards measuring its success both by the quantity and quality of care it provides. In 2006, Operation Smile and representatives from its global medical community established the Global Standards of Care, mandating minimum requirements of practice across 14 aspects of care for cleft lip and cleft palate patients. Global Standard 12, titled "Minimum Patient Follow-Up," states the following:

> *Effective post-operative care is essential for a good surgical result and effective planning for further treatment. Post-Operative care requires good documentation and extensive education of parents and clinicians to be effective. Post-Operative care from an Operation Smile organized team should review patients at the following intervals:*
>
> *12.1 One week post-surgery (4–7 days post-op). The goal is to recognize and manage immediate surgical complications.*
>
> *12.2 Six months–1 year. Team evaluation for documenting outcomes of surgeries and planning for future treatment [1].*

This global standard established Operation Smile's commitment to evaluate its success, not just by the number of surgeries provided, but the quality of care. A preliminary

Surgical Auditing System was pilot tested in 2008 to determine the effectiveness of evaluating the surgical outcomes of patients [2]. However, In order to implement a large-scale Surgical Outcomes Auditing System, Operation Smile has found that investing in the collection of postoperative data is imperative.

2. Measuring Successful Outcomes

Successful outcomes are often measured by the quantity of services provided to patients. However, the quality of the surgical outcomes should play an equal role in measuring the success of surgery. Good outcomes of primary surgeries reduce the cost spent on secondary revisions as well as ancillary services and procedures. In order to measure success in this manner, a method for evaluating surgical outcomes within a short and a long time frame would be necessary [3].

The widely accepted goal of cleft care is to return patients to a "normal" life with little to no handicaps associated with cleft lip and/or palate, or the surgical repair. However, measuring this success is often considered complex as it requires the consideration of numerous factors such as velopharyngeal function (speech) palate integrity (fistulas), nasolabial appearance, hearing capabilities, dentoskeletal development, quality of life, and the psychosocial adjustment of the patient. Final assessment of surgical outcomes in the areas of hearing, speech, and skeletal growth require a decent amount of time to pass after surgery. However, nasolabial appearance, facial symmetry, and fistula occurrence have been shown to be effective early measures of surgical outcomes [4–7].

3. Background

International humanitarian organizations implement a wide variety of medical mission models. Operation Smile's unique method of utilizing medical missions to build local sustainability has enabled the organization to move from having a mere presence in a country to establishing local foundations and support. There are two main mission methods implemented by Operation Smile. International missions are comprised of team members with at least 50% of volunteers from outside the country in which the mission is occurring and usually lasts 7–10 days, two days of screening, five surgical days, and three days for unpacking and packing of cargo. International missions can take place in both countries that do not have local foundations and countries that do have local foundations. Local missions are comprised of at least 50% local volunteers, volunteers from within the country the mission is occurring. Local missions can last for any length of time, usually between 3 and 10 days and are generally held in countries that have local foundations, which are independently run in-country Operation Smile organization that have the support of Operation Smile International. Occasionally, large unique international missions are implemented for unique projects such as the "World Journey of Smiles," which took place in 2007. The World Journey of Smiles was a culmination event for the organization's 25th Anniversary in which a large international mission was implemented.

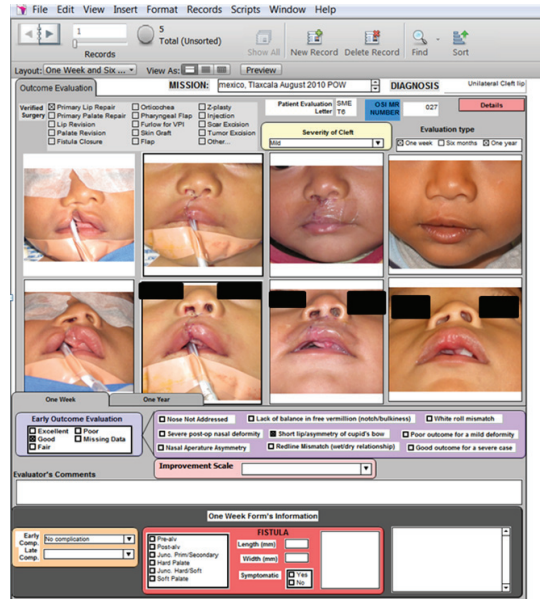


Figure 1

During Operation Smiles' "World Journey of Smiles" in 2007, a Surgical Outcomes Auditing System, using digital photography as media, was developed and pilot tested. Four thousand one hundred patients were operated on in 40 different sites, in 25 different countries over 10 days. During these missions, high-quality images were taken for each patient preoperatively and postoperatively. Postoperative evaluations were held one week after the mission and local foundations were encouraged to schedule six-month and one-year postoperative evaluations for patients. During these postoperative evaluations both standardized images as well as post-operative assessment data collected from PostOperative Exam Forms were collected. This data was then returned to Operation Smile Headquarters where six-month and one-year images were matched with patients' preoperative and immediate postoperative images. Standardized angles of the frontal and basal views as well as images of the hard and soft palates were cropped to protect patients' identities, focusing the reviewer on the surgical area, and to eliminate potential bias of the reviewer [8].

After compiling this data and deidentifying patient and surgeon information, the evaluations were sent to unbiased members of the International Outcomes Evaluation Council, a group of trained surgical evaluators, and utilizing a qualitative assessment system a surgical evaluation was completed for each procedure provided [2]. Figure 1 shows the final evaluations that were returned to surgeons in a confidential manner. The Regional Medical Officer, who provides medical oversight and leadership for any medical programs within their particular region, and the Medical Director, who is the medical leader for their particular foundation, also received these evaluations to spur further discussion of outcomes.

During the pilot test of the Surgical Outcomes Auditing System, a series of challenges were identified that needed to be overcome. The first and foremost was the need to socialize

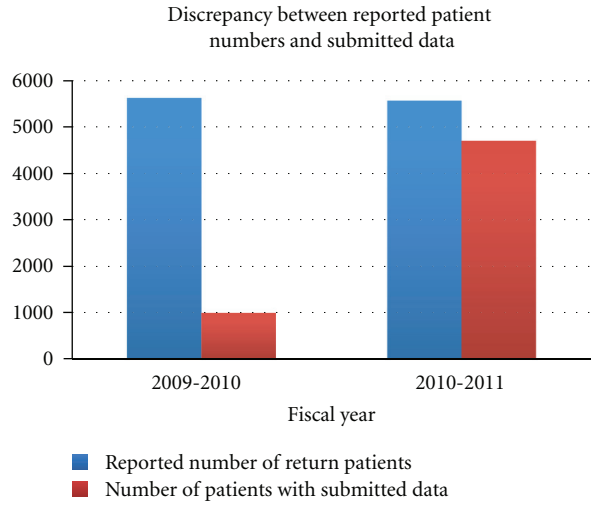


Figure 2

the concept of auditing the results of surgical procedures and the impact it would have on the mission process. It has taken time and the constant education of medical team members to understand new procedures.

After addressing the challenges associated with the capturing of images, the next challenge to overcome was the quality of the photographic data. At the onset, untrained photographers were being used to collect patient images. With little training in the appropriate image capturing techniques and a thorough understanding of the angles needed, the quality of data obtained was of unusable quality.

Once the challenges of acceptance of auditing surgical outcomes and the need for quality trained patient imaging technicians to capture quality standardized images were overcome, the next challenge to overcome was obtaining and analyzing data collected during missions and during postoperative examinations.

4. Method

After the world Journey of Smiles completed in 2007, the postoperative program began to be regularly implemented. Unfortunately, not all of the data from missions were being returned to headquarters. Figure 2 shows the reported number of patients returning for postoperative examinations in comparison with the data returned to headquarters for these patients.

Recognizing the discrepancy between the number of patients attending post-op and the amount of data received, Operation Smile began investing in multiple resources to obtain the missing data necessary to potentially implement a global Surgical Outcomes Auditing System. Existing personnel resources were restructured to focus on post-op program implementation and data acquisition and compilation. Employees responsible for collecting form data and patient image data went from being members of separate teams within different departments to being on the same team within the same department. This enabled team members to more effectively identify which missions were missing data and initiate the process for obtaining that data.

As part of this restructuring, personnel began increasing the amount of direct contact with local foundations by phone and e-mail to request the submission of postoperative forms and patient images that had not been submitted to headquarters. Training materials used by these team members to educate local foundation employees and international employees were reorganized to focus more on how to implement properly the postoperative program and to submit data rather than concentrating on how the Surgical Outcomes Auditing System would work.

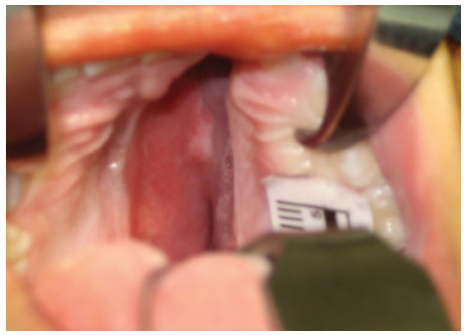
Complete data sets, including both patient images and postoperative information, were also not being received from countries in which more local missions were occurring. An Outcome Data Coordinator role was developed to increase the quality and quantity of data return from countries that implemented more locally run missions. Outcomes Data Coordinators became responsible for training local volunteers in the image and form collections process as well as being responsible for collecting, compiling, and submitting this data to headquarters.

Foreseeing the need to compile the incoming postoperative data and patient images with minimal employee resources, a data entry intern program was established to deal with data compilation. An internship description was created and posted on the headquarters career website. Applicants with interests in medical, nonprofit, or data entry experience were considered and accepted for positions.

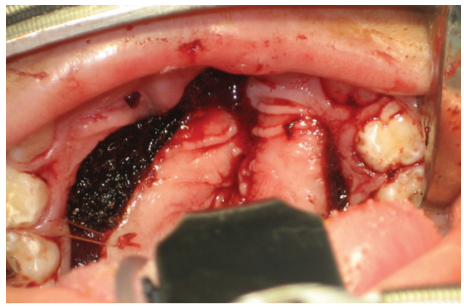
To address the increase in one-week postoperative data and the reporting of early complications such as infection and dehiscence, an Early Outcomes Monitoring System was established to identify surgeons with outlying complication rates. Figure 3 shows an anterior fistula after a cleft palate repair. In the immediate postoperative picture, we can see the presence of a fistula, which was a result of the surgical technique as oral flaps were not designed to achieve complete closure of the anterior palate. Because pictures are taken immediately after surgery, it is often possible to identify the cause of the complication as we can see in Figure 3. These images make it easier to address the complication sooner.

Recognizing that such complications could be detected earlier, surgical information and postoperative data were combined in an Access database comprised of over 12,000 surgeries with data from the one-week postoperative evaluations of patients operated on by over 400 surgeons. This database enables Operation Smile to monitor the more immediate postoperative complications by surgeon, mission site, and country. While no acceptable complication rate should ever exist, a high variation of complication rates has been reported from other organizations and studies, between 0% and 33% [9–13].

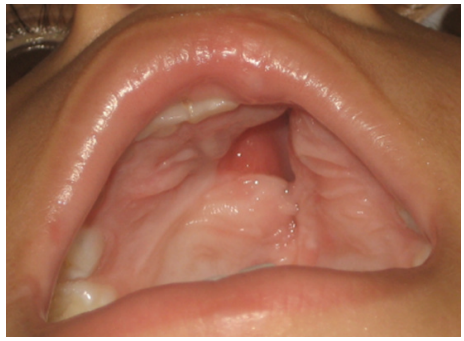
Operation Smile uses these rates as markers to identify surgeons who have outlying complications rates both high and low. When a surgeon is identified as having an outlying complication rate, one that does not fall within the aforementioned range, Operation Smile's Surgical Council receives a report for this surgeon. The report contains



(a) Preoperative picture of the anterior part of a cleft palate



(b) Immediate postoperative picture



(c) Postoperative picture taken 11 months after surgical repair

Figure 3: Clinical Case 1.

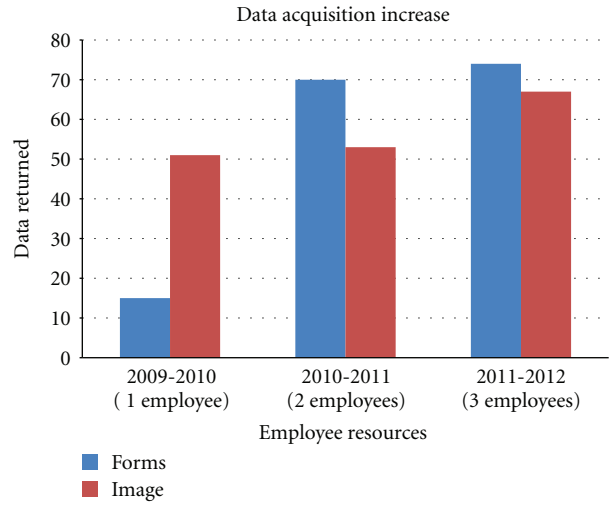


Figure 4

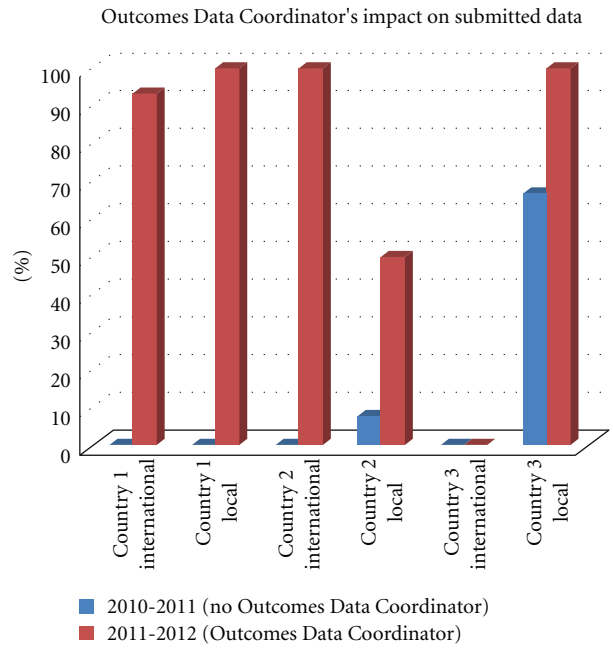


Figure 5

information on the cases identified as having complication along with all of the outcomes evaluations on file for the surgeon. This complete report and their surgical cases are then reviewed. The goal is to review and to help in the education of these surgeons, pairing them with mentors and working to enhance their skills.

5. Results

After making direct requests of foundations for specific missing data, an increase in the number of postoperative forms as well as images submitted to headquarters was demonstrated, as seen in Figure 4.

Figure 5, demonstrates the increase in complete data sets submitted to Operation Smile headquarters for both local and international missions by Outcomes Data Coordinators.

As the amount of data being submitted to headquarters increased, the capacity to compile that data was reaching its threshold. Figure 6 shows that by increasing the number of interns more data could be compiled.

6. Discussion

Good surgical outcomes are part of Operation Smile's commitment to the patients receiving surgery during its medical missions and at its cleft care centers. In order to meet this commitment and continue to address the surgical needs of children with cleft lip and palate, implementation of a Surgical Outcomes Auditing System has been initiated. Many

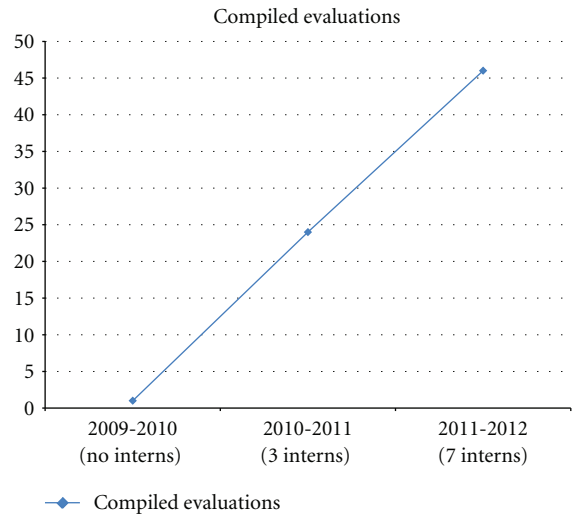


Figure 6

challenges have played a role in the development and implementation of a global Surgical Outcomes Auditing System, the most impactful of these challenges has been obtaining the necessary data. Recognizing this need, Operation Smile invested in resources to collect and compile the data needed for these evaluations. Through the restructuring and reorganizing of existing personnel, a more cohesive understanding of the specific data needed was gained. This understanding facilitated the direct request of missing postoperative forms and patient images. Figure 2 shows that the investment in personnel resources resulted in an increase of both postoperative data and patient images being returned to headquarters. Initial data collected was primarily images. Restructuring allowed for more focus on collecting missing data from specific missions. This focus brought an increase in the number of postoperative forms submitted to headquarters. Adding a third employee allowed for more direct contact with local foundations and the ability to request more images as well as postoperative forms, resulting in a further increase in data submitted.

Another area of focus was on the three countries where high-volume of surgeries were being provided but no data was being received. After the establishment of the Outcomes Data Coordinator position in these three target countries, the percentage of not only data, but complete data sets comprised of patient images and patient information, increased drastically. Countries 2 and 3 increased the amount of international data submitted from less than 50% to 100% and Countries 1 and 3 increased submitted local mission data to 100%.

Creating a data entry internship program preemptively addressed the challenge of insufficient personnel resources to compile the increase of complete data being submitted to headquarters. As more data arrived due to direct contact and the implementation of the Outcomes Data Coordinator role, more personnel power was needed to compile data into the evaluation templates. Figure 5 demonstrates that as the number of interns doubled so did the amount of compiled evaluations.

7. Conclusion

Operation Smile's investment in resources significantly increased both the amount of data received and the data compiled from both local and international missions. As local foundations become more and more accustomed to the implementation of the postoperative program as well as the submission of data to headquarters, the more realistic the implementation of a Global Surgical Outcomes Auditing System becomes. However, if Operation Smile is to be successful in obtaining its goal to return patients to a normal life, it cannot limit itself to simply evaluating the visual outcomes of the surgeries they perform.

Visual outcomes are only some aspects of evaluation that can be used to measure the success of surgical procedures. Speech evaluations can provide further insight into the success of surgeries provided. A perceptual evaluation system has attempted to be implemented in Spanish speaking countries, but the major obstacle is defining what parameters need to be evaluated and how these parameters can be evaluated in order to achieve a good interobserver reliability [14]. Form and functionality is a large portion of returning patients to a "normal life" but it is also very important to determine how well patients are reintegrated into their communities and how they are managing these psychosocial changes.

As Operation Smile moves forward in the development and implementation of a Global Surgical Auditing System, many other outcomes areas can and should still be measured. With its ever growing global impact through the increasing number of surgeries provided annually, Operation Smile is leading the way in working to ensure that the surgeries they provide are of the best quality.

Conflict of Interests

At the time of writing this paper K. Trost and R. Ayala were employees of Operation Smile and L. Bermudez was a paid consultant.

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Hindawi Publishing Corporation
Plastic Surgery International
Volume 2013, Article ID 237308, 6 pages
http://dx.doi.org/10.1155/2013/237308

Clinical Study

The Lateral Port Control Pharyngeal Flap: A Thirty-Year Evolution and Followup

Sean Boutros[1,2] and Court Cutting[3]

[1] *Hermann Memorial Hospital and Hermann Children's Hospital, Houston, TX 77030, USA*
[2] *Houston Plastic and Craniofacial Surgery, 6400 Fannin Suite 2290, Houston, TX 77030, USA*
[3] *Institute for Reconstructive Plastic Surgery, New York University, New York, NY 10016, USA*

Correspondence should be addressed to Sean Boutros; drseanboutros@drseanboutros.com

Received 14 August 2012; Accepted 4 November 2012

Academic Editor: Luis Bermudez

In 1971, Micheal Hogan introduced the Lateral Port Control Pharyngeal Flap (LPCPF) which obtained good results with elimination of VPI. However, there was a high incidence of hyponasality and OSA. We hypothesized that preoperative assessment with videofluoroscopy and nasal endoscopy would enable modification and customization of the LPCPF and result in improvement in the result in both hyponasality and obstructive apnea while still maintaining results in VPI. Thirty consecutive patients underwent customized LPCPF. All patients had preoperative diagnosis of VPI resulting from cleft palate. Patient underwent either videofluoroscopy or nasal endoscopy prior to the planning of surgery. Based on preoperative velar and pharyngeal movement, patients were assigned to wide, medium, or narrow port designs. Patients with significant lateral motion were given wide ports while patients with minimal movement were given narrow ports. There was a 96.66% success rate in the treatment of VPI with one patient with persistent VPI (3.33%). Six patients had mild hyponasality (20 %). Two patients had initial OSA (6.67%), one of which had OSA which lasted longer than six months (3.33%). The modifications of the original flap description have allowed for success in treatment of VPI along with an acceptably low rate of hyponasality and OSA.

1. Introduction

In 1971, Micheal Hogan introduced the lateral port control pharyngeal flap [1–3]. This flap was conceived out of frustration over the inconsistent results obtained in the correction of velopharyngeal insufficiency with pharyngeal flaps. By noting important contributions to the understanding of physiology and dynamics of hypernasal speech by Warren, Isshiki, and Bjork [4–7], he devised a technique that could be universally applied to all patients with velopharyngeal insufficiency and obtain good result with consistent elimination of hypernasal speech [1–3, 8]. In his technique, the superiorly based flap, lined by the nasal side of the soft palate [9–12], was designed so that the lateral aperture size was controlled by the passage of a 4 mm diameter catheter. This effectively created an air passage that allowed the oropharyngeal pressure build up necessary to eliminate hypernasal speech.

After his initial description, the procedure evolved due to observation of the results. At the time Hogan described the LPC pharyngeal flap, sleep apnea had not yet been described as a clinical entity [13, 14]. In terms of speech intelligibility, hyponasality is preferred over hypernasality. The idea that many cleft palate patients with VPI often had good lateral wall movement allowing a "tailored width" pharyngeal flap [15] was also not yet widely known. For this reason, Hogan initially described a single-size flap that tended to produce very small lateral ports. Dr. Hogan intuitively began constructing larger ports in most patients and still maintained adequate results. In the past 30 years, the Hogan LPC flap became well known for the production of hyponasality and sleep apnea. The subsequent modifications of Hogan's original description, which takes these factors into account, are the subject of this paper.

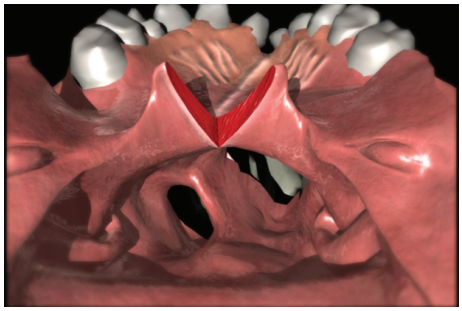

Figure 1: Division of soft palate.

2. Materials and Methods

Thirty consecutive patients undergoing pharyngeal flap procedures for velopharyngeal insufficiency (VPI) were identified. Twenty-seven of these patients had VPI as a result of cleft palate, and 23 of these patients had adequate followup (greater than one year) for inclusion in this study. Patients were treated at the Institute of Reconstructive Plastic Surgery and either operated on or supervised by the senior surgeon (CC). Patients were treated according to the cleft VPI protocol as outlined later on. All patients were followed by the senior surgeon, pediatric otolaryngologist, and speech therapist.

2.1. Preoperative Evaluation. Patients with velopharyngeal insufficiency underwent evaluation with videofluoroscopy or fiberoptic nasal endoscopy [16, 17]. The findings are reviewed in a multidisciplinary clinic with a plastic surgeon, a pediatric otolaryngologist, and a speech therapist. Together, a consensus was reached as to the amount of velar and pharyngeal movement.

In patients between 2.5 and 3 years of age who have not undergone intravelar veloplasty with the initial palate repair (palate closure performed at another institution), this procedure is the first-line treatment [18]. Many patients will attain adequate velar closure and have complete elimination of hypernasality with this procedure alone. These patients were excluded from this study.

In patients over four years, in whom the time course is more pressed due to the difficulty in elimination of compensatory articulations acquired after prolonged time with nasal escape, the pharyngeal flap is the procedure of choice if the nasal endoscopy shows lateral wall movement with poor central closure [8, 15–17, 19]. In a small minority of patients (none in our sample group), there may be good central movement with poor lateral closure. These rare patients are treated with a sphincter procedure. In addition, patients who have had previous intravelar veloplasty are also candidates for pharyngeal flaps. Based on the fiberoptic and videofluoroscopic findings, these patients are assigned to a small, medium-small, medium, medium-large, and large ports sizes. This corresponds with wide, medium-wide, medium, medium-narrow, and narrow pharyngeal flaps [13, 15, 17, 20, 21].

2.2. Operation. Prior to prep and drape, the posterior pharyngeal wall and the soft palate are infiltrated with approximately 10 cc of 0.5% lidocaine with 1 : 200,000 epinephrine. The posterior pharynx should always be palpated prior to infiltration, as patients with undiagnosed velo-cardio-facial syndrome are likely to have medialization of the carotid arteries, and care must be taken to avoid their injury. A Dingman's mouth gag is placed with the smallest tongue gag that will adequately hold the tongue on the floor of the mouth. Placement of a larger gag will limit the ability to reach the posterior pharyngeal wall. The handle of the gag is hung on the Mayo stand edge fully open and protrudes the mandible for optimal access.

The soft palate is split in the midline (Figure 1) and retraction sutures are placed. This split should stop just prior to the hard/soft palate junction (see supplementary video available online at doi:10.1155/2012/237308). The posterior pharyngeal wall is visualized, and the superiorly based pharyngeal flap of the appropriate width is outlined. As the flap is superiorly based, its mucosal surface will be reflected to the nasal side. It should be based as high as possible, approximately 15 mm caudal to the Eustachian tube orifices. The flap is incised to the parapharyngeal space. It is not necessary to incise to the prevertebral fascia as it does not contribute to the vascularity of the flap and results in a more painful donor site. The paired parapharyngeal spaces can be confirmed by the presence of the midline raphe. The flap is elevated with a peanut and the midline raphe cut with scissors. A suture is placed in the tip of the flap for retraction.

The donor site should be closed directly except for the most proximal area. Closure decreases the postoperative pain, infection rate, and decreases downward migration of the flap with time. It will also allow for reestablishment of the sphincteric action of the pharyngeal wall with approximation of the muscles. It is best to close the middle of the donor site first and use the long end of a suture for retraction to expose the most caudal aspect of the donor site. Attempting to close the most cranial or proximal area of the donor site will cause the flap to take a tube shape and make creation of the appropriate size port difficult. Care must be taken to cauterize the edges of the cut posterior pharynx prior to closure as this is the most likely site of postoperative bleeding. This bleeding will most likely be from a cut ascending pharyngeal artery or one of its branches. Bleeding in this area may cause loss of airway and preclude oral intubation. Hemostasis is best performed with a suction cautery device. Although commercial suction cauteries are available, passing a neurotip suction through a red rubber catheter can easily create a suction cautery.

Attention should be turned to the creation of the lining flaps. It is important to consider the width of the lateral port much more than the width of the lining flap. The lining flaps are elevated from the nasal side of the soft palate and will line the oral side of the pharyngeal flap (Figure 2). They are based on the posterior edge of the soft palate, and the tip of the flap is at the hard/soft palate junction. The split soft palate should be reflected laterally. The rhomboidal-shaped flap is elevated off the underlying velar musculature. Starting at the most anterior aspect of the soft palate split, an incision

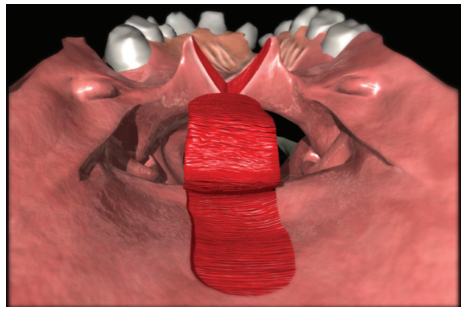

Figure 2: Elevation of superiorly based pharyngeal flap.

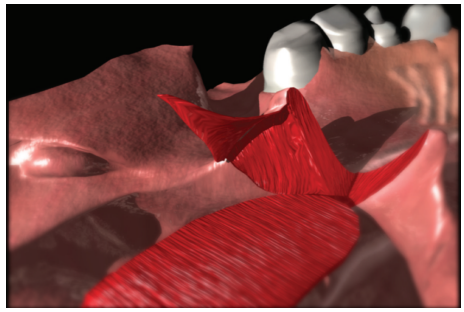

Figure 3: Elevation of the lining flap from the nasal side of the soft palate. Note that the lateral extent of the lining flap will help determine the size of the resulting lateral port.

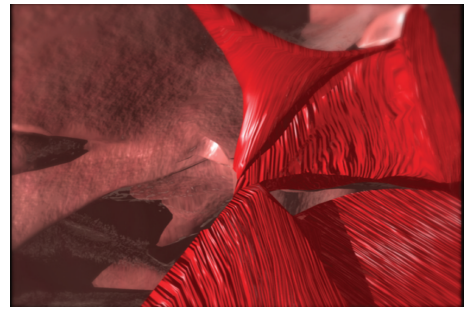

Figure 4: The key suture brings the lateral aspect of the lining flap to the superiorly based pharyngeal flap. This suture sets the size of the lateral port.

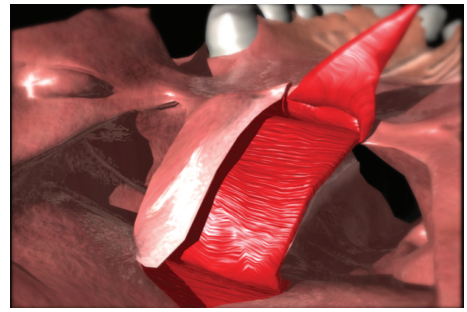

Figure 5: The lining flap is brought down to cover the raw side of the pharyngeal flap. This lining is crucial to prevention of contraction and tabularization of the pharyngeal flap.

is created toward the lateral/posterior edge of the soft palate. The lateral cut edge on the nasal surface of the soft palate will determine the size of the port.

The nasal lining flaps are then turned out to cover the raw surface of the pharyngeal flap. The port is created by suturing of the lateral cut edge to a point 5 mm from the base of the pharyngeal flap (Figures 3, 4, and 5). The lateral edge of the pharyngeal flap is sutured to the lateral cut edge from the elevation of the lining flaps, that is, the nasal side of the soft palate. The final suture is a horizontal mattress suture setting the tip of the flap well beyond the most anterior soft palate split in order to prevent formation of a fistula at this critical location. The suture is passed through and through (oral to nasal) the most anterior soft palate. It is passed through the tip of the pharyngeal flap in a mattress fashion and "through and through" (nasal to oral) the soft palate.

The lateral edge of the tip of the lining flaps, elevated from the nasal side of the soft palate, is sutured to the lateral defect of the posterior pharyngeal wall. The medial edges of both lining flaps are sutured to the midline raphe at the base of the pharyngeal flap and to each other. The medial edges of the lining flaps are sutured together with each suture catching the midline raphe of the pharyngeal flap. The uvula is reconstructed, and the oral side of the soft palate is repaired.

A tongue stitch is placed in lieu of an oral airway as passage of an oral or nasal airway may disrupt the flap. The air and fluid are evacuated from the stomach, and blood is suctioned from the nose and pharynx. The patient is only extubated when fully awake, and the surgeon must be present in the room. After extubation, the patient is placed in a tonsillar position and kept awake. Traction on the tongue suture will both open the airway and stimulate the patient as needed.

2.3. Postoperative Management. In the initial postoperative period, airway observation is critical. The patients are kept on continuous pulse oximetry in the initial postoperative period. The intensive care unit is usually not required. The tongue suture is usually removed the next morning. Patients are given pain control with per rectum acetaminophen and codeine and kept on IV antibiotics to decrease the risk of streptococcal infection until they are taking liquids by mouth at which time they can be converted to oral antibiotics. They are allowed fluids immediately but are unlikely to take anything by mouth for the first few days. At the time they are taking adequate liquids, they can be discharged. The time course for oral intake varies dramatically. It ranges from three to nine days, but most patients take adequate fluids by mouth between three and four days. After several days of liquids, the patient is slowly transitioned to a soft diet, which is maintained for two to three weeks.

3. Results

Based on the preoperative evaluation of lateral wall motion, the procedures were divided as such: 6 patients had large port design (small flaps), 3 patients had large/medium port

design (small/medium flaps), 14 patients had medium port design (medium flaps), and 6 patients had small/medium port design (medium/wide flaps). The incidence of small ports (wide flaps) was zero.

There was one patient with persistent VPI (4.3%). Five patients had mild hyponasality (21.7%). Two patients had initial sleep apnea (8.7%). One of the two had sleep apnea which lasted longer than six months (4.3%). This patient's flap was taken down with resolution of the VPI and no hypernasality. There was no airway compromise most likely due to hemostasis obtained prior to back wall closure.

In all patients, there was some initial nocturnal obstruction due to swelling associated with the procedure. Overall, we have seen two patterns of sleep apnea in our patients. The first is obstruction at five to six weeks when wound contracture is at its highest. The obstruction resolves over several weeks as the contracture relaxes. There is a separate group in whom the contracture does not relax and there is resulting long-term obstruction. This may resolve over the next six to nine months, but if it does not resolve, the flap is taken down. Contraction of the pharyngeal flap may also lengthen the scarred soft palate [22].

4. Discussion

4.1. Preoperative Assessment. At the time of Hogan's original publication, there was no way to accurately assess the amount of velar or lateral pharyngeal movement preoperatively. The only measure of success was the postoperative result. As a result, in patients with some degree of pharyngeal movement, the results were typically good, and in patients with poor movement, the results were poor. There was no way to preoperatively stratify patients into the good or poor responder groups.

Videofluoroscopy and nasal endoscopy opened a new understanding of the movement of the velum and how surgical procedures could benefit patients [8, 16, 17, 23]. Videofluoroscopy allowed for direct visualization of the lateral pharyngeal wall movement, identifying the location and degree of the pathology and allowing formation of a reconstructive plan. This, along with the fundamentals of lateral port control technique of described by Hogan, allow for surgeons to customize the procedure to allow for appropriately sized flaps for each patient based on the amount of movement they have prior to surgery. This results in nasal competence, good speech, and limited hyponasality.

4.2. Port Diameter. Dr. Hogan was inspired to develop the lateral port control pharyngeal flap by the works of Drs. Warren and Isshiki. Both showed that the critical closing diameter allowing normal speech was 20 mm^2 (Dr. Isshiki's critical diameter was 19.6 mm^2). Dr. Hogan observed these facts and made two ports that would have a sum total of 25 mm^2, ("…slightly larger than our threshold value of 20 mm^2. Because of the mesial movement of the lateral pharyngeal walls which occurs during speech") [19, 24]. In his design, Dr. Hogan focused on cross-sectional area of the ports not the airflow through the ports which is more important. According to Poiseuille's law, airflow is directly proportional to the fourth power of the radius. Thus, small changes in diameter have a dramatic effect on airflow.

$$\text{Flow} = \frac{\Pi\ (\text{pressure difference})\ \text{radius}^4}{8\ (\text{viscosity})\,(\text{length})}. \quad (1)$$

A 20 mm port has a radius of 2.526 mm,

$$\text{Flow} = \frac{\Pi\ (\text{pressure difference})\,(2.526\,\text{mm})^4}{8\ (\text{viscosity})\,(\text{length})}. \quad (2)$$

By this, half the flow or flow prime would be described by the following equation:

$$\text{Flow prime} = \frac{\text{Flow}}{2} = \frac{\Pi\,(\text{pressure difference})\,(2.526\,\text{mm})^4}{16\,(\text{viscosity})\,(\text{length})},$$

$$\text{Flow prime} = \frac{\Pi\,(\text{pressure difference})\,(2.526\,\text{mm})^4}{16\ (\text{viscosity})\,(\text{length})},$$

$$\frac{\Pi\ (\text{pressure difference})\,(\text{radius prime})^4}{8\ (\text{viscosity})\,(\text{length})} = \frac{\Pi\ (\text{pressure difference})\,(2.526\,\text{mm})^4}{16\,(\text{viscosity})\,(\text{length})},$$

$$\frac{(\text{radius prime})^4}{8} = \frac{(2.526)^4}{16},$$

$$(\text{radius prime})^4 = 20.36\,\text{mm},$$

$$\text{radius prime} = 2.125\,\text{mm}. \quad (3)$$

Therefore, two ports with a radius of 2.125 mm each (cross sectional area of 14.19 mm^2 each and a total cross sectional area of 28.38 mm^2) would have the same airflow as one port with a radius of 2.5 mm (cross sectional area of 19.63 mm^2 each).

In essence, a 50% larger sum total cross sectional area of two ports would have the exact same air flow resistance as a single port of 20 mm^2. This of course assumes that there would be no pharyngeal movement. It can then be extrapolated that after pharyngeal flap, with the creation of ports, where with pharyngeal and velar movement the size of each of the two ports is reduced to an area of 14.19 mm^2, there would be no clinically apparent hypernasality.

In today's evaluation of the patient with velopharyngeal insufficiency, this becomes more significant as presurgical evaluation of the patient can give a much clearer picture of the pharyngeal movement. The procedure is no longer forced to address the least common denominator, that is, paralytic velum and pharyngeal wall, as it can be customized for each patient depending on the specific needs and level of dysfunction.

Presently, the goal is to have complete velar closure. However, with two ports, even if there is not complete closure, the resulting nasal air escape would be less than that found with one port.

4.3. Sleep Apnea. Not until recently did obstructive sleep apnea come into the attention of physicians treating velopharyngeal insufficiency [3]. Prior to this, nighttime obstruction and the resulting clinical symptoms after pharyngeal flap surgery were largely ignored, and the procedures touted as a success or failure solely on the effect on hypernasality. Nighttime snoring was even considered a measure of success as it indicated a low likelihood of nasal escape. However, more recent studies have shown that this important clinical entity is not only a source of significant morbidities including snoring, excessive daytime sleepiness, learning disabilities, irritability, perioperative aspiration pneumonia, growth retardation, heart disease, and hypertension, but also mortality with perioperative respiratory arrest and sudden death.

The incidence of obstructive sleep apnea is controversial. Some authors report that with objective testing in a series of patients, over 90% will have some degree of sleep apnea after pharyngeal flap, and only some of which are clinically significant [25]. Most generally, it is quoted that an approximately 10% incidence of clinically apparent obstructive apnea and that only a fraction of these cases will require intervention [26–28]. In any event, the risk of postsurgical sleep apnea should be taken into account when approaching patients. With preoperative assessment and procedure individualization as we have shown, the incidence of clinically important sleep apnea can be significantly decreased resulting in few patients with this complication.

5. Conclusions

With some modifications from the original description by incorporation of preoperative diagnostic testing, the lateral port control pharyngeal flap has stood the test of time and has proven to be a powerful procedure in treatment of velopharyngeal insufficiency. Like all pharyngeal flaps, it serves to limit airflow from the oropharynx to the nasopharynx by forming an obstruction in the dysfunctional central area. It does not add any scarring or injury to the area where there is normal anatomy and the muscle function is good, that is, laterally. It uses this lateral pharyngeal sphincteric motion, along with the motion of the levator veli palatini muscle, to create a functional, dynamic obstruction to air flow. The lateral port control method turns the attention of the procedure to what is necessary for cure as it forces the surgeon to design a flap where the goal is the creation of a port of appropriate size that will prevent hypernasality while still resulting in an acceptable incidence of hyponasality and obstructive sleep apnea.

Acknowledgment

This work was presented at the American Cleft Palate Association Meeting, Myrtle Beach, South Carolina in March 2005.

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Hindawi Publishing Corporation
Plastic Surgery International
Volume 2012, Article ID 206481, 8 pages
doi:10.1155/2012/206481

Clinical Study

Lip Height Improvement during the First Year of Unilateral Complete Cleft Lip Repair Using Cutting Extended Mohler Technique

Cassio Eduardo Raposo-Amaral,[1] André Pecci Giancolli,[1] Rafael Denadai,[1] Frederico Figueiredo Marques,[1] Renato Salazar Somensi,[1] Cesar Augusto Raposo-Amaral,[1] and Nivaldo Alonso[2]

[1] *Institute of Plastic and Craniofacial Surgery, SOBRAPAR, Campinas, SP, Brazil*
[2] *Plastic Surgery Division, Department of Surgery, Universidade de São Paulo (USP), São Paulo, SP, Brazil*

Correspondence should be addressed to Cassio Eduardo Raposo-Amaral, cassioraposo@hotmail.com

Received 22 July 2012; Accepted 1 December 2012

Academic Editor: Renato Da Silva Freitas

Objective. To compare the cutaneous lip height at early and late postoperative periods and to objectively determine the average amount of lip height improvement during the first year of unilateral complete cleft lip repair using Cutting extended Mohler technique. *Methods*. In this prospective cohort study, 26 unilateral complete cleft patients and 50 noncleft subjects were included. Photographs were taken between 12 and 16 weeks (T1) and also taken between 12 and 13 months after surgery (T2). The cutaneous lip height distance (photogrammetric lip analysis) obtained in these two periods of time were measured and statistically analyzed. *Results*. The average lip heights were 24% ± 9% in T1 and 8% ± 6% in T2 ($P < 0.01$). The average lip height asymmetry in the noncleft individuals was 4.52% ± 1.89%. *Conclusion*. Since all principles to obtain a symmetrical Cupid's bow were performed, the postoperative pull-up of Cupid's bow is probably owed to the scar contracture, which improves by 2 times during the first year after surgery.

1. Introduction

Ralph Millard revolutionized the treatment of cleft lip by describing the innovative principles to repair a unilateral cleft lip, that allows surgeons around the globe to treat patients with different racial characteristics [1–4]. Consequently, his principles remain as a foundation to the development of surgical strategies and tactics to improve the results in the cleft lip repair worldwide [5–7]. Mohler [8] used Millard's principles to develop his own technique, that adds a more vertical incision in the cleft philtrum column, creating a final faint scar that represent a mirror image of the contralateral philtrum column. In the Mohler technique [8], the Millard's C-flap is used to fill the gap created by the downward rotation of the cleft lip segment, instead of the lateral advancement segment as proposed by Millard [5]. Thus, a short lip height may be produced as a consequence of these maneuvers (straight-line scar and absence of the lateral advancement segment fulfilling the medial gap after the back-cut incision).

Cutting's modifications of the Mohler technique are the following: (1) an extension of the medial incision toward the columella, (2) the Millard's back-cut incision never passes the noncleft philtral column, (3) a more vertical incision than that described by Millard, that creates a, and (4) wider C-flap that fills the medial rotation defect [9]. Cutting and Dayan [9] subsequently analyzed cleft patients who underwent a cheiloplasty, using the Cutting extend Mohler technique, in order to respond whether this technique produces a short lip height and lip width in two different postoperative periods of time. Cleft and noncleft distances in each patient were measured preoperatively and postoperatively at two different periods of time (1 to 13 months and at 2 years or more) and statistically compared [9]. Their data did not show statistically significant changes in lip height over time and

showed statistically increased cleft-side lip width over time [9].

Interestingly, some surgeons [10–13] have observed the lip height changes using Millard and other cheiloplasty techniques. Even Cutting and Dayan [9] acknowledged in the same study that the peak of Cupid's bow pulls up short at the sixth postoperative week in some patients who had undergone surgery. The authors [9] concluded that the short lip height usually normalizes at 12 months after the surgery. In a small percentage of their patients, a cleft lip height remained short, possibly owing to the scar contracture of the straight-line closure [9]. Even the authors [9], although shown that the lip height does not statistically change over time, recognized the importance of warning the parents regarding the phenomenon of scar contracture that pulls up Cupid's bow and shortens the lip around the sixth week in the postoperative period.

We have been performing the Cutting extended Mohler technique and also, anecdotally, observed the decrease of the lip height in a latter period than Cutting and Dayan, that ranges from 12 to 16 weeks in the postoperative period. Interestingly, the majority of the parents also observed a short lip height at 12 to 16 weeks in the postoperative period in comparison to the period that comprehended the first week after surgery. Thus, we strongly believe that objective prospective data, based on the lip height measurement in this period of time (from 12 to 16 weeks after surgery) is necessary to counsel and calm the parents, giving them an average percentage of improvement during this time frame.

Since Cutting and Dayan used a long time frame (from immediate postoperative period to 13 months postoperative period) in their study to analyze the lip height [9], we believe that a prospective study is necessary to objectively quantify the lip height in the period of time that ranges from 12 to 16 weeks, using a lower variation of time frame. Thus, we decided to restrict the time frame of the study performed by Cutting and Dayan [9] to verify if there is a statistical difference in the cutaneous lip height at early postoperative period (from 12 to 16 weeks), in comparison to a late postoperative period (between 12 and 13 months after surgery) in patients who underwent unilateral cleft lip repair, by modified Cutting extended Mohler technique without facial orthopedics. Additionally, this study aimed to objectively quantify the average amount of lip height improvement during the first year of surgery, which may ultimately be used to calm the parents during follow-up consultations and to determine the average amount of lip height discrepancy in a noncleft population.

2. Patient and Methods

A prospective observational study was conducted of 35 nonsyndromic unilateral complete cleft lip patients only, who underwent primary cleft lip repair by modified Cutting extended Mohler technique [9], without facial orthopedics performed from 2008 to 2010. The inclusion criteria were all patients who presented unilateral complete cleft lip repair, who underwent surgery using a Cutting extended Mohler technique and who had more than a year of follow-up time. All patients, who did not return to follow-up consultation in this time frame (from 12 to 16 weeks) and at 12 to 13 months after surgery, were excluded from this study.

To determine whether perfect symmetry is encountered, data from 50 noncleft, Brazilian individuals were obtained. The children chosen to be controls were volunteers recruited from a group of 120 children with good general health and no visible facial asymmetry that had been previously selected from a local primary school by two plastic surgeons (not involved in the present study); 50 volunteers were allocated via a computer-generated process for the study group.

All subjects (cleft lip patients and healthy volunteers) were enrolled upon a consent form signed by their parents, in accordance with the Helsinki Declaration of 1975, as amended in 1983. A local institutional research ethics board approval was obtained for this study.

2.1. Photographic Documentation. Two-dimensional photographs were employed for the evaluation of the perioral region of the cleft patient's face. Photographic full face frontal view using the camera at the same level of the patient's head was standardized [14], prior to the study initiation by the first author and a professional photographer of the Institution. The photographs of cleft patients were taken at 12 to 16 weeks (T1), after surgery, and at 12 to 13 months after surgery (T2), while the photographs of noncleft individuals were performed in a single period. All photographs were taken at least 5 times in a professional studio with 3 flashes by the professional photographer. Only one photograph for each patient was chosen to execute the measurements.

The distance, (approximately 1 m) between the photographer and the patient, was marked with lines on the ground. All photographs were taken with a Nikon D200 digital camera and 100 mm Nikon macro lens in a 1 : 1 ratio (Nikon Corp, Tokyo, Japan). All photographs were archived for later analysis and codified using randomly assigned numbers by one of the investigators.

2.2. Standardization of the Anatomic Landmarks. The anatomical landmarks used for measurements were defined preoperatively. Prior to the study, two surgeons (not involved in the operation) were taught the anatomic landmarks where the measurements should be done. The anatomical landmarks were defined and marked with a red dot by one of them, and the measurements were consecutively reproduced by both two weeks later.

2.3. Anatomic Landmarks. The cutaneous lip height was defined as the distance from each peak of Cupid's bow (transition between the white roll and vermillion) to the virtual plane generated by the initial lateral aspects of the collumelar base [15–17].

2.4. Photogrammetric Analysis. Photogrammetric lip analysis was performed from a frontal view processed by Photoshop CS4 extended (Adobe System, Inc., San Jose, CA, USA).

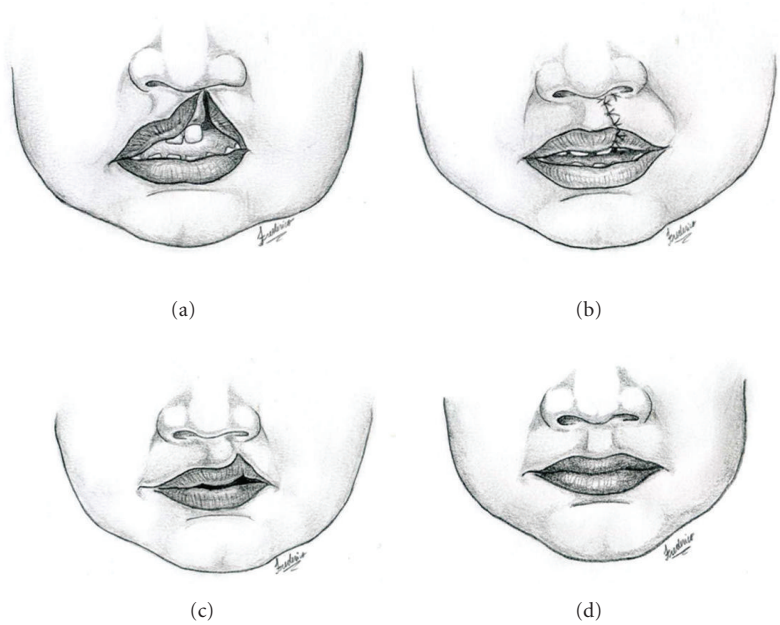

Figure 1: This drawing illustrates the sequence of preoperative 2-year-old cleft patient (a), the on-table result (b), the dynamic pull up of Cupid's bow at T1(c), and its average improvement at T2 (d). This study was designed to quantify the amount of lip movement and improvement during the first year after surgery.

To calculate the difference in the cutaneous lip height between the two sides of the cleft population, the noncleft lip height ($L1$) was compared with the cleft lip height ($L2$) in each patient, using the following formula: Lip height difference (LHD) = $L1 - L2/L1 \times 100$. For the noncleft individuals: LHD = length of the longest side − length of the shorter side/length of the longest side $\times$ 100. This formula yields a percent difference, which was calculated for each patient. The same formula to evaluate nasal alar contour was initially proposed by Wong et al. [18] and subsequently modified by Fudalej et al. [15]. The lip height difference was defined as an index of asymmetry of the lip.

The amount of lip height difference improvement in each cleft patient was determined by the difference in LHD at T2 and LHD at T1. A LDH equal to zero indicated perfect symmetry and any deviation from that determined asymmetry of the lip.

The three asymmetry lip scores are descriptively presented using a four point scale: asymmetry ≤4%, from 5% to 10%, from 11 to 20%, and more than 20%. This lip score was adapted [19] to determine the lip asymmetry in the second period of time (T2) (Figure 1).

2.5. Statistical Analysis. In the descriptive analysis, the mean and standard deviations were used for metric variables, and percentages were given for categorical variables. All measurements related to upper lip height were summarized as means and standard deviations. Friedman tests were used to compare the measurements in the two postoperative periods of time. Person's correlation test was performed to correlate the measurements performed by the two observers. The Statistical Package for Social Sciences (SPSS version 16.0 for Windows, Chicago, IL, USA) was used for all statistical calculations. Values were considered significant for a confidence interval of 95% ($P < 0.05$).

3. Results

Twenty-six cleft patients (74.29%) and fifty noncleft patients were included in the study. Nine cleft patients (25.71%) were excluded for not presenting themselves to the craniofacial clinics at proper timing. The average age at the operation was 6.31±8.64 months (range from 3 to 48 months). The noncleft individuals had neither syndromes nor midface hypoplasia affecting the soft tissue (lip) metrics. The average age of noncleft individuals was 38.4 ± 13.07 months (range from 7 to 48 months).

The average lip heights (index of asymmetry of the cutaneous lip height) in the cleft patients were 24% ± 9% in T1 and 8% ± 6% in T2. The comparison between the two postoperative periods of time showed statistically significant difference ($P < 0.01$). The average improvement of the lip height during the first year after surgery was 16%. Seven patients (26.92%) presented asymmetry of less or equal than 4%, 11 (42.31%) patients presented asymmetry from 5% to 10%, 6 (23.08%) patients from 11% to 20%, and 1 patient (3.85%) more than 20% (Figures 2, 3, and 4; Table 1).

The average lip height asymmetry in the noncleft individuals was 4.52% ± 1.89% (Table 2).

The reliability score of interobserver measurement was 0.9, indicating great similarity of the measurements. No additional complication was seen in the early and late postoperative periods.

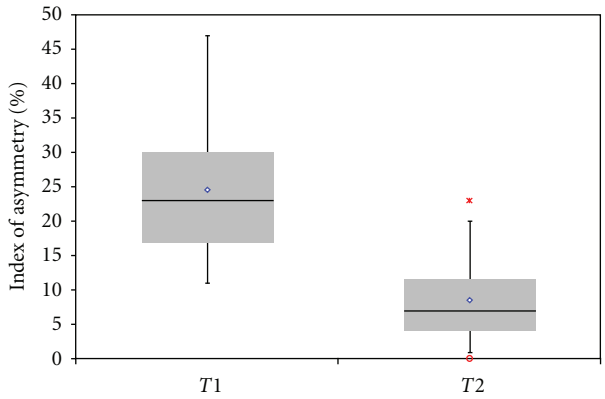

Figure 2: Boxplot showing the dispersion of the values of index of asymmetry based on objective evaluation. The index of asymmetry in period T1 (2 to 6 months after surgery) was higher ($P < 0.01$) than the index in period T2 (12 to 13 months after surgery). The diamond symbol represents the mean value. The heavy line is the median. The bars represent the data range. The symbols "∗" and "◦" indicate the outliers.

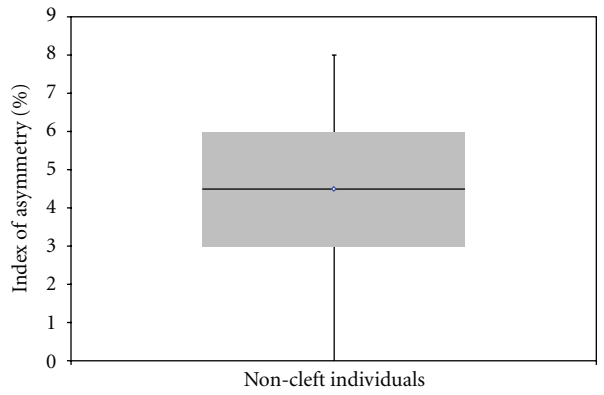

Figure 3: Boxplot showing the dispersion of the values of index of asymmetry based on objective evaluation. The diamond symbol represents the mean value. The heavy line is the median. The bars represent the data range.

4. Discussion

Andewalla and Narayanan [11] also observed that a straight-line part of the Millard incision often contracts and pulls Cupid's bow up in the first few months and it descends at one year after surgery, without the need of a secondary surgery. Thus, we designed this study to objectively quantify the amount of pulls up of Cupid's bow, when it appeared to be maximum. The percentage yielded by the formula used in this study was interpreted as an index of asymmetry of the lip. Thus, our data showed that the average asymmetry of the lip at T1 was 24%, in comparison to a more favorable index of 8% at T2. The results of this study demonstrate statistically significant improvement in the cutaneous lip height over time, meaning that the symmetry of the lip improves by 2 times. This findings corroborate to our primary hypotheses that the lip pulls up short at the period of time that ranges from 12 to 16 months and subsequently improves. Considering that all principles of cleft lip repair were performed to obtain a symmetric Cupid's bow, this vertical decrease of the lip height is probably owed to scar contracture, that is apparently maximum when straight-line lip repair is advocated. We hypothesized that the lips that remained short at 1 year after surgery will descend in a longer follow-up period, since we respect the principles of the rotation advancement and the on-table result showed complete symmetry between the cleft and noncleft sides.

The key element in these principles is the proper rotation of the cleft segment, achieved by the back-cut incision [20]. One should emphasize the release of the muscle and dermis instead of trimming the skin during this maneuver [20]. Another aspect to obtain a symmetric Cupid's bow is the preoperative markings on a fine-tip pen [21]. The Noordhoff's point has been used by surgeons worldwide to identify the optimal height of the lateral Cupid's bow and represent the greatest width of the vermilion border across from the white roll [22].

Before Millard's era, the simple straight-line closure introduced by Thompson [23], without using the principles of the rotation-advancement, were rejected by many surgeons [24, 25]. Some authors [26, 27] started closing the cleft lips using Z-plasts techniques that apparently would solve the problem of the scar contracture. On the other hand, at least one limb of the Z may obliterate the philtrum dimple, that is naturally concave. The natural concavity of the philtrum dimple can only be created without scars crossing this region. In the Cutting extended Mohler technique, the scar crosses only one set of the Langer's line at the collumelar base, further from the lowest and deepest region of the philtrum dimple [9]. The philtrum dimple can be created during the *orbicularis oris* muscle undermining and repair and final cutaneous closure [28]. An interposing orbicularis muscle repair proposed by Cutting and end-to-end muscle repair with vertical mattress sutures proposed by Mulliken helps evert the muscle to form the philtral ridge and accentuates the concavity of the philtum dimple [5]. An additional 1 mm deephitelization of the skin of the lateral segment during cutaneous closure may also contribute to its formation. The decrease of lip height discrepancy over the follow-up period is probably attributed to meticulous closure of the *orbicularis oris* muscle. Additionally, the upper medial portion of the *orbicularis oris* is fully trimmed and rotated downward to accentuate the proper rotation of the cleft segment and to help decrease the lip height discrepancy, improving lip symmetry in the follow-up period [5]. These maneuvers allow the surgeon to try a more straight-line incision that potentially simulates the position of the contralateral noncleft philtrum column [8]. The cutaneous closure may also play a role in the final lip height discrepancy. We have been using a nylon suture with an atraumatic needle to decrease the postoperative inflammation and scar contraction. We believe that the benefits of using them outweigh the disadvantages of stitch removal, usually accomplished under sedation in the operation room.

Even using all these principles, we observed an average of 8% lip asymmetry in one year follow-up period. However, measurements performed in 50 noncleft, Brazilian children

(a) (b) (c)

Figure 4: (a) A 3-month-old, complete cleft patient who underwent a cleft lip repair using the Cutting extended Mohler technique. (b) The initial result at T1 showing the pull up of Cupid's bow, owing to the scar contraction in this period of time. (c) The T2 result shows a better positioning of Cupid's bow and satisfactory lip height in the cleft side.

Table 1: Distribution of complete cleft lip patients according to demographic and anthropometric parameters ($N = 26$).

Patient	Gender	Age (m)	Index of asymmetry		
			T1 (%)	T2 (%)	T1 − T2 (%)
1	Male	32	28	23	5
2	Male	29	30	20	10
3	Female	42	29	18	11
4	Male	23	23	16	7
5	Male	35	43	14	29
6	Male	90	33	12	21
7	Male	46	16	11	5
8	Male	41	32	10	22
9	Female	23	23	9	14
10	Female	21	27	9	18
11	Male	47	12	8	4
12	Male	16	21	7	14
13	Male	40	47	7	40
14	Female	42	23	7	16
15	Male	42	22	6	16
16	Male	21	29	5	24
17	Female	47	26	5	21
18	Female	22	17	5	12
19	Male	40	15	4	11
20	Female	24	15	4	11
21	Female	20	36	4	32
22	Female	34	17	3	14
23	Female	16	11	3	8
24	Female	19	30	2	28
25	Female	32	12	1	11
26	Male	22	22	0.4	21.6
M ± SD		33.3 ± 15.4	24.5 ± 9.2*	8.1 ± 6*	16.2 ± 9.1

M: mean, SD: standard deviation, m: months, T1: 2 to 6 months after surgery, T2: 12 to 14 months after surgery, −: subtraction, $^*P < 0.01$ for the comparison between the periods (T1 > T2).

Table 2: Distribution of noncleft individuals according to demographic and anthropometric parameters ($N = 50$).

Patient	Gender	Age (m)	Index of asymmetry (%)
1	F	29	8
2	M	18	7
3	M	21	7
4	M	17	7
5	M	40	7
6	M	43	7
7	F	50	7
8	F	48	7
9	F	46	7
10	M	39	7
11	F	23	6
12	F	39	6
13	F	51	6
14	F	42	6
15	M	42	6
16	M	22	6
17	F	31	5
18	M	11	5
19	F	35	5
20	M	45	5
21	M	54	5
22	M	48	5
23	M	54	5
24	F	47	5
25	M	51	5
26	M	10	4
27	M	35	4
28	F	7	4
29	F	49	4
30	F	40	4
31	F	55	4
32	F	48	4
33	F	40	4
34	M	37	4
35	F	39	4
36	M	23	3
37	M	15	3
38	F	28	3
39	M	48	3
40	M	54	3
41	M	49	3
42	F	45	3
43	F	37	3
44	F	34	2
45	M	54	2
46	M	46	2
47	M	38	2
48	M	54	1
49	F	37	1
50	F	52	0
M ± SD		38.4 ± 13.07	4.52 ± 1.89

M: mean, SD: standard deviation, m: months.

using the same methodology determined the "normal" index of lip asymmetry. Interestingly, noncleft, Brazilian individuals may present 4% lip asymmetry, meaning that some degree of lip asymmetry is always expected, suggesting that one side of the face is rarely, completely identical to the contralateral side [29]. Interestingly, the Millard Society statement on its logo is "know the normal," which may prove not to be the complete symmetry [30].

As also stated by Millard [31] in his treatise "*Cleft Craft*," in the treatment of unilateral cleft lip, the normal side sets the standard and the ideal pattern to be simulated. All surgical effort has been made to have the length of the cleft philtrum column matched with length of the noncleft side. However, wide clefts with more than 10 mm of horizontal and vertical discrepancies in the alveolar region may turn the rotation maneuver somehow challenging to perform.

Cutting and Dayan [9] did not show lip height discrepancy over the follow-up period and included in their cohort, patients with unilateral complete cleft previously treated with facial orthopedics. Although laboring, facial orthopedics has the advantage to approximate the palatal shelves and decrease the severity of the cleft defect, which may facilitate closure by decreasing its tension, that is ultimately related to scar contraction. Thus, further studies may identify the role of facial orthopedics on decreasing the tension of the final cutaneous suture, scar contraction, and lip height deficiency, especially in severe patients with wide clefts. Facial orthopedics, not performed in our patients, may be one variable that contributed to the remaining 8% of lip height discrepancy in our patients.

In our study, we could quantify the exact amount of lip height in two different periods of time and demonstrate that the average asymmetry of the lip improves by 2 times during the first 12 months after surgery. Cutting and Dayan [9] also investigated the lip height at 2 years or more after surgery and found lower rate of lip asymmetry at this period of time. Since we evaluate the lip height at 12 to 13 months, it is possible that the lip continues to descend during the second year after the operation. Thus, further studies on this subject may elucidate this question.

Our study may present some limitations. Three-dimensional distances performed by two-dimensional photography may carry an inherent bias [32], thus we exclusively measured the lip height distance and disregarded the lip width distance. The anatomic landmarks that allow the measurement of the lip height are almost at the same plane that exponentially decrease the inherent error of this methodology. The professional studio allowed a fast set of photographs and the possibility to adjust the proper positioning of the child's head and simultaneously have the pictures taken. Additionally, a lip height ratio was determined to avoid potential flaws generated by the parallax effect, caused by movement of the head and subtle modification of the distance between the patient and photographer. Digital, two-dimensional photographs still carry the advantages of being practical, cheap, and a noninvasive method [33]. However, proper equipment, a photography studio, and a professional photographer may help the standardization of the process and may decrease the inherent possibility of error during measurement [32]. Furthermore, as inherent errors from computer-based markings of two-dimensional photographs may exist [32], it is recommended that some time would be taken to become familiar with the software and the procedure for marking images, prior to data collection [33], as adopted in this study.

Although three-dimensional imaging indeed opened a new perspective in the facial measurements [32], it is limited by the current unavailability of equipment for routine clinical use, the training required and the cost of the equipment [33]. It is especially useful when the distance of two anatomical points located in two different planes is performed (e.g., tip of the nose and peak of Cupid's bow). The anthropometry of a child's face, performed by a caliper, lacks accuracy due to the usual lack of collaboration from children and eventually from parents, and it is highly operator-dependent.

Van Loon et al. [29] compared the measurements of the lip in complete unilateral cleft lip after primary cheiloseptoplasty to a noncleft control using 3D stereophotogrammetric analysis and stressed the difficulty to obtain near normal symmetrical relations. They [29] also emphasized, as our data showed in this study, that noncleft individuals also show some degree of asymmetry. Thus, all surgical efforts should be made to achieve the normal, which is not the perfect symmetry.

5. Conclusion

Our data demonstrated lip height improvement during the first year of unilateral complete cleft lip repair using Cutting extended Mohler technique. Since all principles to obtain a symmetrical Cupid's bow were performed, the postoperative pull up of Cupid's bow is probably owed to the scar contracture, which improves by 2 times during the first year after surgery.

Disclosure

The authors hereby certify that no financial support has been received from any commercial source by any coauthor or any individual or entity, that is, related directly or indirectly to the scientific work, which is presented in this paper.

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Hindawi Publishing Corporation
Plastic Surgery International
Volume 2012, Article ID 892437, 10 pages
doi:10.1155/2012/892437

Review Article

An Opportunity for Diagonal Development in Global Surgery: Cleft Lip and Palate Care in Resource-Limited Settings

Pratik B. Patel,[1,2] Marguerite Hoyler,[1,2] Rebecca Maine,[1,2,3] Christopher D. Hughes,[1,2,4] Lars Hagander,[1,2,5] and John G. Meara[1,2]

[1] *Program in Global Surgery and Social Change, Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA 02115, USA*
[2] *Department of Plastic and Oral Surgery, Boston Children's Hospital, 300 Longwood Avenue, Enders 1, Boston, MA 02115, USA*
[3] *Department of Surgery, University of California San Francisco Medical Center, San Francisco, CA 94131, USA*
[4] *Department of Surgery, University of Connecticut Health Center, Farmington, CT 06030, USA*
[5] *Department of Pediatric Surgery and International Pediatrics, Faculty of Medicine, Lund University, Lund SE-221 00, Sweden*

Correspondence should be addressed to John G. Meara, john.meara@childrens.harvard.edu

Received 3 August 2012; Accepted 20 November 2012

Academic Editor: Renato Da Silva Freitas

Global cleft surgery missions have provided much-needed care to millions of poor patients worldwide. Still, surgical capacity in low- and middle-income countries is generally inadequate. Through surgical missions, global cleft care has largely ascribed to a vertical model of healthcare delivery, which is disease specific, and tends to deliver services parallel to, but not necessarily within, the local healthcare system. The vertical model has been used to address infectious diseases as well as humanitarian emergencies. By contrast, a horizontal model for healthcare delivery tends to focus on long-term investments in public health infrastructure and human capital and has less often been implemented by humanitarian groups for a variety of reasons. As surgical care is an integral component of basic healthcare, the plastic surgery community must challenge itself to address the burden of specific disease entities, such as cleft lip and palate, in a way that sustainably expands and enriches global surgical care as a whole. In this paper, we describe a diagonal care delivery model, whereby cleft missions can enrich surgical capacity through integration into sustainable, local care delivery systems. Furthermore, we examine the applications of diagonal development to cleft care specifically and global surgical care more broadly.

1. Introduction

The inadequacy of surgical and anesthetic capacity in resource-limited settings is well demonstrated [1–5], as is the particular need for more robust pediatric surgical services [6–8]. Total surgical disease burden, estimated at 11–15% of disability-adjusted life years (DALYs) lost worldwide, disproportionately affects low- and middle-income countries (LMICs) [9–11]. Cleft lip and palate (CLP) and other congenital anomalies account for approximately 9% of this burden [9], and the consequences of untreated CLP range from social ostracism to death [12–14]. Although the economic burden of untreated CLP and the value and cost effectiveness of global cleft treatments have been proven [15–17], CLP treatment capacity remains insufficient in LMICs [18, 19]. Historically plastic surgeons' efforts to address this need have focused on short-term, service-oriented commitments—a vertical approach to healthcare [20].

Narrowly focused, disease-specific, and vertical programs tend to operate outside the existing national and local healthcare structures, supplying their own facilities and delivery mechanisms [21–23]. By contrast, the horizontal approach focuses on developing and strengthening existing public infrastructure, with an emphasis on primary care and broadly applicable health interventions [22, 23].

Although humanitarian cleft care missions have provided crucial treatments for many patients in LMICs who would not otherwise have had access to care, there is an untapped potential in optimally channeling the resources and skills of mission groups into sustainable, local care-delivery systems.

As the plastic surgery community continues to evaluate the ideal role of missions in providing comprehensive cleft care in LMICs, an emphasis should be placed on the concept of diagonal development: an integration of vertical and horizontal approaches in a way that enriches the overall educational and surgical capacity of LMICs. In this paper, we explore the benefits and limitations of the vertical and horizontal approaches to healthcare delivery (Table 1) and apply that framework to global CLP care.

2. Horizontal and Vertical Approaches: Benefits and Limitations

2.1. Vertical Programs. The vertical approach to global health is disease specific and has been a particularly common approach among global infectious disease initiatives [22, 24, 25]. Proponents cite milestones like the eradication of smallpox and dramatic decreases in rates of new HIV infection as evidence of vertical intervention success [22, 26]. Vertical interventions are relatively scalable and are thus ideal for urgent humanitarian responses to disasters or epidemics, which have traditionally garnered significant attention from donors [27]. Additionally, vertical programs efficiently deliver necessary surgical supplies and equipment for disease-specific use in LMICs [28].

However, the vertical approach may also yield parallel and uncoordinated interventions, detract attention from the systemic weakness of national healthcare institutions, compromise countries' autonomy and participation in healthcare initiatives, alienate patients whose healthcare needs exceed the narrow range of provided services, and divert funds from other important causes of morbidity and mortality [22, 29, 30]. The vertical approach has also been criticized for not adequately developing the infrastructure and workforce necessary to address even disease-specific needs, letting alone broader healthcare demands [31–33]. Finally, given the complexity of socioeconomic and environmental disease determinants, narrow vertical efforts, which are not designed to address these issues, may be less effective or even harmful to the populations they aim to serve [22, 24].

2.2. Horizontal Programs. The horizontal approach to healthcare delivery emphasizes long-term investments in healthcare infrastructure and the expansion of publicly funded healthcare systems [20, 34, 35]. Examples include WHO efforts to strengthen primary care systems and World Bank-guided reforms of district-level health administrations [21, 27, 36]. Although the horizontal model of public health interventions preceded the vertical model [20] it has seen renewed emphasis in recent years, particularly as infectious disease treatment groups such as PEPFAR, Human Resources for Health (HRH), and The Global Fund to Fight AIDS, Tuberculosis, and Malaria, transition away from strictly vertical models [21]. Proponents of the horizontal model even argue that disease-specific therapies can be delivered most efficiently through a functional primary healthcare system. Furthermore, horizontal approaches have greater potential to address patients' comorbidities and other health needs, and they intentionally strengthen healthcare systems for the benefit of all current and future patients [21]. As surgery is increasingly acknowledged as an integral part of healthcare worldwide [3], the horizontal model has begun to be applied to surgical disease, through investments in surgical infrastructure and human capital [37].

In surgery and in other domains, however, horizontal development has been hindered by concerns regarding the scope and time frame of horizontal interventions. Horizontal initiatives take extended periods of time to be implemented, may be less suitable to humanitarian emergencies, and depend heavily on governmental legitimacy and functionality in order to be effective [27]. Additionally, defining objective metrics for success in horizontal interventions may be particularly challenging due to larger patient cohorts and diverse causes of morbidity and mortality [21]. For all of these reasons, horizontal development has been of limited appeal to private funding organizations [21]. Lastly, horizontal projects may seem incompatible with the domestic commitments of many global health-oriented physicians in practice in wealthy countries.

2.3. Diagonal Programs. "Diagonal" approaches refer to programs which are neither purely vertical nor purely horizontal [34, 35]. Rather, these programs find synergy between the immediate advantages of vertical inputs and the long-term benefits of horizontal aims, ultimately increasing access and enriching capacity of surgical services (Figure 1).

Diagonal interventions are becoming increasingly common [21], particularly as the horizontal approach is recognized as an effective means of delivering disease-specific care [24, 27]. In addition to infectious disease [38], family planning and maternal and child health are areas in which the integration of vertical and horizontal care has been reported [11, 39, 40]. Although the vertical approach may also yield positive "spill-over," in which focused health initiatives in one disease area or population also benefit the health system as a whole [41]; the diagonal approach embraces these broader impacts as a primary aim instead of as a welcome externality.

3. Building Capacity While Addressing Specific Needs: A Diagonal Approach to Global CLP Care

The traditional "missions" model of cleft care rests partially on the premise that one-time interventions can effectively treat craniofacial anomalies, that they produce a high return for time and resources invested, and that they are feasible commitments for visiting providers [18, 42–44]. However, as cleft palate missions have grown in scale and scope, they have demonstrated a willingness to think critically about their care delivery models. As a result, many cleft treatment groups have begun to integrate vertical and horizontal approaches in order to maximize their positive impact and minimize any negative consequences [42, 43, 45–49]. In the case of Interplast, these changes include an emphasis on local partnerships with the explicit goal of creating self-sufficient,

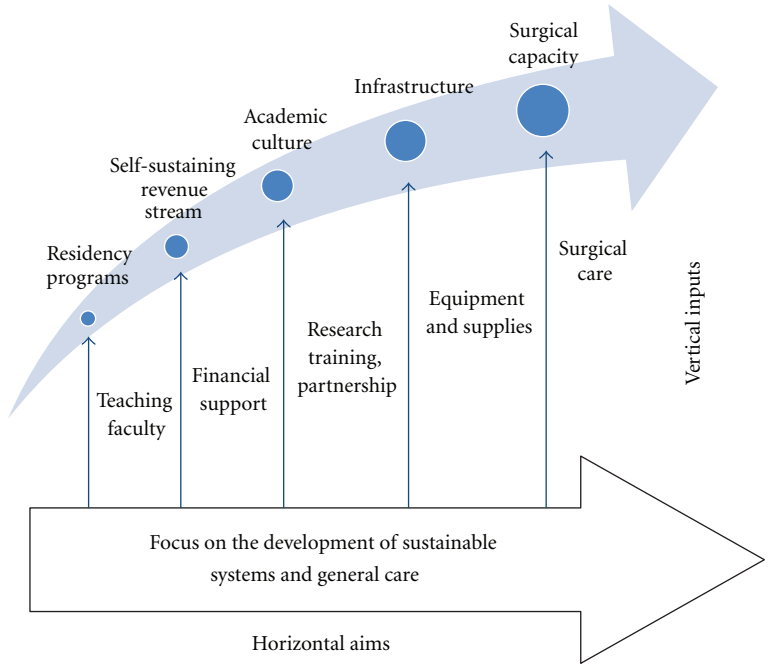

Figure 1: A diagonal approach harnesses the power of horizontal aims and vertical inputs.

Table 1: The vertical-horizontal debate: benefits and limitations of each approach.

Approach	Description	Examples	Advantages	Disadvantages
Vertical	(i) Disease specific (ii) Narrowly focused (iii) Operates outside the existing healthcare structures and systems (iv) Often privately funded	(i) Polioimmunization program (ii) HIV/AIDS treatment programs (iii) Male circumcision programs (iv) DOTS	(i) Demonstrated effectiveness (HIV/AIDS) (ii) May have a limited, positive impact on other areas of healthcare delivery ("spill over") (iii) Fast implementation (iv) Scalable (v) Donor attractiveness (vi) Efficient delivery of disease, specific equipment and supplies	(i) May not address other diseases, healthcare needs, and health determinants (ii) May yield redundant and poorly coordinated efforts (iii) May divert funds from other diseases and medical priorities
Horizontal	(i) Not disease specific (ii) Focuses on broadly applicable healthcare infrastructure (iii) Long-term interventions and investments	(i) Strengthening primary care systems (ii) Healthcare provider education and training (iii) Human resources for health (HRH)	(i) Strengthens health systems as a whole (ii) Benefits all patients, regardless of disease or diagnosis (iii) May facilitate disease, specific treatments (iv) Builds capacity for long-term change	(i) Long-term interventions (ii) Large, unwieldy projects (iii) Often less attractive to donors, funders (iv) Require functional state and local governments (v) More difficult to measure impact of horizontal interventions

independently functioning local sites [50]. Operation Smile and others have evolved from purely vertical care providers to integrated system creators through a continued emphasis on mindful and reflective practice [18].

We build upon these shifts in global cleft care delivery and argue that a diagonal approach can build on the strengths of the vertical model, while also addressing its weaknesses. In the case of global CLP repair, diagonal programs would retain the focused services and resource inputs of surgical missions, while incorporating efforts to expand surgical capacity, increase human capital, and provide comprehensive care in general. As a result, through diagonal development, surgical care in LMIC can be broadly enriched in several key deliverable areas (Table 2).

Table 2: Superior impact of diagonal interventions in global cleft lip and palate care.

	Vertical approach	Diagonal approach
Continuity of care	Short-term interventions	Long-term presence
Interdisciplinary care	Focus on cleft surgery services	Focus on surgical, perioperative, dental, feeding, hearing, speech, and rehabilitation services
Equitable access	Service-driven patient selection	Needs-driven patient selection
Outcomes monitoring	Postoperative	Long term
Local workforce development	Unilateral exchange focusing on cleft surgeons	Bilateral exchange focusing on surgeons, anesthesiologists, surgical intensivists, scrub technicians, perioperative nurses, ward nurses, dentists, feeding specialists, speech therapists, and audiologists
Equitable trainee experiences	Enhanced visiting trainee experience in specialized surgical practice	Enhanced visiting trainee experience in global healthcare delivery; enhanced local trainee experience in surgical practice
Academic culture of investigation and empowerment	Clinical emphasis, transfer of clinical skills, data collection and analysis by visiting providers, research-driven medical missions	Academic emphasis, transfer of research skills, data collection and analysis by local providers, and research-driven local practice
Increased financial sustainability	Dependence on external funding; return on investment may not be optimal	Goal of self-sustained revenue streams; emphasis on increasing ethical, fiscal and systems-wide returns on investments
Implications for local general surgical capacity	"Spill-over" as a welcome positive externality	"Spill-over" as a primary objective

3.1. Integrated, Longitudinal CLP Care. The optimal care of patients with cleft lip and palate patients is complex, longitudinal, and interdisciplinary [51–54]. Children with cleft anomalies benefit from dental and orthodontic services, speech therapy, otologic care, and occasionally revision surgeries [9, 55, 56]. In many wealthy nations, participation in integrated cleft centers allows for parental education and support often from the time of prenatal diagnosis through the postoperative care. Cleft centers provide not only the essential followup to identify and address surgical complications, but also permits tracking of long-term outcomes to support general quality improvement projects. Multidisciplinary services are frequently lacking in LMICs, and often access to long-term followup is limited as well. Unfortunately these same patients in LMICs face increased risk for surgical complications due to higher incidences of malnutrition and concurrent illness [23, 44].

The traditional vertical structure of CLP missions is not well suited to longitudinal, integrated CLP care in LMICs [57], especially because effective delivery of these services may require multiple visits that are beyond the scope of a purely vertical treatment model [14, 58]. Adopting a diagonal approach to cleft palate care would address many of these limitations by transitioning care from fragmented efforts of visiting providers to a more sustained local physician practice over the long term. This could be achieved either by a limited permanent staff complemented by frequent missions or by a constant rotation of visiting teams with no coverage gaps. Additionally, specialized cleft centers, similar to those described in wealthy nations, have been described as feasible and sustainable delivery models to ensure comprehensive CLP care in LMICs [59]. The diagonal approach takes this concept one step further, by integrating specialized surgical care into the longitudinal services of local healthcare systems and structures. This can foster trust in and utilization of the local healthcare system, both by CLP patients and their families and community members.

The logistical challenges of contacting and locating former patients, varying degrees of patient compliance, especially in the setting of insufficient patient education, and coordinating followup with local professionals [14, 56, 60–63] have been barriers to follow up on vertical missions. Follow-up rates have been correspondingly low: among medical mission groups that do provide postoperative care, rates range from 5% to 35% of patients [58]. Cleft missions groups have made progress in monitoring surgical outcomes, for instance through the development of outcomes databases [18, 43, 49, 62]. However, an increased focus on outcomes is needed. One paper examining the long-term results of palatoplasties, performed by local and visiting surgeons in Ecuador, found a significantly higher rate of fistula formation among Ecuadorian patients than among their counterparts in wealthy countries [56]. Other international researchers have noted that palatal dehiscence and residual or recurrent fistulae were frequently encountered during their studies, even when palate integrity was not an outcome in question [60]. Through its emphasis on longitudinal care, diagonal development provides an optimal framework for outcomes research, which is essential to identify and address the underlying causes of these troubling results.

Furthermore, diagonal approaches can facilitate outcomes monitoring through emphasis on general, not disease-specific, infrastructure improvements, such as electronic medical records, clinical measurement tools, and a culture of medical documentation and outcomes-driven practice. Once in place, these infrastructure improvements could help optimize quality and safety of all clinical care delivery, including CLP treatments.

Improved infrastructure for followup and outcomes monitoring through a diagonal delivery model can also improve access to the variety of specialists needed to provide comprehensive CLP care. While some programs have implemented interdisciplinary, comprehensive services for cleft patients in LMICs [64], for instance by using telemedicine to provide speech therapy [47, 65, 66], this type of care depends on broad manpower and healthcare structure capabilities, neither of which is the focus of a vertical model. By reinforcing the importance of surgical care, a particular strength of the vertical approach, while simultaneously building capacity for other necessary CLP services, the diagonal model has the potential to improve the outcomes of patients in LMICs. Additionally, effective patient education regarding the comprehensive treatment options for CLP would result from utilization of the significant outreach capacity of the existing healthcare system.

An investment and focus on interdisciplinary care would also benefit resource-limited communities at large. Many children and adults without cleft anomalies have need for services like speech therapy and audiologic care, in addition to surgery and anesthesia. If promoted as a component of CLP care in LMICs, these services could be available for patients with and without CLP. In addition, each service would represent a channel by which patients could seek their first contact within the broader healthcare system, promoting a culture of individual health agency.

By providing long-term follow-up of cleft patients, supporting the growth of essential complementary services and developing quality improvement projects through outcomes monitoring, the diagonal model of cleft care delivery would help achieve the ethical goal of providing the same treatment to patients in poor countries which is the standard of care in wealthy countries.

3.2. Equitable Access. Equitable access results from a focus on patient-centered interventions that are able to prioritize diverse patient needs without the logistical constraints of short-term missions. In wealthy countries, standard of care for patients with cleft anomalies involves careful timing of surgical correction. Patients treated on annual missions have a lower likelihood of being operated on within recommended windows [63], which can impact surgical outcomes, development of facial structures, speech, and hearing [56, 67, 68]. Longitudinally focused, diagonal efforts remove the need to operate based on visiting provider availability, allowing for interventions at the appropriate developmental stage, and enabling more timely and equitable cleft care.

Inadequate physical access—lack of transportation or long travel distances to care facilities—is a significant barrier to care for patients in resource-limited settings [69]. Improved patient transportation and high-quality facilities can help reduce morbidity and mortality attributable to multiple causes in LMICs [70]. A diagonal model could address these barriers, for instance by devoting funds and resources to patient transportation and lodging needs. One might also envision a health-services bus, perhaps integrated with existing local public transport infrastructure, which would travel to remote communities in order to provide regularly-scheduled medical care to patients there. For cleft patients, this service would facilitate initial assessments, transportation to the surgical center, and followup, as needed. For all patients, this service would provide a critical link between communities, clinics, and hospitals, promoting equitable access to care.

3.3. Local Workforce Development. Cleft missions have been criticized for undermining the efforts and authority of local providers [71]. Importing surgical services may suggest to patients and community members that surgery requires large teams and equipment that may not be accessible locally. This diminishes confidence in local providers, lowers professional morale, and decreases revenue for local facilities as patients with means to pay for local providers to perform their operations rely on visiting surgeons [72].

In response to these criticisms, many cleft missions groups have adopted the training, promotion, and support of local surgeons as a primary objective [58, 73]. However, this method often consists of choppy, "on the spot" intraoperative lectures by the visiting surgeon, with little structure regarding teaching objectives, and even less time for reciprocal teaching by host providers [58]. This unilateral approach to knowledge transfer undermines the important contributions of local surgeons and other healthcare professionals, who are critical to all steps of care delivery and capacity building in resource-limited settings and whose clinical skills are well adapted to the local resource limitations and epidemiology of disease [71]. Additionally, a lack of structure regarding teaching objectives likely impairs the systematic mastering of skills and knowledge for both local and visiting surgeons [74]. Finally, an educational focus on surgeons as providers of cleft care strictly misses the opportunity to train other essential perioperative and interdisciplinary staff—pediatric anesthesiologists, surgical intensivists, scrub technicians, operating room nurses, and speech therapists—in the provision of safe and comprehensive cleft care.

More robust academic partnerships, as fostered by diagonal development, would also promote local academic leaders and would enhance training programs for numerous types of healthcare providers. In particular, greater numbers of well-trained surgeons, scrub technicians, nurses, and anesthesiologists would improve surgical care for all patients in LMIC; cleft patients are included.

3.4. Equitable Trainee Experiences. It is not uncommon for general or plastic surgery residents from wealthy countries to complete an international rotation in LMICs [75, 76]. Research shows that these experiences enhance the training of the visiting surgical residents [77, 78], but it is less clear

that host institutions benefit equally. As institutional partnerships between academic centers in wealthy LMIC become increasingly common [10, 37], the cleft care community, and the surgical community at large, must look beyond the needs of visiting trainees to the needs of students, residents, faculty and staff in host institutions and communities [79].

Diagonal development in cleft care can facilitate equity between visiting and local trainees and providers through its longitudinal view of the surgical care. For instance, the educational objectives for rotating trainees from wealthy countries could perhaps center on tackling systems-based and logistical challenges of surgical care delivery in resource-limited environments, in addition to the acquisition of operative experience. Visiting trainees could be mentored and instructed in these areas by local providers with expertise in local systems and care-delivery challenges. Furthermore, visiting trainees could complement the experiences of local trainees by enabling local residents to spend more time with visiting faculty, learning clinical skills through intraoperative teaching sessions, formal lectures, and skills-based workshops. This approach would benefit local trainees and, ultimately, the patients they will serve in their home communities.

3.5. An Academic Culture of Investigation and Empowerment. A diagonal approach to cleft care would foster research experience for local trainees and practitioners in countries where its importance may not be emphasized during medical education. Although a majority of plastic surgeons and volunteer pediatric surgeons express their desire to teach clinical skills to colleagues in LMICs, research skills are largely neglected on mission trips. Relatively few (40%) cleft mission organizations regard research as a priority, citing limited funding, manpower, and time [58]. Research is particularly difficult given the heavy operative census and short duration of medical missions. Transitioning away from a strictly vertical model toward a diagonal model could promote research in several ways. For instance, the diagonal goal of increased surgical capacity would reduce the "backlog" of patient need, and lengthier visits and prolonged collaborations between local and visiting providers could alleviate pressure to operate on as many cleft patients as possible during a short mission. As has been suggested by general surgeons and other surgical subspecialists [79], such changes would allow additional time for research planning and execution.

A greater emphasis on global surgery research is important for several reasons. Surgeons in LMICs self-report a need for increased research training and skills, in addition to clinical assistance [80]. Additionally, improving the quality of particular treatments in LMICs, such as cleft surgeries, requires a better understanding of the local needs, barriers to care, outcomes, and predictive factors that define cleft anomalies and other diseases in those countrie, and which may be unique to resource-limited settings. Finally, promoting research partnerships with local providers and investigators could empower local healthcare professionals to take a more active role in determining how best to address the healthcare needs of their populations.

International research partnerships as a component of diagonal development would also challenge researchers in wealthy countries to address previously neglected research topics. For instance, despite the long-accepted model of coordinated care for CLP [51, 53, 81], there is relatively little comparative outcomes research of cleft care in wealthy countries. In order to identify and learn from the weaknesses of current cleft care models, the global cleft community must incorporate research and research capacity building into care delivery models in all settings. Thus, diagonal development can foster research-driven local practice, outcomes-driven quality improvements, and data-driven infrastructure development, for the benefit of all surgical patients.

3.6. Increased Financial Sustainability. Although the cost effectiveness of surgical treatment of cleft palate is well demonstrated by analytic models [15, 16, 82], medical missions may not optimize the return on relatively scarce financial investments in cleft care, in terms of value to individual patients and local communities. The significant financial overhead of medical missions may ultimately detract resources from the patients who need those resources the most. Dupuis [71] estimate that $920 US could be saved, per surgery, if operations were performed by local providers instead of by volunteers from abroad. Additionally, analytic models may not take into account the negative externalities of vertical interventions. While transitioning to a diagonal approach may initially increase some costs, by investing in health systems, infrastructure, human capital, and research capabilities, the diagonal approach can increase the overall value of cleft treatments in LMIC. Indeed, just as domestic programs must justify their value proposition to society [83], the international cleft treatment community must increasingly demonstrate to public and private funders that cleft care investments yield sizable long-term benefits for patients and communities alike. Demonstrating increased capacity could attract funders to global surgery because it offers a superior "return on investment," both financially and ethically. Looking ahead, diagonal approaches can also move local institutions toward the goal of self-sustained revenue streams by promoting increased patient engagement, health systems development, and government involvement in healthcare.

4. Future Directions

4.1. Implications for Global General Surgical Capacity. To reiterate, diagonal development turns attention away from importing clinical resources and services, emphasizing deliverables that not only increase capacity for CLP surgery, but also enrich the surgical ecosystem as a whole. Under the current vertical cleft care mission models, surgeons and trainees make significant contributions, but may not increase local capacity to address those surgical diseases that account for the majority of mortality and morbidity: obstetrical complications, trauma, and acute abdominal emergencies [84]. Just as the capacity to provide cleft lip and palate treatment is necessarily affected by the overall

shortages in operating theatres and supplies, the converse holds true: an emphasis on diagonal development would yield infrastructure, manpower, and self-sustaining revenue that could have positive implications for treatment of other surgical diseases. In this way, a diagonal approach makes the "spill-over" effect a primary aim, rather than a welcome positive externality.

4.2. Advocacy and Implementation. The full extent of surgical care needed in resource-limited settings cannot be addressed by global plastic surgeons alone. However, what plastic surgeons can directly do is very powerful—the transformation of a face or the reconstruction of an injury is a metaphor for involvement creating change, which can reach exponentially to more patients [18]. Each specialty must work both within and outside of the global health community both to offer its expertise—whether that is caesarian sections or CLP repair—and also assist in the development of comprehensive surgical care delivery services, not merely concentrate on a specific disease or intervention [9]. Medical mission NGOs have taken the lead in these efforts; it is now incumbent upon academic surgeons, trainees, and researchers to join medical missions groups in further defining and promoting the global surgery agenda.

5. Conclusions

Global surgery is still, in many ways, in its infancy. As we move forward in global CLP care, it is essential to learn from the strengths and limitations of the vertical and horizontal approaches in order to maximize the benefit of these programs to healthcare systems in LMICs. We recognize an ongoing need for vertical humanitarian missions and admire the legacy of many cleft treatment groups. Indeed, it is because of the successes of cleft missions that the cleft care community is now in the position to contribute diagonally to increase surgical capacity and promote quality of care. As funding becomes increasingly available for global surgery interventions, care delivery methods will come to the forefront in terms of achieving optimal outcomes. At this critical juncture, plastic surgeons must serve as thought leaders in global surgery, and a diagonal approach to CLP care is a means of achieving that goal.

Authors' Contribution

Patel and Hoyler contributed equally to the development of the paper.

Conflict of Interests

The authors declare no conflict of interests in the development and submission of this paper.

Acknowledgment

The authors acknowledge P. B. Patel and M. Hoyler as co-first authors.

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Hindawi Publishing Corporation
Plastic Surgery International
Volume 2012, Article ID 731029, 4 pages
doi:10.1155/2012/731029

Research Article

Beyond Fifty Years of Millard's Rotation-Advancement Technique in Cleft Lip Closure: Are There Many "Millards"?

Renato da Silva Freitas,[1] Pedro Bertoco Alves,[1] Gisele Keiko Machado Shimizu,[1] Júlia Fortes Schuchovski,[1] Marlon Augusto Câmara Lopes,[1] Ivan Maluf Jr.,[1] Antonio Jorge V. Forte,[2] Nivaldo Alonso,[3] and Joseph Shin[4]

[1] *Section of Plastic and Reconstructive Surgery, Federal University of Paraná, 80060-240 Curitiba, PR , Brazil*
[2] *Section of Plastic and Reconstructive Surgery, Yale University School of Medicine, New Haven, CT 06510, USA*
[3] *Section of Plastic and Reconstructive Surgery, São Paulo University, 01246-903 São Paulo, SP , Brazil*
[4] *Section of Plastic and Reconstructive Surgery, Albert Einstein College of Medicine, Bronx, NY 10461, USA*

Correspondence should be addressed to Renato da Silva Freitas, dr.renato.freitas@gmail.com

Received 2 August 2012; Accepted 4 November 2012

Academic Editor: Luis Bermudez

In 1955, Millard developed the concept of rotation-advancement flap to treat cleft lip. Almost 6 decades later, it remains the most popular technique worldwide. Since the technique evolved and Millard published many technical variations, we decided to ask 10 experienced cleft surgeons how they would mark Millard's 7 points in two unilateral cleft lip patient photos and compared the results. In both pictures, points 1 and 2 were marked identically among surgeons. Points 3 were located adjacent to each other, but not coincident, and the largest distances between points 3 were 4.95 mm and 4.03 mm on pictures 1 and 2, respectively. Similar patterns were obtained for points 4, eight of them were adjacent, and the greatest distance between the points was 4.39 mm. Points 5 had the most divergence between the points among evaluators, which were responsible for the different shapes of the C-flap. Points 6 also had dissimilar markings, and such difference accounts for varying resection areas among evaluators. The largest distances observed were 11.66 mm and 7 mm on pictures 1 and 2, respectively. In summary, much has changed since Millard's initial procedure, but his basic principles have survived the inexorable test of time, proving that his idea has found place among the greatest concepts of modern plastic surgery.

1. Introduction

In 1955, Millard developed the concept of rotation-advancement flap to treat cleft lip, which became the most popular technique worldwide [1]. Many other authors published their variations of the original Millard technique [2]. The procedure consists of a lateral flap advancement into the upper lip combined with downward rotation of the medial segment, preserving the philtrum. After that, the author published 41 indexed papers and several book chapters [3–10]. In 1976, Millard published the "trilogy" entitled *Cleft Craft: The evolution of its surgery*, which eventually became instrumental in facial cleft treatment [11].

We reviewed these articles to identify the evolution of the technique described by Ralph Millard Junior [1, 3–10] and compared its variation among 10 well-known cleft surgeons.

2. Methods

We carried out a systematic review of all indexed articles published by Millard since 1957. In addition, two photographs (picture 1 and picture 2) of patients with unilateral cleft lip were sent to 10 well-known Brazilian craniofacial surgeons, and we asked them to draw on them Millard's markings (Figures 1 and 2). They were asked to mark the seven standard points on the pictures and to draw the flaps

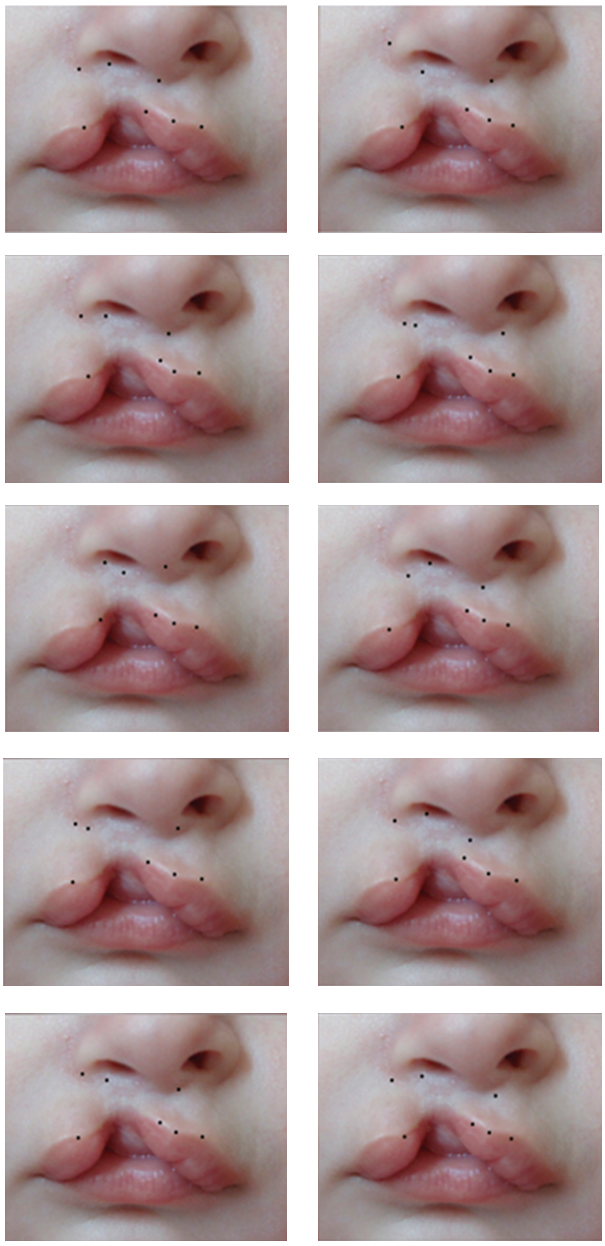

Figure 1: Millard's seven standard points marked by 10 respected craniofacial plastic surgeons separately on picture 1.

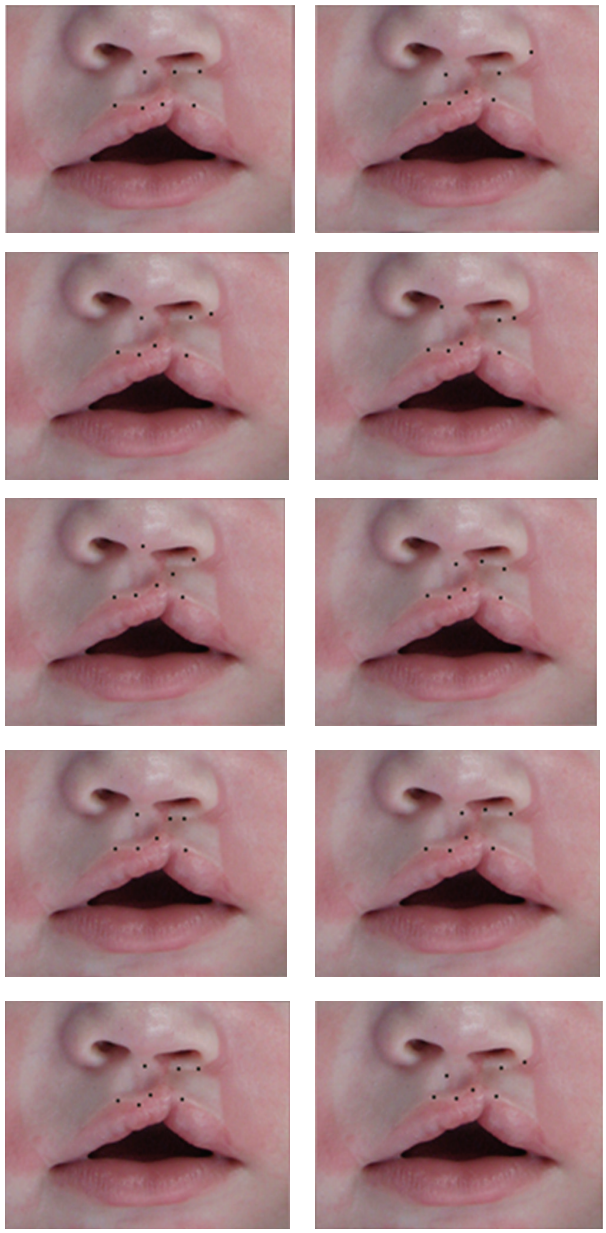

Figure 2: Millard's seven standard points marked by 10 respected craniofacial plastic surgeons separately on picture 2.

afterwards. Point 1 was placed in the center of cupid bow at the vermillion border. Point 2 was in the normal side philtrum at the vermillion border. Points 3 were in the affected side philtrum at the vermillion border. Point 4 was in the mucous cutaneous border on the lateral segment of the affected side. Point 5 was at the end of the C flap. Point 6 was at the alar base and defines the height of the lateral incision. Point 7 was at the end of the lateral segment incision, around the nostril sill. Adobe Photoshop 12.0 was used to superimpose the markings on the same picture. ImageJ software (National Institutes of Health, Bethesda, MD) was employed to measure the distances between markings.

3. Results

It is interesting to analyze the evolution of the technique. The first diagram proposed by Millard in 1957 describes the X-Y-C flaps [1]. In 1958, he renames the flaps A-B-C and slightly modifies their designs [3]. In 1964, the B flap design changed again [6]. Then, in 1968, the B flap incision goes around the nostril sill and the back cut is introduced on the A flap [7]. In 1990, he also depicts his rhinoplasty markings on the drawing published in his paper [12]. Finally, similar markings are shown on his last published paper regarding his technique from 1998 [10].

In both pictures, points 1 and 2 were marked identically among surgeons. Point 3 was located adjacent to each

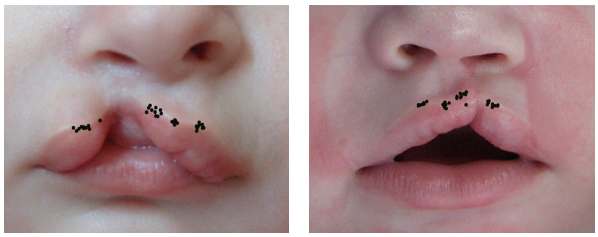

Figure 3: Superimposed image showing marking pattern for point 1, 2, 3, and 4 on picture 1 (left) and picture 2 (right).

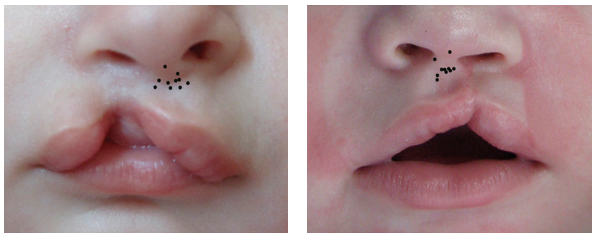

Figure 4: Superimposed image showing marking pattern for point 5 on picture 1 (left) and picture 2 (right).

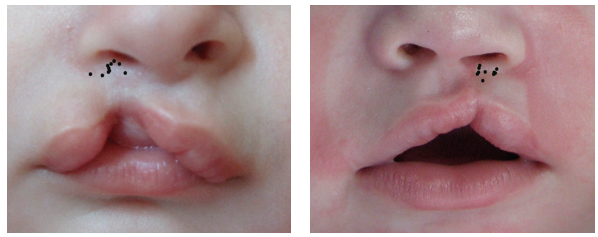

Figure 5: Superimposed image showing marking pattern for point 6 on picture 1 (left) and picture 2 (right).

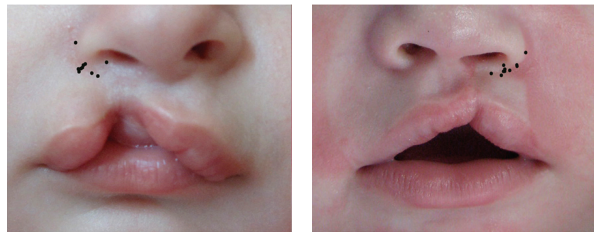

Figure 6: Superimposed image showing marking pattern for point 7 on picture 1 (left) and picture 2 (right).

other, but not coincident, and the largest distance between points 3 was 4.95 mm and 4.03 mm on pictures 1 and 2 respectively (Figure 3). Similar patterns were obtained for point 4, eight of them were adjacent, and the greatest distance between points was 4.39 mm. Two cases were marked very differently, one was 3.2 mm laterally and the other was 6.3 mm medially (picture1). Regarding picture 2, three evaluators had coincident markings, 3.81 mm medial to the other seven, which were also coincident.

Points 5 had the most divergence between the points among evaluators, which were responsible for the different shapes of the C flap (Figure 4). The greatest distances between these points were 11.20 mm on picture 1 and 10.86 mm on picture 2. The most contrasting points were located in one case on the columella and in another case in the medial portion of the unaffected nostril opening.

Points 6 also had dissimilar markings, and such difference accounts for varying resection areas among evaluators. The largest distances observed were 11.66 mm and 7 mm on pictures 1 and 2, respectively (Figure 5). Regarding points 7, only one surgeon extended his marking more laterally, going around the nasal alae on both pictures. Six plastic surgeons placed coincident markings, and three set the points more medially on picture 1, but on picture 2 eight evaluators set the markings medially compared to picture 1. The largest distances between the points were 13.45 mm and 14.08 mm on pictures 1 and 2, respectively (Figure 6).

4. Discussion

Millard described in his first paper his well-known technique: "...why not radically free the entire medial lip element from its attachment to the nose and rotate it as a whole into its rightful position." And he continues saying "...has the philtrum groove been preserved and the cupid's bow brought into functioning position, a small flap (c) continuous with the columella has been created which later will turn up to make the nostril sill." When he described the lateral flap, he pointed that "the triangular gap left is to be filled by advancement of the upper portion of the lip element from the weak side. It is probably better to begin incision Y with its transverse cut just inferior to the alar base and let it curve slightly downward to facilitate the advancement. The length of this cut is a matter of judgment." To finalize, he alerted saying "yet the last few millimeters which make all the difference must depend upon the *sculptor* and *his clay*" [1].

Later on, he described some details: (1) the rotation incision must be radical and extend just past the midline to allow adequate drop of the Cupid's bow component A; (2) advancement of flap B from the lateral lip element in severe clefts requires tension which may be hazardous in the newborn whereas at two to three months of age this tension becomes a minor concern; (3) criticism of this technique has been aimed at the long oblique scar. Actually, the scar disappears into the philtrum line; (4) approximation of the vermillion, with or without interdigitating flaps, usually calls for a minor trimming or revision after six months to perfect symmetry of the free edge of the bow; (5) medial advancement of the lateral lip flap B with lateral advancement of little flap C achieves a striking nasal correction even in severely distorted noses; and (6) absolute minimal discard of tissue [4].

After 50 years of the first rotation-advancement procedure by Millard on the lip of a small Korean boy [11], many changes happened in the original technique, including his personal changes. His first diagrams were not intelligible enough, as he previously wrote, but we added them in due

to their importance. As we noticed in our study, different surgeons designed distinct flaps, all following the same technique, which brings up the point that this technique will adapt to fit the great array of possible anatomic variations within a cleft lip. More specifically, point 7, which represents the end of the lateral segment incision, around the nostril sill, has suffered the most change. A very short incision up to the medial portion of the nostril sill was proposed on 1957, which was subsequently modified in 1968 by Millard himself, comprising in a lateral extension to better address the alar rotational deformity. However, due to the poor scar quality accompanying this long incision, other craniofacial surgeons have decided reinstate the initial short incision to prevent full nostril encirclement. In fact, our study shows that only one surgeon extended his marking more laterally, while all others preferred a shorter cut. Furthermore, point 5 markings exhibit great discrepancy, which accounts for the wide C flap variation in size and design. A small or large backcut, decided upon surgeon's personal experience, aims to provide adequate advancement, which would decrease the likelihood of scar revision in the future secondary to closure under tension or tissue retraction.

Moreover, surgeons that do not obtain good results with this technique must ask themselves whether modification is required or whether a different pattern of markings needs to be done. In fact, Millard brought up the point that his technique would allow great variability of flaps and such plasticity inherent to this operation allows the experienced surgeon to shine. Nevertheless, the novice apprentice must be aware that, without proper markings, his surgery is destined to fail. In summary, much has changed since Millard's initial procedure, but his basic principles have survived the inexorable test of time, proving that his idea has found place among the greatest concepts of modern plastic surgery.

Acknowledgment

The authors would like to thank all the surgeons that collaborated with this project and were kind enough to send them their markings.

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Hindawi Publishing Corporation
Plastic Surgery International
Volume 2012, Article ID 973240, 4 pages
doi:10.1155/2012/973240

Research Article

Weight Gain in Children with Cleft Lip and Palate without Use of Palatal Plates

Renato da Silva Freitas,[1] Andrey Bernardo Lopes-Grego,[1] Helena Luiza Douat Dietrich,[1] Natacha Regina de Moraes Cerchiari,[1] Tabatha Nakakogue,[1] Rita Tonocchi,[1] Juarez Gabardo,[1] Éder David Borges da Silva,[1] and Antonio Jorge Forte[2]

[1] *Center for Integral Assistance of Cleft Lip and Palate, Federal University of Paraná, Cuitiba, PR, Brazil*
[2] *School of Medicine, Yale University, New Haven, CT 06510, USA*

Correspondence should be addressed to Renato da Silva Freitas, dr.renato.freitas@gmail.com

Received 2 August 2012; Accepted 13 November 2012

Academic Editor: Nivaldo Alonso

Goals/Background. To evaluate children's growth in the first year of life, who have cleft palate and lip, without the use of palatal plates. *Materials/Method*. Chart review was conducted, retrospectively, in the Center for Integral Assistance of Cleft Lip and Palate (CAIF), in Brazil, between 2008 and 2009. Results for both genders were compared to the data published by the World Health Organization (WHO) regarding average weight gain in children during their first year of life. *Results*. Patients with syndromic diagnosis and with cleft classified as preforamen were excluded, resulting in a final number of 112 patients: 56 male and 56 female. Similar patterns were seen comparing the two genders. Although it was observed weight gain below the average until the 11th month in male patients and until 9 months in female patients, both genders remained at the 50th percentile (p50) and improved after the 4th month of age for boys and the 9th month of age for girls. *Conclusion*. Children with cleft palate weigh less than regular children during their first months of life. At the end of the first year, weight gain is similar comparing normal and affected children. However, factors that optimized weight gain included choosing the best treatment for each case, proper guidance, and multiprofessional integrated care.

1. Introduction

Cleft lip and palate is the most common craniofacial malformation and is often associated with swallowing impairment and decreas growth rate, likely secondary to children's inability to feed appropriately [1]. According to the literature, children with either cleft lip or palate have a short, fast, uncoordinated, and ineffective intraoral suction, which may cause asphyxia, the entrance of milk in the nose cavity, and as excessive air ingestion [2, 3]. The cleft is considered the main anatomic issue leading to these dysfunctions. In fact, studies showed that children with clefts have lower height and weight when compared to a control group, especially during the first year of life [4–6].

On the other hand, Mcheik and Levard report that the growing curves of children with cleft palate, and regular children are equivalent if patients have no syndrome or severe malformations associated [7]. Consequently, the growing pattern might be more influenced by external factors, such as parents' adaptation to the children's condition or the feeding method used [8]. Adjustments on the care of these children may be helpful to assure appropriate nutrition and significant weight gain [9].

Therefore, the main priority during the first months of life, including those with cleft palate, should be appropriate nutrition. This is especially important to those who are candidates for future surgery. Healthy weight in children is not only related to good response to infections or surgery stress but also to adequate recovery during the postoperative period [9].

Different feeding techniques were described for children with clefts to improve nutritional status. They vary from breastfeeding and special dietary supplements to spoons and modified syringe use [10]. However, the best choice is the

one that the family and the child learn from providers who work on reference centers [7]. One technique, intending to increase the suction of these patients, is the use of palatal plates. Palatal plates intend to facilitate suction for these patients. Some authors also report that plates contribute to remodel the palatal arch, helping intraoral suction during the first months of life [11]. However, in our center, we do not use palatal plates. Therefore, our study evaluates the growth of children with cleft palate and cleft lip in their first year of life, without the use of palatal plates.

2. Methods

This study was approved by the Ethics in Research Committee of the Hospital de Clínicas from the Federal University of Paraná in Brazil, registration number: Banpesq 2012025932. Medical records from patients treated in the Center for Integral Assistance of Cleft Lip and Palate (CAIF), in the city of Curitiba, Brazil, during the period from 2008 to 2009 were carefully analyzed. All new cases of cleft lip, with cleft palate associated and cleft palate isolated from patients under one year of age, were included in this study. The data was obtained retrospectively.

The following data points were considered: (1) patient's name, gender, and birth date; (2) cleft classification; (3) type of milk consumed: human breast milk, cows' milk, or formula; (4) time length of exclusive breastfeeding; (5) age of solid food consumption; (6) weight at birth; (7) monthly weight during the first year of life.

The results found for boys and girls were then compared to the data published by the World Health Organization (WHO) regarding average weight gain in children during their first year of life.

3. Results

135 patients were included in this study. Patients with syndromic diagnosis and with cleft classified as preforamen were excluded, resulting in a final number of 112 patients: 56 male and 56 female.

Regarding food type, the most prevalent was the use of nutritional formulas alone (36.6% of the sample), followed by the combined use of breast milk and formula (25%). Exclusive use of breast and cow's milk were 8.9% and 2.7%, respectively. The average duration of exclusive breastfeeding was 46 days, and the average age for initiation of solid foods was 8 months.

Interestingly, a similar weight gain pattern was seen on both genders. Figure 1 shows that the weight gain in affected male patients is below the average for their age; by the 11th month, on the other hand, the curves were almost superimposed. At birth, the boy's weight is about 200 g below the average for this age. This difference increases as time goes by, reaching almost 900 g in the third month of life; however, after the third month, the difference between the average weight gain begins to decrease. In fact, around the tenth month, affected infants weight gain exhibit a similar pattern to normal.

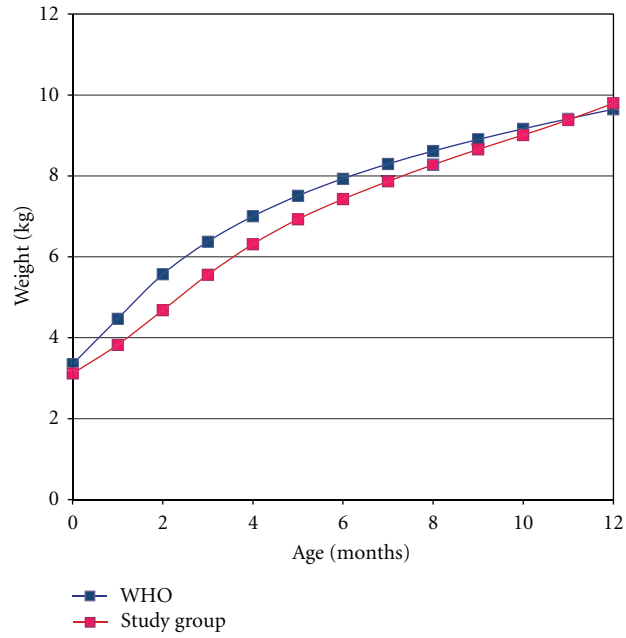

Figure 1: Comparison between the average weight gain of boys with cleft lip and palate estimated by WHO. Blue dots: WHO; pink dots: study group.

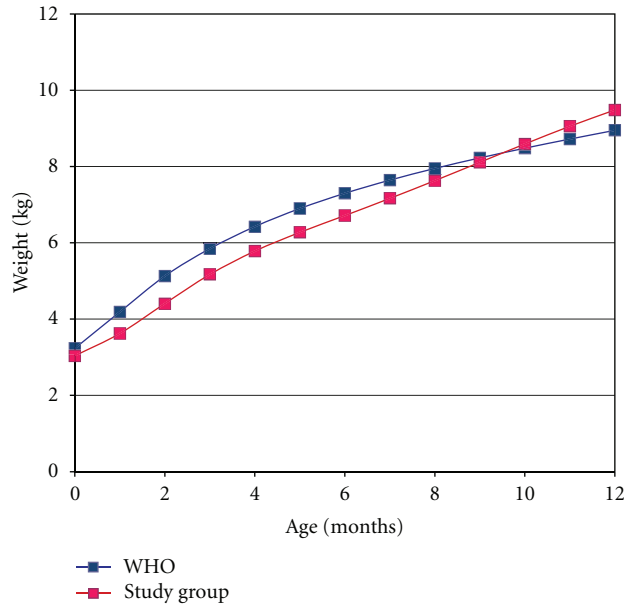

Figure 2: Comparison between the average weight gain of girls with cleft lip and palate estimated by WHO. Blue dots: WHO; pink dots: study group.

Figure 2 represents the weight gain of female patients compared with normal values. Girls weight gain shows a difference of almost 200 g compared to the expected weight gain. There is a gradual increase of this discrepancy up to the third month of life, when it peaks at almost 750 g. Afterwards, the gap diminishes reaching a similar pattern near the ninth month of life.

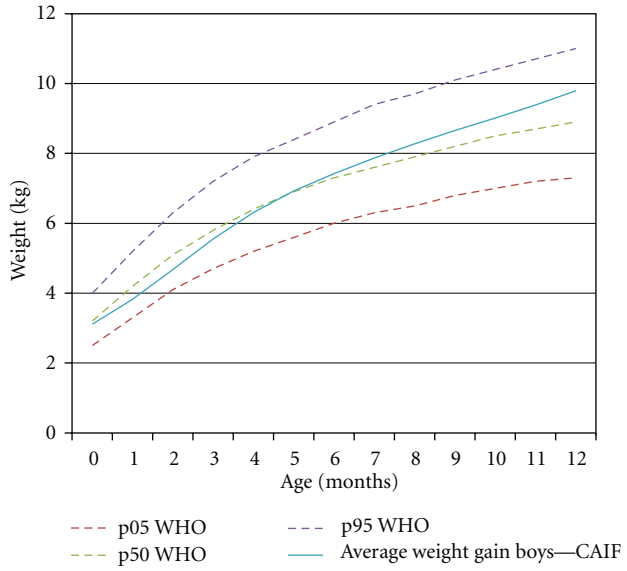

Figure 3: Curve of weight gain for boys compared to percentiles estimated by WHO.

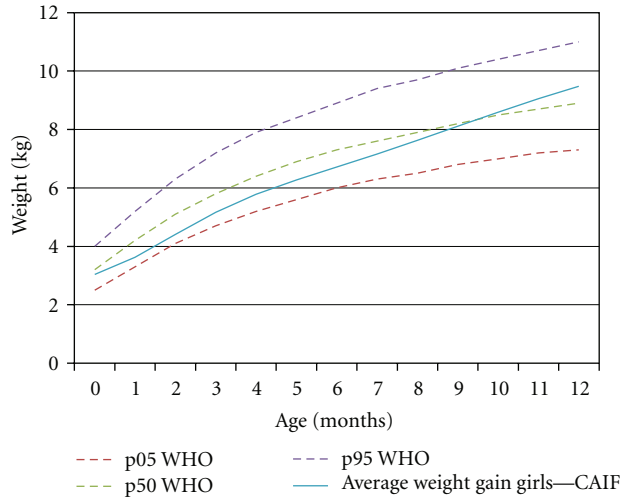

Figure 4: Curve of weight gain for girls compared to percentiles estimated by WHO.

Weight gain curve in both genders, demonstrated in Figures 3 and 4, is plotted near the 50th percentile (p50) line for each time of assessment, crossing it after the 4th month of age for boys and 9th months of age for girls.

4. Discussion

Children with clefts have a higher rate of malnutrition secondary to suctioning impairment. This was first presented by Fabricius and Aquapendente in 1916 [7]. Since then, multiple discussions about the actual interference of clefts in growth rate and weight gain have taken place [9].

Weight gain and growing becomes an issue during the first month of life, probably due to their difficulty to generate negative intraoral pressure, necessary to accomplish a good suction [12]. As a result, the process becomes quick, inefficient, and not coordinated with the swelling movements, that can result in insufficient absorption of nutrients and deficiency in weight gain [13]. In this context, the majority of children require some mechanical support to facilitate the flow of milk [10]. However, the most effective solution to this problem is the palate corrective surgery, which occurs between 9 and 12 months in most centers. The use of devices that facilitate suction and allow a greater intake of breast milk, such as the palatal plate, is an alternative protocol followed by some services [14, 15]. These centers promote the benefits and advantages of palatal plate use. Consequently, some families and pediatricians question the choice of not using it. Trying to shed some light into this discussion, a randomized study compared the weight gain and growth of children who used and did not use the prosthesis, finding no statistically significant difference in the variables evaluated. For that reason, the research did not recommend the universal use of the palatal plate [15].

Another aspect widely discussed is the role played by different nutritional formulas and the use of breast milk on the growth pattern and weight gain in infants with cleft palate [16]. In our study, we did not identify any association between the milk type and the weight gain measured. Our study noticed a predominant use of nutritional formulas, despite the policy of supporting breastfeeding adopted by our hospital. This is probably due to the intrinsic difficulty to collect breast milk and the convenience of formula use.

Affected patients experience an obvious growth deficit in the early months of life in both genders. It is possible that this lower weight gain during this period is a consequence of cleft infant's adaptation to new methods of nutrition [17]. It is important to emphasize that, even though the initial weight gain is lower than the one established by WHO (Figures 1 and 2), the sample data is near to p50, especially the boys (Figures 3 and 4). Breastfeeding is often hampered by the lack of knowledge of parents or caregivers about the proper ways of feeding the cleft child and difficult access to appropriate treatment centers for education and care.

After patients' initial access to health care professionals, it was noted improvement in growth and weight gain, indicating that affected infants, when appropriately stimulated to reach a targeted nutritional level, can achieve normal infant's growth. Therefore, proper orientation and access to followup are factors that contribute to improve patient's nutritional status [18]. Weight gain greater than WHO's mean percentile after 10 months of age reaffirms the success of the current feeding guidelines, follow-up regimen and treatment.

5. Conclusion

In our study, none of our cleft palate patients used palatal plates, and both genders weighed less than regular infants during their first months of life, in comparison to the curves established by the World Health Organization. However, at the end of the first year, they presented similar weight gain in both groups. In addition, we noticed that the type of cleft palate and the type of milk consumed had no influence

neither on weight gain nor on growth. Therefore, the factors that improved weight gain were: choosing the best treatment for each case, support, education, integrated multiprofessional care and regular following up. Parents' collaboration, working together with health professionals, allowed adequate growing of cleft palate children, minimizing health risks.

Conflict of Interests

The authors declare no conflict of interests.

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Hindawi Publishing Corporation
Plastic Surgery International
Volume 2012, Article ID 620302, 4 pages
doi:10.1155/2012/620302

Research Article

Profile Evaluation of Patients with Cleft Lip and Palate Undergoing Surgery at a Reference Center in Rio de Janeiro, Brazil

Diogo Franco,[1] Marcella Iani,[2] Ronaldo Passalini,[1] Ivan Demolinari,[1] Marcio Arnaut,[1] and Talita Franco[1]

[1] *Plastic Surgery Division, HUCFF-UFRJ, Rua Ramon Franco, 98 Urca, 22290-290 Rio de Janeiro, RJ, Brazil*
[2] *Medical School, HUCFF-UFRJ, 22290-290 Rio de Janeiro, RJ, Brazil*

Correspondence should be addressed to Diogo Franco, diogo@openlink.com.br

Received 29 August 2012; Revised 12 October 2012; Accepted 3 November 2012

Academic Editor: Renato Da Silva Freitas

In Brazil, the classic timeline for operating on cleft lip and palate is three months old for cheiloplasty and is 12 to 18 months old for palatoplasty. As from Brazilian treatment centers are usually located in major cities, patients living in more remote areas are often unable to receive treatment at the ideal ages. Data were analyzed retrospectively on 45 patients with cleft lip and/or palate, consecutively operated at the Reference Center, Rio de Janeiro Federal University, Brazil. Particularly noteworthy among these data are gender, clinical presentation, operations performed, age of surgery, and the distance between their homes and the hospital. The average age of patients undergoing primary cheiloplasty was 9.4 months, with primary palatoplasties performed at an average age of 7.2 years. As 67% of these patients lived in other towns, they encountered difficulties in seeking and continuing specialized care. Despite attempts to decentralize cleft palate care in Brazil, suitable conditions are not yet noted for following the treatment protocols in a full and adequate manner.

1. Introduction

Cleft lip and palate are among the most common facial congenital anomalies [1]. In addition to adverse effects on appearance, they also cause problems with speech, occlusion, facial growth, and otological disorders.

The treatment for this pathology is complex, extending from birth through to the end of puberty and involving practitioners in a broad range of specialties, including physicians, dentists, and speech therapists. Treatment is intended mainly to maintain nasal respiration and foster adequate facial growth, closing the cleft lip and providing tongue-palate coaptation and orofacial tonus. Patients are generally treated in specialized centers with adequate experience.

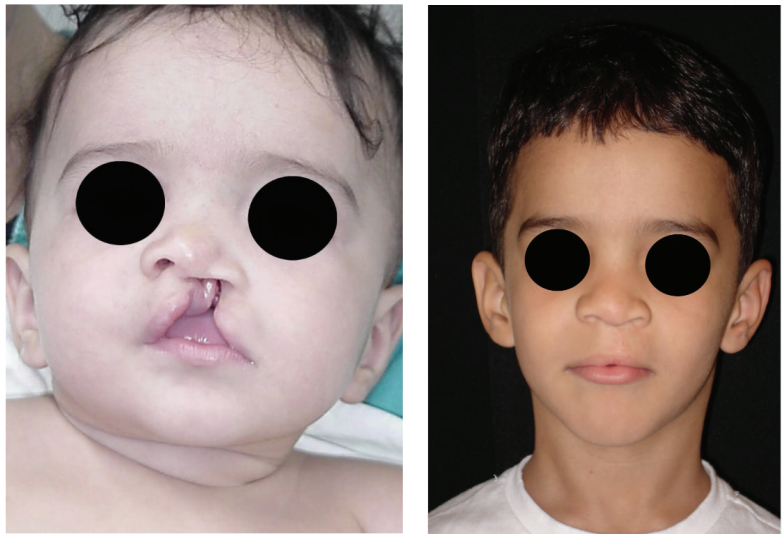
In Brazil, the classic timeline for operating on cleft lips and palates consists of cheiloplasty at around three to four months old, with palatoplasty at 12 to 18 months old. As Brazilian treatment centers are usually located in major cities, patients living in more remote areas are often unable to receive treatment at the ideal ages, resulting in more limited outcomes for such treatment.

2. Objective

The objective of this paper is to evaluate the profile of patients with cleft lip and palate undergoing surgery at the Cleft Palate Treatment Reference Center at the University Hospital, Rio de Janeiro Federal University, Brazil.

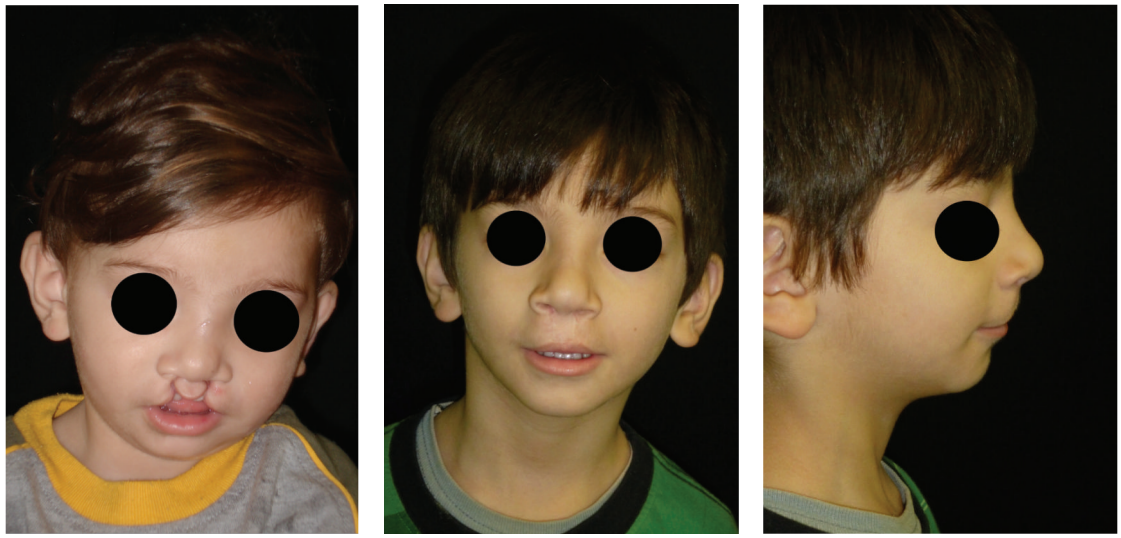
3. Methods

Data were analyzed retrospectively on 45 patients with cleft lip and/or palate, operated on consecutively by the Plastic Surgery Unit at the Clementino Fraga Filho University Hospital, Rio de Janeiro Federal University. Specific attention was paid to gender, clinical presentation, operations undergone, age of surgery, and distances between homes and the hospital.



(a) (b)

Figure 1: (a) Preoperative patient with complete left cleft lip and palate; (b) five years postoperative, after rhinocheiloplasty (Millard + McComb techniques).



(a) (b) (c)

Figure 2: (a) Preoperative patient with complete bilateral cleft lip and palate; (b) and (c) four years postoperative, after rhinocheiloplasty, in a single operation (Mulliken technique).

Only patients with at least three months postoperative monitoring after primary surgery were considered in the study.

4. Results

Twenty-three male and 22 female patients were analyzed (Table 1).

Surgeries consisted of 60% palatoplasties, 38% cheiloplasties (Figures 1 and 2), and 2% cheiloplasties associated with palatoplasties (Table 2).

The average age of patients undergoing primary cheiloplasty was 9.4 months, with 74% operated on up to six months, and 26% above this age (Table 3).

With regard to the primary palatoplasties, the average age was 7.2 years, with 53% operated on between 12 and 18 months and 47% later (Table 4). The only patient undergoing combined lip and palate surgery was one year and eight months old.

Among the patients, 33% resided in the city of Rio de Janeiro, 54% lived in this state, and the remaining 13% came from elsewhere.

Table 1: Distribution of clinical presentations at birth.

	Female	Male	Female + male
Unilateral left cleft lip	3	3	6 (13%)
Unilateral right cleft lip	1	2	3 (7%)
Bilateral cleft lip	1	0	1 (2%)
Unilateral left cleft lip and palate	4	8	12 (27%)
Unilateral right cleft lip and palate	2	1	3 (7%)
Complete bilateral cleft lip and palate	1	1	2 (4%)
Incomplete bilateral cleft lip and palate	0	1	1 (2%)
Complete cleft palate	4	0	4 (9%)
Incomplete cleft palate	6	7	13 (29%)
All clefts	22	23	45 (100%)

Table 2: Operations performed.

Palatoplasties	29 (60%)
Cheiloplasties	18 (38%)
Cheiloplasties + palatoplasties	1 (2%)

Table 3: Average age of patients undergoing primary cheiloplasty.

Up to six months	74%
Older than six months	26%

Table 4: Average age of patients undergoing primary palatoplasty.

12–18 months	53%
Older than 18 months	47%

5. Discussion

Proper treatment for cleft lip and palate requires preparation, meticulous surgery, and careful postoperative monitoring besides lengthy periods of followup, involving practitioners in a wide variety of specialties, including physicians, dentists and speech therapists. The approach to these patients is complex, and in Brazil, this is normally provided at specialized centers in large cities [2]. The city of Rio de Janeiro is one of the main medical treatment hubs in Brazil, with an inflow of patients from all over the country [3].

However, facilities may be precarious or even nonexistent in poorer or more remote parts of the country. Consequently, many patients were recorded as arriving at our hospital beyond the ages rated as ideal for treatment.

In 1967, Pitanguy and Franco studied a group of 686 Brazilian patients with facial clefts. Among these, there were 84 nonoperated adults, six with cleft lip, 47 with cleft lip and palate, 14 with cleft palate, and 17 with rare facial clefts. It was noted that facial skeleton development reached a certain level of harmony, due to the balance between the growth potential of the structures and the lack of resistance normally offered by neighboring tissues. They were compared with children improperly operated at early ages, showing a final result rated as superior, due to an abundance of soft tissue that makes it easier to close combined clefts in a single operation [4].

Since then, Brazil had achieved considerable progress in terms of treating cleft lips and palates, although almost 50% of these patients are still unable to undergo surgery at the ideal time, with ratings that vary from good in major cities to extremely poor in underprivileged regions. Even today, it is not unusual to find adults who have not undergone surgery.

In our cleft palate patients, the disparity between treatment age and ideal age was significant. Only 53% of the patients were operated on at the best time, between 12 and 18 months with the average age being 7.2 years, which is far from acceptable [5–10].

For cheiloplasties, the disparity was not as great as for palatoplasties. In 74% of the cases, surgery took place up to six months of age, with an average of 9.4 months. As cleft lips are more visible, there are perhaps more pressures prompting their correction.

What contributes greatly to later presentation is the fact that many of these patients live outside the city of Rio de Janeiro (67%). This requires expenses for travel and accommodation, with days off work for caregivers, greatly hampering not only the initial presentation for surgery but also for monitoring these patients during the post-operative stage.

These geographical stumbling blocks also cause difficulties with the correct maxillary orthopedic preparation and orthodontic monitoring of these patients, which are important factors for good outcomes [11].

Many of our cleft lip and palate patients (91%) arrive with a cheiloplasty already done at another institution, before being referred to our hospital. In smaller towns, non-specialized local surgeons sometimes attempt to perform cheiloplasties, wrongly considered to be easier than palatoplasty, instead of referring these patients to a specialized Center. Consequently, most of the operations in our study consisted of palatoplasties (60%). This suboptimum conduct should be avoided, particularly as the number of cleft palate treatment centers has increased over the past decade, even in more remote areas, staffed by specialists trained to perform any procedures [2, 3].

Cleft lips were noted as being more frequent on the left side (62%), affecting the right side in 21% of cases, and bilateral in 17%. These findings are similar to those in the literature [5–10].

Recently, joint efforts by the Brazilian Government, NGOs, and groups of healthcare practitioners have managed to enlighten the public regarding treatment possibilities and organized medical programs that streamline and extend treatment facilities for this type of patient [12]. Nevertheless, there is no public health structure that encourages care-givers to seek specialized treatment at an early age for these patients, followed by the appropriate maintenance procedures. In a continent-sized country such as Brazil, where most cleft palate patients are found among the underprivileged classes, outlays on treatment may hamper and even completely prevent compliance with the protocols established by the cleft palate treatment centers.

6. Conclusions

The data obtained through this study show that many cleft palate patients seek treatment at ages older than those rated as ideal. The main factor behind this seems to be difficulties encountered by people living in more remote areas, who find it hard to travel to specialized centers that are generally located in major cities. Despite attempts to decentralize cleft lip and palate treatment in Brazil, adequate conditions are still not in place as required to follow the treatment protocols in a full and appropriate manner.

Ethical Approval

This study was conducted with the understanding and the consent of the patients and approved by the hospital ethical committee.

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Hindawi Publishing Corporation
Plastic Surgery International
Volume 2012, Article ID 542078, 6 pages
doi:10.1155/2012/542078

Research Article

Anatomical Variations in Clefts of the Lip with or without Cleft Palate

K. Carroll and P. A. Mossey

Dental Hospital and School, University of Dundee, 1 Park Place, Dundee DD1 4HR, UK

Correspondence should be addressed to K. Carroll, kris.m.carroll@gmail.com and P. A. Mossey, p.a.mossey@dundee.ac.uk

Received 3 August 2012; Accepted 19 October 2012

Academic Editor: Nivaldo Alonso

Objective. Few orofacial cleft (OFC) studies have examined the severity of clefts of the lip or palate. This study examined associations between the severity of cleft of the lip with cleft type, laterality, and sex in four regional British Isles cleft registers whilst also looking for regional variations. *Design*. Retrospective analysis of cleft classification in the data contained in these four cleft registers. *Sample*. Three thousand and twelve patients from cleft registers based in Scotland, East England, Merseyside, and Belfast were sourced from the period 2002–2010. Submucous clefts and syndromic clefts were included whilst stillbirths, abortuses, and atypical orofacial clefts were excluded. *Results*. A cleft of the lip in CLP patients is more likely to be complete in males. A cleft of the lip in isolated CL patients is more likely to be complete in females. Variation in the proportion of cleft types was evident between Scotland and East England. *Conclusions*. Association between severity of cleft of the lip and sex was found in this study with females having a significantly greater proportion of more severe clefts of the lip (CL) and CLP males being more severe ($P < 0.0003$). This finding supports a fundamental difference between cleft aetiology between CL and CLP.

1. Introduction

Maintaining a register of children born with orofacial clefts is recognised as important with regards to audit, research, and the planning and provision of services [1]. The use of a simple classification, such as the LAHSAL system proposed by Kriens in 1989 [2] to describe clefts is recognised as being of prime importance and allows for the accurate recording of cleft types and comparison between locations [3].

The evidence available at a global and European level indicates very significant regional variation in the birth prevalence of orofacial clefts, both cleft palate (CP) and cleft lip and palate (CLP) [4]. It is well known that the aetiology of orofacial clefts is characterised by heterogeneity and that the aetiology is polygenic multifactorial with both environmental and genetic factors contributing to nonsyndromic type [5], which comprises approximately 70% of all orofacial clefts.

The increase in CP seen in some UK studies and in parts of Scandinavia may be as a result of factors associated with their northern position [6]. The proportion of CP in Sweden was shown to increase with the increase in latitude at which the comparison was carried out [7].

Several studies have shown that females are affected more often than males with regards to isolated CP [6, 8, 9]. Conversely, a predilection for the male sex is observed in clefts involving the lip [9, 10].

With regards to laterality, most studies show a left-sided dominance of clefts involving the lip [11–13]. Contrasting results have been obtained upon examining for a link between sex and laterality. In South-East Scotland, a male dominance for left-sided clefts was recorded [14]. Despite an earlier report in Northern Ireland of a predilection for right-sided clefting in females, a subsequent analysis over a twenty-year period failed to find an association between sex and laterality [15].

Animal studies have shown that during development, the left palatal shelf takes longer to rotate into the horizontal position leaving this side susceptible to developmental interruption for longer [16]. A suggested reason for this is the lower arterial pressure on the left side compared to the internal carotid artery on the right side [13]. Conversely with

regard to all other external congenital anomalies, an excess on the right side has been noted [17].

A possible hypothesis for this is revealed in rat embryos where the mitochondrial maturation rate is delayed on the right side making this side more susceptible to prenatal hypoxia [17]. Although this right-sided correlation for most congenital anomalies is not replicated in orofacial clefts, the author goes on to explain that male sex hormones lower mitochondrial respiration rates which could help to explain the male predominance of CL.

Very significant progress has been made in recent years with respect to genetic determinants and a range of environmental risk factors [18]. Current research has resultantly focussed on finding out more about the interactions between genes and environment, the influence of epigenetics, and the targeting of environmental factors that in the presence of genetic polymorphisms become teratogenic.

Research in this field in the past has been hampered by individual population studies, small sample sizes, pooling of a range of different cleft phenotypes in a single analysis, and potentially masking any differences between different subphenotypes of clefts.

One aim of this study was to profile the details of cleft lip ± palate patients from four British Isles cleft registers, recorded in accordance with the LAHSAL system. The majority of papers that have profiled cleft registers do so with regard to the relative proportions of cleft type, sex and laterality. Emphasis has recently been placed on elucidating further subphenotypes associated with orofacial clefts and determining characteristics such as heritability and transmission patterns of orofacial cleft subphenotypes [18]. Research has been carried out to determine further subphenotypes of clefts, including parental features, in order to help unravel the genetic basis for the condition [19].

A further aim of this study was to analyse the registers with regards to the severity of the cleft of the lip and possible associations with laterality and sex. Until recently, the importance of the severity of the cleft of the lip was described only in relation to the optimum timing of surgery and the surgical technique involved [20]. Criticism has recently been apportioned to the recording of cleft type by its presence or absence as being too simplistic which may hamper the genetic determination of orofacial clefts [18]. The identification of subphenotypes within cleft lip could aid recurrence risk estimations and help to refine gene mapping. The profiling of the "severity of cleft" subphenotype in conjunction with the other main variables may present a finding that is relevant as an expression of the genetic and environmental factors underpinning clefts.

2. Method

A retrospective study was undertaken to identify all children born with a cleft of the lip ± cleft palate in the areas covered by the cleft registers in Scotland, East England, Belfast, and Mersey during the period January 2002 to April 2010. The criteria for entering clefts onto the databases were similar in all 4 regions in that abortuses, stillbirths, and atypical orofacial clefts were excluded. Otherwise all typical clefts of the lip and palate were placed on the register, whether or not they were diagnosed at that point with a syndrome, and submucous clefts if detected were also included.

The purpose of selecting these geographical locations was due to the reported differences in prevalence of the various forms of cleft in these areas. Studies report a majority of cleft palate cases in Scotland [5, 13, 21] and Northern Ireland [8].

The databases were downloaded at the commencement of the study in January 2010. The aim was to record information from anonymised data relating to the cleft type, date of birth, sex, side affected, and the severity of the cleft. The registers were compared by interpreting the LAHSAL code assigned to each patient registered with a cleft, where the letters of LAHSAL represent the two sides of the lip and alveolus (the first L and A indicate the right lip and alveolus) and the hard and soft palate. Upper and lower case letters are used to depict "complete" and "incomplete" clefts.

The definition of complete cleft is an area of contrasting explanations in the literature. For the purpose of this study, "complete cleft" relates to a cleft which involves the full height of the lip to the nasal sill (and therefore is the most severe type), whereas "incomplete cleft" relates to those which only involve a portion of the height of the lip (and is less severe). Many articles refer to a complete cleft as one which communicates between the lip and the palate, that is, CLP.

Whilst bilateral cases were included in the totals of clefts for each region, they were excluded from the analysis examining for a link between cleft type and severity, on the basis of the need to record one type of phenotype per case i.e. some bilateral cleft patients had one complete cleft on one side and an incomplete cleft on the contralateral aspect.

3. Results

In this retrospective comparative analysis of cleft classification of populations contained in four British Isles cleft registers, a total of 3012 patients from cleft registers based in Scotland, East England, Mersey, and Belfast were sourced from the period 2002 to 2010. The number of patients in each category is indicated in the Figure 1 and Tables 1, 2, 3, and 4.

4. Discussion

4.1. Cleft Type Proportions in Scotland and East England. The proportion of cleft palate as a percentage of all clefts in Scotland was 50%. The proportion for CLP was 29%. This finding is in keeping with previous results from the west of Scotland [21] which showed a predominance of cleft palate at 52%. The result for CP is also similar to the 53% figure obtained in N. Ireland [15] which is nearby geographically and could be said to have a similar population to Scotland in the genetic sense. The proportion of CP detected in East England was 43%. This is in keeping with the lower prevalence of CP detected in previous English studies in Birmingham [22], Northumberland [9], and the Trent region [23] which recorded CP at 40%, 33%, and 39%, respectively.

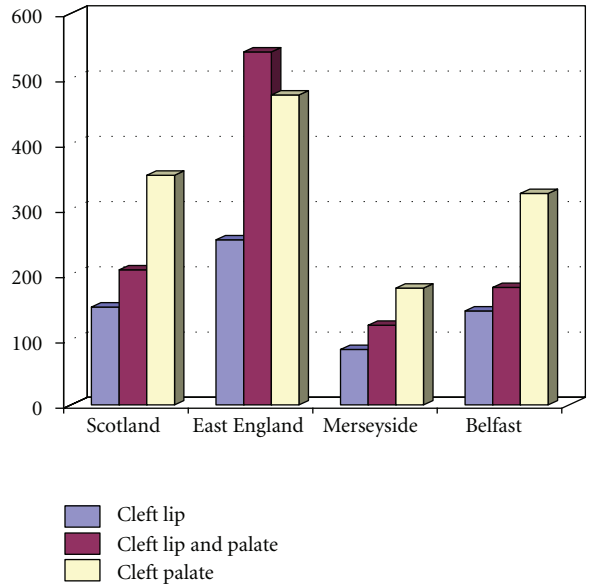

Figure 1: The distribution of different types of OFC across 4 UK regions.

Table 1: Cleft types in all four UK regions.

	Cleft lip	Cleft lip and palate	Cleft palate
Scotland	150	207	352
East England	253	541	475
Merseyside	85	122	179
Belfast	144	180	324

The prevalence of CLP in Scotland in this study at 29% again compares favourably with the results gained from the west of Scotland [21] in 1987 (34%) and N. Ireland [8] in 1994 (30%). The prevalence obtained from East England in this study was 37%. The same figure of 37% was obtained from Birmingham [22] in 1953 and 36% from Northumberland [9] in 1962. In 1988, Trent region [23] recorded a combined figure for CL and CLP of 61%. The corresponding figure from this study was 57%.

The percentages of cleft type, sex and laterality proportions were found to be very similar between the datasets from Scotland, Merseyside, and Belfast.

4.2. Severity of Cleft—Association with Cleft Type. In the four registers examined, the cleft in unilateral CL was found to be predominantly incomplete—69%. The opposite was true with unilateral CLP where the cleft of the lip tended to be complete—88%.

Only two previous studies describing the complete versus incomplete proportions of clefts of the lip and palate have been found in the literature in Brazil and Norway. In the Brazilian study from a cleft and craniofacial centre in Bauru, the majority of unilateral cleft lip cases were incomplete [24], while the Norwegian study reported that for CL, 18% were complete clefts of the lip and primary palate, and for CLP 81% of the lips were complete [25]. This represents consistency in the association between cleft type and the severity of the cleft of the lip. Severity of the cleft of the lip in unilateral CLP was not described in the Brazilian study.

Several studies have shown that comparing congenital anomaly data from different locations can reveal variable characteristics and proportions. A difference in the proportion of cleft types is reported upon in Glasgow in comparison to other locales with the suggestion that this may be due to the interaction of an unidentified environmental teratogen with a susceptible population [21].

An epidemiological study in the UK has shown that true regional variation exists in the prevalence of specific congenital anomalies such as neural tube defects (NTDs), diaphragmatic hernia, and gastroschisis with higher prevalence rates in northern regions such as Glasgow and the north of England [26].

No association could be found regarding the severity of the cleft of the lip and the sex of the patient. Males and females both had a statistically significant level of complete cleft lip in unilateral CLP. While cleft lip is consistently more frequent on the left side, the laterality of the cleft was not associated with the severity of the cleft in either this UK study and the report from Norway. In the Norwegian study it was also reported that in bilateral cleft lip severity was similar on both right and left sides.

4.3. Severity of Cleft—Association with Sex. Upon combining the data from the four British Isles registers, complete cleft of the lip in CLP patients was found to occur in 90% of males and 85% of females. In isolated CL patients, complete cleft of the lip occurred in 39% of females and 25% of males. Logistic regression analysis of the data revealed that the differences in proportion of complete and incomplete clefts between males and females for these two groups of patients (CL and CLP) were significant ($P < 0.0003$, $\chi^2 = 13.23$).

When CL and CLP patients were considered as one entity, that is, CL ± P, no association was found between severity of cleft and the sex of the patient ($P < 0.356$, $\chi^2 = 0.852$) or between the severity of cleft and the side affected ($P < 0.530$, $\chi^2 = 0.394$).

This study utilised datasets which excluded atypical lip and facial clefts but did not specifically exclude syndromes which included orofacial clefting as part of the phenotype. The majority of syndromic cleft cases involve patients where the cleft is of the palate only. For example, in Scotland 67% of cases of syndromic clefts where the cleft type was described involved cleft of the palate. This study was concerned with severity of clefts of the lip, and there is evidence of overlap between syndromic and nonsyndromic clefts in terms of aetiology, so for the purposes of this study it was considered acceptable to retain the full data set for the severity analyses.

4.4. The Multifactorial Threshold Model. The multifactorial threshold (MFT) model is often used to describe the aetiology of orofacial clefting, that is, no one single causative factor accounts for the development of orofacial clefting.

The MFT model does apply to the data in this study when examining the severity of cleft data for cleft lip and

Table 2: Cleft lip—severity of cleft according to gender and laterality.

	Scotland		Cambridge		Belfast		Liverpool	
	C	*I*	*C*	*I*	*C*	*I*	*C*	*I*
Overall	38	95	72	137	39	87	23	53
Males	19	60	36	94	20	57	15	37
Females	19	35	36	43	19	30	8	15
Right side	11	38	24	46	10	35	13	14
Left side	27	57	48	91	29	52	11	38
Males—left	11	34	26	61	13	31	4	28
Females—left	16	23	22	30	16	21	5	10
Males—right	8	26	10	33	7	26	11	9
Females—right	3	12	14	13	3	9	3	5

These figures for CL reveal a reasonable level of consistency across regions in proportions of complete to incomplete clefts with incomplete clefts being consistently more prevalent than complete ones. Also complete clefts of the lip seem to occur more frequently in females. Bilateral clefts were excluded from this analysis.

Table 3: Cleft lip and palate—severity of cleft according to gender and laterality.

	Scotland		Cambridge		Belfast		Liverpool	
	C	*I*	*C*	*I*	*C*	*I*	*C*	*I*
Overall	125	20	273	35	111	17	66	8
Males	81	11	169	17	73	9	55	7
Females	44	9	104	17	38	8	22	2
Right side	52	5	88	16	47	5	23	4
Left side	73	15	185	19	64	12	53	7
Males—left	45	8	115	9	42	6	37	5
Females—left	28	7	70	9	22	6	16	1
Males—right	36	3	54	8	31	3	17	2
Females—right	16	2	34	8	16	2	6	1

These figures for CLP reveal a reasonable level of consistency across regions in proportions of complete to incomplete clefts with complete clefts being consistently more prevalent than incomplete clefts. Bilateral clefts were excluded from this analysis.

Table 4: Cleft severity categories for CL and CLP according to sex.

(a)

	Male Cleft lip Incomplete	Female Cleft lip Incomplete	Male Cleft lip Complete	Female Cleft lip Complete
Scotland	60	35	19	19
Cambridge	94	43	36	36
Belfast	57	30	20	19
Liverpool	37	15	15	8

(b)

	Male Cleft lip and palate Incomplete	Female Cleft lip and palate Incomplete	Male Cleft lip and palate Complete	Female Cleft lip and palate Complete
Scotland	11	9	81	44
Cambridge	17	17	169	104
Belfast	9	8	73	38
Liverpool	7	2	55	22

These data reveal that the most common single cleft subphenotype in every region in the UK is a complete cleft of the lip on the left side in a male, with an accompanying cleft of the palate. Bilateral clefts were excluded from this analysis.

palate (CLP) patients. More males than females are affected by CLP as would be predicted by the MFT model; this study shows that more males have a complete cleft of the lip than females. However, for CL the results of this study do not appear to be compatible with the MFT model of aetiology when considering gender and severity combined. The MFT model for isolated cleft lip (CL) would predict more males to be affected by the more severe (complete) cleft of the lip than females. However, the opposite is observed in CL patients, in that females are affected by a complete cleft of the lip more often than males. This points to a different mechanism for the cause or predisposition to CL as opposed to CLP, supporting previous epidemiological findings [27–29] and genetic evidence [30], and thus providing further circumstantial evidence for a different genetic mechanism in these 2 cleft subphenotypes.

5. Conclusion

Cleft lip and cleft lip and palate have traditionally been grouped together epidemiologically as cleft lip ± palate (CL(P)) and considered as one genetic entity in separation from isolated cleft palate (CP), and this has undoubtedly hampered genetic investigations. Based upon the findings in this study relating to severity of cleft and sex, this study provides further evidence that cleft lip may be a distinct genetic entity to cleft lip and palate.

This UK-based study reveals that substantial variation in the proportion of cleft types was evident between Scotland and East England. Furthermore among CLP patients, the cleft of the lip is more severe in males, while the cleft of the lip in isolated CL patients is more severe in females. This association between severity of cleft of the lip and sex was statistically significant ($P < 0.0003$) and supports a fundamental difference between cleft aetiology between CL and CLP.

Further studies are required to determine proportions of cleft severity subphenotypes from centres around the world and to examine possible association with aetiology; more work is also required to standardise and validate the codes in cleft registers to ensure the accuracy and consistency of recording by referring to original clinical photographs and models.

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Hindawi Publishing Corporation
Plastic Surgery International
Volume 2012, Article ID 247104, 5 pages
doi:10.1155/2012/247104

Research Article

Preliminary Analysis of the Nonsynonymous Polymorphism rs17563 in *BMP4* Gene in Brazilian Population Suggests Protection for Nonsyndromic Cleft Lip and Palate

Tânia Kawasaki Araújo,[1] Milena Simioni,[1] Têmis Maria Félix,[2] Liliane Todeschini de Souza,[2] Marshall Ítalo Barros Fontes,[3] Isabella Lopes Monlleó,[3,4] Josiane Souza,[5] Agnes Cristina Fett-Conte,[6] Rodrigo Secolin,[1] Iscia Lopes-Cendes,[1] Cláudia Vianna Maurer-Morelli,[1] and Vera Lúcia Gil-da-Silva-Lopes[1]

[1] *Department of Medical Genetics, Faculty of Medical Sciences, University of Campinas (UNICAMP), 13083-887 Campinas, SP, Brazil*
[2] *Medical Genetics Service, Hospital de Clinicas de Porto Alegre, 90035-903 Porto Alegre, RS, Brazil*
[3] *Medical Genetics Sector, State University of Alagoas, 57010-300 Maceio, AL, Brazil*
[4] *Clinical Genetics Service, University Hospital, Federal University of Alagoas, 57072-970 Maceio, AL, Brazil*
[5] *Centro de Atendimento Integral ao Fissurado Labiopalatal (CAIF), 81050-00 Curitiba, PR, Brazil*
[6] *Department of Molecular Biology, Medicine School of São José do Rio Preto (FAMERP FUNFARME), 15090-000 São José do Rio Preto, SP, Brazil*

Correspondence should be addressed to Vera Lúcia Gil-da-Silva-Lopes, vlopes@fcm.unicamp.br

Received 27 July 2012; Accepted 3 November 2012

Academic Editor: Renato Da Silva Freitas

Cleft lip with or without palate (CL±P) is common congenital anomalies in humans. Experimental evidence has demonstrated that bone morphogenetic protein 4 gene (*Bmp4*) is involved in the etiology of CL±P in animal models. The nonsynonymous polymorphism rs17563 T>C (p.V152A) in the *BMP4* gene has been associated to the risk of nonsyndromic CL±P in Chinese population and microforms from different ethnic backgrounds. The aim of this study was to investigate the role of *BMP4* gene in CL±P in Brazilian sample using genetic association approach. Our sample was composed by 123 patients with nonsyndromic CL±P and 246 controls, in which absence of CL±P was confirmed in 3 generations. The rs17563 polymorphism was genotyped by PCR-RFLP technique. Logistic regression was performed to evaluate allele and genotype association. Our data showed statistical power to detect association (86.83%) in this sample. Logistic regression results showed significant association between C allele and CL±P ($P = 0.00018$, OR = 0.40, and 95% CI = 0.25–0.65), as well as CC genotype and CL±P ($P = 0.00018$, OR = 0.35, and 95% CI = 0.19–0.66). So, there is a strong association between nonsyndromic CL±P and *BMP4* rs17563 polymorphism in our sample and the C allele had a protective effect against the occurrence of nonsyndromic CL±P.

1. Introduction

Nonsyndromic cleft lip with or without palate (CL±P) is a congenital defect with multifatorial transmission. It is a birth defect that occurs with a prevalence of 1 in 500 to 1 in 2500 live births in different populations, varying with geographic location, ethnic group, and socioeconomic conditions [1–3]. Populations of either American native descent or Asian descent have the highest birth prevalence [4]. In Latin America, according to the ECLAMC (Latin American Collaborative Study of Congenital Malformations), the incidence of this malformation is 1 in 850 births [5]. CL±P has a complex etiology that includes strong genetic and environmental factors.

Clinically, CL±P are classified as nonsyndromic (isolated) or syndromic based on the presence of other congenital anomalies or mental disabilities [1, 6]. Around 400 recognizable syndromes that have CL±P as part of the

phenotype are described [7, 8], however, 70% of CL±P cases are nonsyndromic. Approximately 12–25% of the genetic variations associated with nonsyndromic CL±P have been identified [1, 6]. Although genetic studies have identified a number of candidate genes and chromosomal regions associated with CL±P, findings from different studies have been inconsistent [9, 10].

Candidate genes for CL±P have been proposed as result of studies using knockout mice models. One interesting candidate gene is the Bone morphogenetic protein 4 (*BMP4*; MIM#112262). Experimental evidences have postulated that *Bmp4* is involved in the etiology of CL±P in mice. Bilateral cleft lip was presented in all knockout mice for *Bmp4* at 12 days after conception, however after 14.2 days only 22% of the embryos showed cleft lip. Moreover, Bmp signaling is also required for cell proliferation at earlier stages, in the maxillary process mesenchyme [11].

BMP4 gene, located in 14q22-q23, is a member of the BMP family and a member of the transforming growth factor-b (TGF-b) of secretory signaling molecules that play essential roles in embryonic development [12]. This gene is a well-characterized mammalian growth factor. Expression of the *Bmp4* gene occurs in a wide spectrum of normal tissue in mouse embryos, as cardiac [11], limb [13], and face tissue [11, 14].

In addition, possible association between *BMP4* gene and nonsyndromic CL±P in humans was firstly suggested in a case-control study performed with Chinese children in 2008 [15]. Authors analyzed the single-nucleotide polymorphism (SNP) rs17563 (p.Val152Ala) and found an increased risk of nonsyndromic CL±P among carriers of the C allele.

A missense and nonsense mutations were found in *BMP4* gene in a sample of patients from different genetic background (Mongolia, Philippines, United States of America, Colombia, Guatemala, and Europe) diagnosed with subepithelial, microform, and overt cleft lip. These mutations were not found in a control population [16].

Furthermore, Suazo et al. [17] reported a mutation screening analysis of *BMP4* in a sample of 150 Chilean nonsyndromic CL±P case-parent trios. Significant deviations from expected transmissions were observed for haplotypes conformed by rs1957860 and rs762642. These polymorphisms delimitate a genomic region where a promoter and an enhancer of *BMP4* are located [18]. Then, Suazo et al. [19] searched for nonsyndromic CL±P risk variants within the two *BMP4* promoters by direct sequencing in a 167 Chilean nonsyndromic CL±P cases and 336 controls. They found three novel variants considered as cleft risk factors, as they are not present in controls.

Lately, Chen et al. [20] provided further evidence of association between *BMP4* gene and nonsyndromic CL±P. They tested for possible association between markers in and around the *BMP4* gene and nonsyndromic CL±P in Asian and Maryland trios. Nominal significant evidence of linkage and association was observed for three SNPs (rs10130587, rs2738265, and rs2761887) in 221 Asian trios and for one SNP (rs762642) in 76 Maryland trios.

Brazilian population presents a heterogeneous ethnic origin which includes Native Americans, Europeans, Africans, and some degree of Asians. Relative contribution of each one of these ethnic groups is variable according to the geographic region of the country. This characteristic gives a unique and richly blended genetic and cultural background to the country [21–25].

Therefore, since Brazilian population presents a diverse genetic background, the purpose of this study was to investigate the role of the rs17563 polymorphism of *BMP4* gene in CL±P in a sample of Brazilian population.

2. Materials and Methods

2.1. Study Population. The sample consisted of 369 individuals enrolled in Craniofacial Brazil Project. All cases were evaluated by clinical geneticist using the same clinical protocol, including family history. Subjects were recruited between 2009 and 2011 from five centers of research involved in Craniofacial Brazil Project located in six cities from three different regions of Brazil (Southeast region: Campinas and São José do Rio Preto, South region: Porto Alegre and Curitiba, Northeast region: Maceió). Case group was compound of 123 individuals (62 males and 61 females) with nonsyndromic CL±P (98 cleft lip and palate and 25 cleft lip only). Control group were recruited from Southeast region by universitary e-mail included 246 phenotypically normal unrelated individuals (102 males and 144 females) without family history of oral cleft in three generations and no Japanese or Chinese ancestry. Their family history was collected by a participant researcher.

The study was approved by the local Institutional Review Boards and the National Research Ethics Committee (CEP 059/2008). All participants provided informed consent. The informed consent for patients under 18 years old was obtained from their parents.

2.2. Molecular Analysis. Genomic DNA was extracted from peripheral blood lymphocytes according to the method described by De Araujo et al. [26].

SNP genotyping was performed using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. The PCR primers were designed based on the SNP flanking sequence described in the Ensembl Genome Browser (http://www.ensembl.org/index.html).

Primer sequences for PCR reactions were 5′AGTTTG GCTGCTTCTCCC3′ (forward) and 5′AGTTTGGCTGCT TCTCCC3′ (reverse). The PCR reaction were performed in a total volume of 15 μL containing 1.5 μL KCl_2 (10X), 0.6 μL $MgCl_2$ (25 μM), 1.5 μL dNTP (2 μM), 0.35 μL of each primer *primer sense* (5pmoles), 0.5 μL $DMSO_4$, 0.2 μL Taq DNA Polimerase (5U) (New England BioLabs, Ipswich, MA, USA), and 1 μL DNA (200 ng/μL) e 9 μL H_2O. The PCR cycle conditions consisted of an initial denaturation step at 94°C for 5 min followed by 35 cycles of 1 min at 94°C, 1 min at 56°C, 1 min at 72°C, and a final elongation at 72°C for 7 min.

Adequate restriction endonuclease for SNP was selected using the Gene Runner software (Hastings Software Inc., Hastings, NY, USA; http://www.generunner.net/). Primers, restriction enzyme, and the length of digested fragments for the SNP are listed in Table 1.

Table 1: Primers, restriction enzyme, and fragment lengths for rs17563 of *BMP4* gene.

SNP	Primer	Annealing temperature	Restriction enzyme	Fragment lengths
rs17563	Forward 5′CACCATTCATTGCCCAAC3′ Reverse 5′AGTTTGGCTGCTTCTCCC3′	56°C	HphI	T Allele: 195pb + 229pb C Allele: 424pb

Table 2: The genotype and allele distribution of rs17563 in nonsyndromic CL±P patients and controls and result of logistic regression.

SNP rs17563		Controls *n* (%)	Cases *n* (%)	χ^2	*P*	OR	95% CI
Genotype	TT[1]	52 (21,1)	49 (39,8)	—	—	1.00	—
	TC	130 (52,8)	53 (43,1)	10.645	0.00110	0.43	0.26–0.71
	CC	64 (26,1)	21 (17,1)	11.217	0.00081	0.35	0.19–0.66
Allele	T[1]	234 (47,6)	151 (61,4)	—	—	1.00	—
	C	258 (52,4)	95 (38,6)	13.992	0.00018	0.40	0.25–0.65

[1] Reference factor.

The digestion reaction were performed in a total volume of 20 μL containing 15 μL PCR, 0.5 μL enzyme, and 2.0 μL buffer e 2.5 μL H_2O. The PCR products were digested overnight at 37°C with *Hph*I enzyme (New England BioLabs, Ipswich, MA, USA). PCR products were electrophoresed through 1% agarose gel in the presence of ethidium bromide and visualized by fluorescence in UV light; the digested PCR products were resolved on 12% polyacrylamide gels and visualized by a silver staining protocol.

2.3. SNP Association Analysis. Gender distribution was evaluated using Fisher's exact test in *R* statistical environment [27]. Minor allele frequency (MAF) and Hardy-Weinberg equilibrium were estimated using Haploview software [28] (http://www.broadinstitute.org/haploview). Allele and genotype association analysis were performed by logistic regression using *R* statistical environment [27]. We evaluated posthoc statistical power of our sample by GPOWER software [29], using the following parameters: logistic regression test; two-tail; OR = 1.5; statistical significance level $\alpha = 0.05$; $n = 369$.

2.4. In Silico Test. In silico tests were performed to analyze whether the substitution c.538T>C in the *BMP4* gene (rs17563) modifies the structure or function of the encoded protein. The sequence of amino acids used in the tests was obtained from NCBI database (http://www.ncbi.nlm.nih.gov/).

Three *in silico* tests were used: Grantham scale [30], PolyPhen [31] (http://genetics.bwh.harvard.edu/pph/), and SNAP [32] (http://rostlab.org/services/snap/) for the analysis of rs17563.

3. Results

The gender distribution was similar between groups (Fisher's exact test $P = 0.1198$). MAF was 0.478 and SNP rs17563 was in Hardy-Weinberg equilibrium ($P = 0.9664$) in the sample. There were significant differences in the genotypes and allele frequencies of the rs17563 between nonsyndromic CL±P and control groups.

Logistic regression revealed association between C allele and CL±P ($P = 0.00018$, OR = 0.40, and 95% CI = 0.25–0.65). Genotype logistic regression analysis showed rs17563 CC genotype was associated with decreased of CL±P susceptibility ($P = 0.00081$, OR = 0.35, and 95% CI = 0.19–0.66) (Table 2). The sample analyzed showed statistical power to detect genetic association (86.83%).

The results obtained of *in silico* tests were similar for the three. Grantham's scale showed that SNP was considered "moderately conservative" (value 64). The PolyPhen algorithm aligned sequences "wild" and "altered" to 75 homologous sequences and estimated the change as "benign" (score 0416). In addition, SNAP demonstrated that p.Val152Ala is neutral (reliability index = 3, expected accuracy = 78%).

4. Discussion

Mutant mice for *Bmp4* gene with CL±P phenotype suggest a possible role for this gene in lip and palate development [11]. Moreover, have been reported few studies of association between *BMP4* gene and CL±P in population.

Lin et al. [15] found significant differences in genotype distribution and allele polymorphism rs17563 of *BMP4* gene between 184 nonsyndromic CL±P cases and 205 controls. In a study with 1614 individuals from different countries (Mongolia, Philippines, United States of America, Colombia, Guatemala, and Europe), missense and nonsense mutations in *BMP4* gene were detected in 5 of 968 individuals with overt CL±P, 1 of 30 cases with microforms and 2 of 87 cases with orbicular oris muscle. They also found a borderline difference in the frequency of SNP rs17563 in cases compared with controls [16]. Thus, the results of this study support the hypothesis that this polymorphism might be clinically important in the genesis of CL±P.

Recently, Chen et al. [20] tested for possible association between markers in *BMP4* gene and nonsyndromic CL±P in 297 Asian and Maryland trios. Their results does not support the evidence of linkage and association for the SNP rs17563.

However, in the present study the polymorphism rs17563 in *BMP4* gene was associated with decreased susceptibility for nonsyndromic CL±P (P = 0.00081, OR = 0.35, and 95% CI = 0.19–0.66). This result was the opposite found by Lin et al. [15] and Suzuki et al. [16]. The difference could be attributed to the clinical selection of individuals, the well-defined control group, and the statistics power herein used. As well, this study obtained a strong association between nonsyndromic CL±P and *BMP4* rs17563 polymorphism and suggested that C allele had a protective role in the occurrence of nonsyndromic CL±P in the Brazilian sample.

The rs17563 polymorphism replaces the amino acid valine by alanine at position 152 of the protein. It would seem that the structure and function of the protein are not significantly affected by the substitution due to physicochemical similarities between the involved amino acids. In our study, results of the *in silico* test using Grantham's scale, PolyPhen, and SNAP were similar and showed the moderately conservative, benign, and neutral character of the rs17563 polymorphism. These results corroborate the hypothesis of a protective effect of this polymorphism.

Although cleft lip with cleft palate and cleft lip only are usually grouped into the same category, Dixon et al. [33] suggested that they could be etiologically distinct. Thus, further genetic association studies designed to examine these two conditions separately would be helpful in elucidating the role *BMP4* rs17563 in orofacial clefts.

5. Conclusions

This study found a strong association between nonsyndromic CL±P and *BMP4* rs17563 polymorphism and a possible protective effect of the C allele against nonsyndromic CL±P in a Brazilian sample. In this regard it could be speculated that rs17563 polymorphism plays different roles in oral cleft pathogenesis in specific populations. It would be interesting to replicate this study in individuals with similar and different ethnicity. As well, this association reinforces the importance of this gene as candidate for oral cleft.

Acknowledgments

The authors would like to thank the subjects and their families for cooperation in this study and Renata Barbosa for technical assistance. This study was supported by FAPESP (Grant no. 2008/10596-0) and CNPq (Grants nos. 01300.000433/2008-00, 502438/2010-0, and 136414/2009-5).

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Hindawi Publishing Corporation
Plastic Surgery International
Volume 2012, Article ID 563734, 7 pages
doi:10.1155/2012/563734

Research Article

Esthetic Composition of Smile in Individuals with Cleft Lip, Alveolus, and Palate: Visibility of the Periodontium and the Esthetics of Smile

Luis Augusto Esper,[1] Michyele Cristhiane Sbrana,[1] Mércia Jussara da Silva Cunha,[1] Guilherme Santos Moreira,[2] and Ana Lúcia Pompéia Fraga de Almeida[2,3]

[1] *Oral Rehabilitation, Bauru School of Dentistry, University of São Paulo, 17012-901 Bauru, Brazil*
[2] *Setor de Periodontia do Hospital de Reabilitação de Anomalias Craniofaciais da Universidade de São Paulo, Rua Silvio Marchione, 3-20 Vila Universitária, 17012900 Bauru, SP, Brazil*
[3] *Department of Prosthodontics at Bauru School of Dentistry, University of São Paulo, 17012-901 Bauru, SP, Brazil*

Correspondence should be addressed to Ana Lúcia Pompéia Fraga de Almeida, analmeida@usp.br

Received 3 August 2012; Accepted 19 September 2012

Academic Editor: Nivaldo Alonso

Objective. To evaluate characteristics of smile related to visibility in individuals with cleft lip, alveolus, and palate. *Design*. Cross-sectional. *Setting*. HRAC/USP, Brazil. *Patients*. Individuals with repaired complete unilateral cleft lip and palate ($n = 45$), aged 15–30 years. *Interventions*. Frontal facial photographs were obtained in natural and forced smiles ($n = 135$). Six specialists in periodontics evaluated the photographs as to the smile line, thickness, and curve of the upper lip. *Main Outcome Measures*. The cleft area was compared with the contralateral region. Results were expressed as percentages and means. The findings were compared between groups of periodontists. *Results*. Statistically significant relationship was observed in the smile line between examiners and between natural and forced smiles, regardless of the association with the cleft side. The lip was thicker at rest and thinner in the forced smile, as also evaluated by the group not experienced with cleft care. The curve of the upper lip in natural and forced smiles was considered as close to straight by both groups, regardless of the cleft. *Conclusion*. The smile in individuals with clefts was regarded as average for both cleft and noncleft sides. The thickness was characterized as average to thin, being thinner in forced smile and when analyzed by the group not experienced with cleft care. In the average, the curve of the upper lip was considered as straight. The present study elucidates some characteristics related to the smile in individuals with repaired unilateral cleft lip, alveolus, and palate.

1. Introduction and Literature Review

The facial appearance is a key element in the psychosocial development of individuals with cleft lip, alveolus, and palate, who usually present characteristics of social introversion [1, 2]. Their rehabilitation should be conducted with a view to enhance the functional and esthetics characteristics and consequently the quality of life.

The smile is one of the most important facial expressions and should be carefully analyzed as a whole before the accomplishment of dental treatment, aiming to establish the harmony between the teeth and adjacent soft tissues, achieving an esthetic and pleasant smile [3]. Evaluation of the face should be conducted together with the intraoral examination for the establishment of treatment goals that may meet the patient's expectations and reestablish the most esthetic conditions as possible [4].

The esthetic analysis of smile by the visual perception should consider it as a unique composition, in which some elements act in combination to make the smile harmonious and pleasant for the observer. Significant disruptions in the composition deviate the attention to the undesired element; alterations in the gingival component, lip shape, and filling of the gingival papillae call the attention due to their distinguished role in the composition of smile [5].

Concerning the position of the upper lip, the smile may be classified as high, average, and low [6], which is very

important in the indication of periodontal plastic surgeries and restorative procedures performed in esthetic areas. The high smile reveals the entire cervicoincisal length of maxillary anterior teeth and the adjacent gingiva; in the average smile, 75% to 100% of the maxillary anterior teeth and the interproximal gingiva are observed; in the low smile, less than 75% of the anterior teeth are visible. Higher smiles usually expose the gingival margin and restorations in esthetic areas, and any imbalance may affect the esthetics [7].

Few studies have analyzed the teeth and visibility of the soft tissue periodontium (gingival tissue) during smile. Liébert et al. [8] suggested a classification of the smile line (both in the normal and reduced periodontium) considering the visibility of the periodontium and gingival embrasures during natural and forced smiles.

The thickness of lips should also be observed, since individuals with thinner upper lip usually present greater exposure of teeth and higher smile compared to individuals with thicker lips.

Analysis of the symmetry of smile is very important, yet the curve of the upper lip should also be considered, based on the position of the mouth angle in relation to the center of the lower border of the upper lip, according to the following three categories: ascendant, descendant, or straight, being that the ascendant and straight patterns are considered more esthetic [9].

The literature on the aspect of the lip in individuals with unilateral cleft lip and palate mentions the aspect of scar contraction and muscle misalignment, causing esthetic and functional damages to these individuals after primary cheiloplasty surgeries [10]. Some studies suggest that the upper lip in these individuals differs from the normal upper lip because it presents lower elasticity and shortened height [11].

Some authors consider the average smile as more frequent in the population (ranging from 56% to 68.94%), followed by the low smile (15% to 20.48%), and high smile (10.48% to 29%). Therefore, in most cases, only the interproximal papillae are visible during smile [6, 12].

The adequate contour of the gingival tissue following the regular concave shape and filling of the interdental spaces by the interproximal papillae are extremely important in the analysis of the gingival component of smile and its esthetic aspect as a whole [13]. A harmonious gingival contour is observed in the composition of smile in which the teeth present adequate relationship with the gingival tissue, since changes in the gingival contour may disturb the harmony of smile and impair the overall facial esthetics of the individual.

This study evaluated the characteristics of smile directly related to the visibility of the periodontium during natural and forced smiles in individuals with unilateral cleft lip, alveolus, and palate, and the possible influence from the cleft on the smile, comparing the evaluation of specialists in periodontics experienced or not with cleft care.

2. Material and Methods

The sample was composed of 45 Caucasoid individuals with unilateral cleft lip, alveolus, and palate aged 15 to 30 years, of both genders, repaired as to the dental treatment, and who had received definitive discharge from the Plastic Surgery sector.

Figure 1: Photograph of patient in position, with the olives of the cephalostat placed in the cartilaginous tragus, during natural smile.

Individuals with syndromes, presenting facial paralysis or using anticonvulsant drugs upon selection were excluded from the sample.

Three photographs were obtained from the face of each individual in the selected sample, in frontal view at the following positions: at rest, during natural, and forced smiles, adding up to 135 photographs (Nikon, model Coolpix 8700 ZOOM NIKKOR ED 8.9–71.2 mm 1 : 2.8–4.2 35–280 mm, 8.0 megapixels), for evaluation of the smile line, curve and thickness of the upper lip on each smile. In order to establish the adequate standardization, the photographs were obtained in a photo studio in natural head positioning of the individual on the cephalostat, with the camera placed on a rigid support located at a distance of 97 cm from the cephalostat [14].

During the achievement of photographs, the individuals were maintained in straight position, with the feet 10 cm apart, looking at the camera ahead them with the infraorbital plane parallel to the ground. In all photographs, the olives of the cephalostat were introduced in the cartilaginous tragus keeping light contact with the skin, to prevent the individual from raising the head and neck (Figure 1).

The photographs were analyzed by two groups of examiners, composed of 6 dentists specialists in periodontics, one composed of 3 periodontists experienced with cleft care (group 1), and another composed of 3 periodontists not experienced with cleft care (group 2). The 135 photographs were individually analyzed by the examiners, at different orders of the individuals, and each side of the smile was evaluated in relation to the midline without previous knowledge on the cleft side.

Concerning the smile line, the examiners were asked to classify the smile into one of the categories proposed by Liébert et al. [8].

(I) Class 1—Very high smile line: more than 2 mm of the marginal gingiva visible or more than 2 mm apical to the cementoenamel junction visible for the reduced but healthy periodontium (Figure 2).

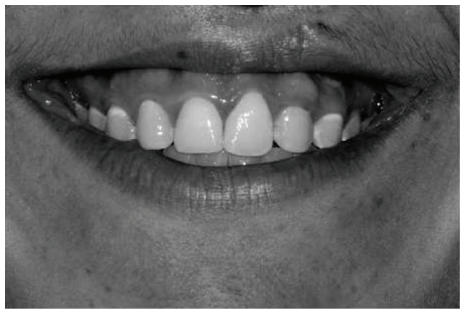

Figure 2: Very high smile.

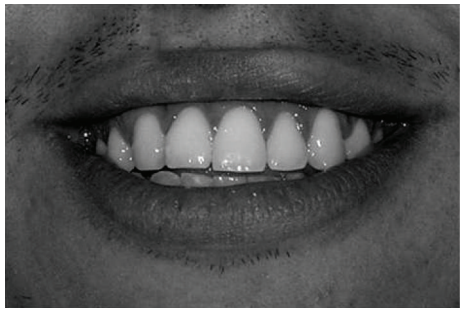

Figure 3: High smile.

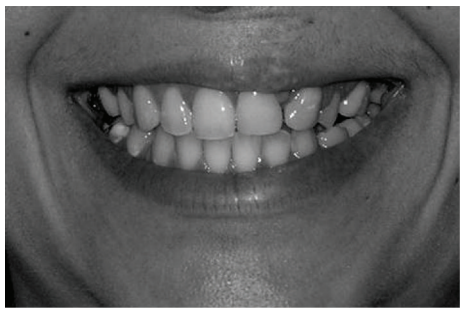

Figure 4: Average smile.

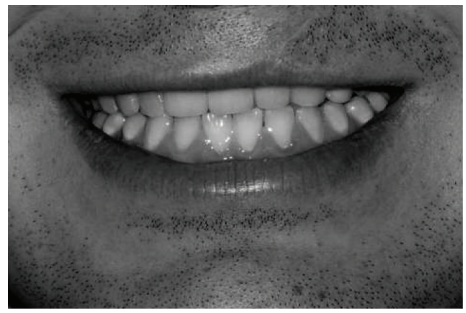

Figure 5: Low smile.

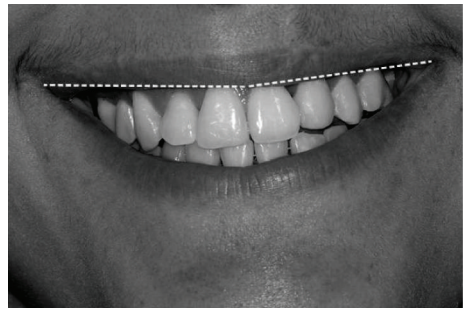

Figure 6: Straight curve of the upper lip at the patient's right side and slightly ascendant curve of the upper lip at the patient's left side.

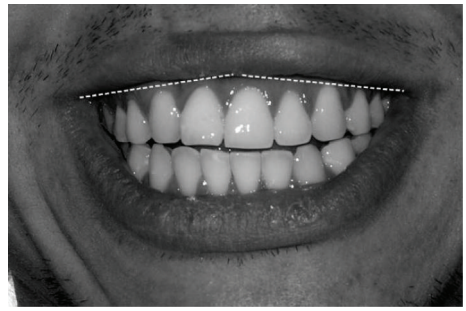

Figure 7: Descendant curve of the lip at both sides.

(II) Class 2—High smile line: between 0 and 2 mm of marginal gingiva visible or between 0 and 2 mm apical to the cementoenamel junction visible for the reduced but healthy periodontium (Figure 3).

(III) Class 3—Average smile line: only gingival embrasures visible (Figure 4).

(IV) Class 4—Low smile line: gingival embrasures and cementoenamel junction not visible (Figure 5).

All examiners classified the photographs during smile and at rest according to a score ranging from 1 to 9, as follows: 1, 2, and 3 represented unpleasant esthetics; 4, 5, and 6 indicated acceptable esthetics; 7, 8, and 9 revealed pleasant esthetics [15]. Concerning the thickness, the examiners were asked to classify the lip on each photograph as: thick (score 2), intermediate or average (score 1), or thin (score 0) (at rest and during each smile). The examiners also scored the curve of the upper lip as ascendant (score 1), straight (score 2), or descendant (score 3) during natural or forced smiles, characterized by the relationship between the lower border of the upper lip and the mouth angle (Figures 6 and 7).

The results were statistically evaluated by analysis of variance (ANOVA) for repeated measurements, considering an unstructured covariance matrix, at a significance level of 5%.

This study was approved by the Institutional Review Board of HRAC/USP.

3. Results

3.1. Smile Line. Evaluation of the classification of smile during natural smile at the noncleft side revealed predominance of average and low smile lines, accounting for 44.44% and 41.48% of cases, respectively, while the very high smile line was the least prevalent, being observed in only 2.96% of cases. At the cleft side, 55.19% of cases presented low smile line and 2.59% very high smile line (Table 1).

Table 1: Height of smile.

Height of smile	Smile types							
	Natural (*n*) NC side	Natural (%) NC side	Natural (*n*) C side	Natural (%) C side	Forced (*n*) NC side	Forced (%) NC side	Forced (*n*) C side	Forced (%) C side
Very high (class 1)	8	2.96%	7	2.59%	29	10.74%	24	8.89%
High (class 2)	30	11.11%	24	8.89%	86	31.85%	70	25.93%
Average (class 3)	120	44.44%	90	33.33%	108	40.00%	95	35.19%
Low (class 4)	112	41.48%	149	55.19%	47	17.41%	81	30.00%
Total	270	100%	270	100%	270	100%	270	100%

Table 2: Men scores in the evaluation by both groups of examiners.

Effect	Estimate	Confidence interval lower limit	Confidence interval upper limit
Group 1-Group 2*	−0.1352	−0.2238	−0.04652
Natural–Forced*	0.5759	0.3420	0.8098

*statistically significant ($P < .05$).

During forced smile, at the noncleft side, the average smile was the most prevalent, accounting for 40% of cases, and the very high smile line was the least prevalent (10.74%). At the cleft side, 35.19% were characterized as average smile line and 8.89% as very high smile line (Table 2).

Comparison of the mean scores in the evaluations by both groups of examiners, during natural smile, group 1 indicated the average smile at both cleft (3.19) and noncleft sides (3.33). Group 2 also classified the smile line as average at the cleft (3.31) and noncleft sides (3.46). During forced smile, the examiners in group considered the smile as close to the average (2.6) at the cleft and noncleft sides (2.75). Group 2 also evaluated the smile as close to the average at the cleft (2.74) and noncleft sides (2.90) (Table 3).

There was statistically significant relationship in the smile line between the groups of examiners and between the natural and forced smiles, regardless of the association with the cleft side. The scores were higher during natural smile compared to the forced smile, and group 2 assigned the highest scores ($P < .0001$) (Table 3).

Concerning the evaluation by gender, during natural smile, both groups scored the smile as close to the average and the female gender exhibited lower scores compared to the male gender, for both cleft and noncleft sides. However, there was no statistically significant difference between genders when evaluated by the two groups ($P > .05$) (Tables 4 and 5).

3.2. Thickness of Upper Lip. At rest, the thickness of the upper lip was close to the average at the cleft side when evaluated by groups 1 and 2. This was also observed at the noncleft side.

During natural and forced smiles, the lip was considered close to the average by group 1 and closer to thin by group 2, at both sides.

There were statistically significant associations between the type of smiles and the thickness of upper lip, as well as between the thickness and the groups of examiners, being the lip thicker at rest and thinner at forced smile, also when evaluated group 2 (Table 6).

3.3. Curve of the Upper Lip. The curve of the upper lip at natural and forced smiles, regardless of the cleft, was considered as close to straight by the two groups, yet statistically significant differences were found between groups ($P < .0001$). The score assigned to all cases was higher for group 1 compared to group 2, being closer to the score representing the straight smile concerning the curve of the upper lip ($P < .050$) (Table 7).

4. Discussion

Understanding the characteristics of a smile is extremely important to guide the dentist in the establishment of the principles of esthetics [9]. The smile line is one of the first characteristics that should be observed before any rehabilitative treatment in esthetic areas, since any disruption in the balance between the teeth, lips, and gingiva may become visible during speech or forced smile, impairing the esthetics [16, 17].

The characteristics of the lips are directly related to the smile, with influence of lip shape and volume on the quantity of teeth and gingival tissue exposed at rest, function, and smile [18]. Even though many individuals do not expose the gingival tissue during smile, those with a shortened upper lip or presenting lip hypermobility usually expose gingival tissue during the wide smile [19].

Concerning the smile line in the population, some authors state that the average smile is the most prevalent [6]. In the literature review on the principles to be considered in the esthetics of smile, the average smile line was also the most prevalent, followed by the high smile line (29%), being the low smile line the least prevalent (15%) [9, 12].

Even though the literature on the characteristics of smile in individuals without clefts is thorough, few studies have reported the characteristics of smile in individuals with clefts.

The findings of Liébert et al. [8] reported that, at the age of 21 to 35 years, the average smile line was more frequent during natural (50%) and forced smile (46.3%), and that a higher frequency of exposure of the periodontium was observed in the forced smile (93.3%) compared to the natural smile (64.9%) at this age range. In this study,

Table 3: Estimate of mean differences in the scores of smiles (ANOVA).

Side	Smile type	Examiner group	Mean score	Standard deviation
Cleft side	Natural	Group 1	3.19	0.76
		Group 2	3.31	0.69
	Forced	Group 1	2.60	0.87
		Group 2	2.74	0.83
Non cleft side	Natural	Group 1	3.33	0.72
		Group 2	3.46	0.70
	Forced	Group 1	2.75	0.88
		Group 2	2.90	0.86

Table 4: Mean scores in the evaluations of group 1 according to gender.

Side	Smile type	Gender	Mean score	Standard deviation
Cleft side	Natural	Male	3.41	0.61
		Female	2.89	0.77
	Forced	Male	2.70	0.94
		Female	2.47	0.76
Non cleft side	Natural	Male	3.52	0.56
		Female	3.07	0.83
	Forced	Male	2.84	0.83
		Female	2.63	0.94

there was predominance of low smile line at the cleft side and average smile line at the noncleft side during natural smile, suggesting greater visibility of the periodontium at the noncleft side, in which only the papillae are visible in the average.

Comparing the forced and natural smiles at both sides, there was greater exposure of teeth and gingival tissue, because the smile was closer to the average smile line. Classes 1 and 2 (that expose the gingival margin) at the noncleft side were increased from 14.07% to 42.89%, while at the cleft side the percentages were increased from 11.48% to 34.82%.

There are reports that the high smile line is more common among females at a ratio of 2 : 1, while the low smile line is predominant in males at a ratio of 2.5 : 1 [20]. In the present study, the females presented lower scores in both natural and forced smiles.

The assignment of higher scores by the group of specialists not experienced with cleft care may be related to the fact that they do not present detailed knowledge on the cleft condition and present a more critical view because they consider individuals without clefts as standard. We assume that individuals with clefts may present less lip mobility and consequently less exposure of teeth and gingival tissue, yet this analysis should be carefully performed.

The thickness of the upper lip was greater at rest, being decreased in the natural smile, and thinner in the forced smile. Even though the literature on individuals without clefts reports that individuals with thin upper lips tend to present high smile line and greater exposure of teeth, this relationship was not observed among individuals with clefts. A more critical evaluation may have been conducted by the examiners in group 2, who scored the thickness of the upper lip as thin in natural and forced smiles. The thickness of the lips may also be influenced by the plastic surgeries (cheiloplasty) to which these individuals are submitted [21] and did not determine a greater smile line in these individuals.

According to Dong et al. [9], the curve of the upper lip is considered as more esthetic when it is straight or slightly ascendant. In the present study, in most cases, the curve of the upper lip during smile was characterized as straight; in the comparison between evaluations, group 2 may have probably considered the curve as ascendant in more evaluations. Little clinical significance may be assigned to this difference between groups, since ascendant and straight curves are reported in the literature as being more esthetic compared to the descendant [9].

It should be highlighted that the evaluation of smile should be performed before the planning of oral rehabilitation, considering the characteristics of the lips that may interfere with the visibility of the periodontium and the esthetics of smile.

5. Conclusions

It may be concluded that the smile line in individuals with unilateral cleft lip, alveolus, and palate varied according to the type of smiles (natural or forced), being scored as average at the cleft and noncleft sides, with low prevalence of high and very high. During forced smile, both the cleft and noncleft sides were scored as average, yet with an increase in the proportion of high and very high smile lines.

The thickness of the upper lip was considered from average to thin, being the lip thinner during forced smile. The curve of the upper lip was predominantly considered as straight.

Several characteristics should be evaluated in the dentolabial analysis, combined with the facial analysis for the determination of esthetics. The group of examiners not experienced with cleft care considered the characteristics of smile in a more critical manner, because they consider individuals without clefts as standard. The cleft side may play a role in the esthetics of smile, with lower visibility of the periodontium at this area, which is extremely important in the clinical practice when planning the oral rehabilitation of these individuals.

Table 5: Mean lip thickness.

Smile type	Side	Examiner group	Mean score	Standard deviation
Rest	Cleft	Group 1	0.89	0.65
		Group 2	0.66	0.59
	Non cleft side	Group 1	0.88	0.61
		Group 2	0.73	0.59
Natural smile	Cleft	Group 1	0.65	0.50
		Group 2	0.40	0.52
	Non cleft side	Group 1	0.72	0.55
		Group 2	0.42	0.52
Forced smile	Cleft	Group 1	0.53	0.42
		Group 2	0.30	0.47
	Non cleft side	Group 1	0.53	0.48
		Group 2	0.30	0.48

Table 6: Estimate of mean differences of lip thickness (ANOVA).

Effect	type	Estimate	Standard derivation	*P*	Inferior	Superior
Type	1-2	0.2407	0.02752	<.0001*	0.1587	0.3228
Type	1–3	0.3722	0.02752	<.0001*	0.2901	0.4543
Type	2-3	0.1315	0.02752	<.0001*	0.04941	0.2136
Group	1-2	0.2309	0.02247	<.0001*	0.1639	0.2979

*statistically significant ($P < .05$).

Table 7: Mean curve of the upper lip.

Side	Smile types	Examiner group	Mean score	Standard deviation
Cleft side	Natural	Group 1	1.84	0.50
		Group 2	1.68	0.41
	Forced	Group 1	1.83	0.59
		Group 2	1.60	0.43
Non cleft side	Natural	Group 1	1.82	0.54
		Group 2	1.66	0.40
	Forced	Group 1	1.85	0.59
		Group 2	1.68	0.52

The esthetic principles are well established for individuals without clefts, yet there is lack of studies delineating these characteristics in individuals with clefts. This study meets these expectations and elucidates some characteristics related to the smile in individuals with repaired unilateral cleft lip, alveolus, and palate.

Acknowledgments

The authors would like to thank Mr. Marcel Frederico de Lima Taga for the statistical analysis of this study and the specialists who analyzed the photographs.

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Hindawi Publishing Corporation
Plastic Surgery International
Volume 2012, Article ID 259419, 5 pages
doi:10.1155/2012/259419

Clinical Study

Use of Three-Dimensional Computed Tomography to Classify Filling of Alveolar Bone Grafting

Antonio Jorge V. Forte,[1] Renato da Silva Freitas,[2] and Nivaldo Alonso[3]

[1] *Section of Plastic and Reconstructive Surgery, Yale University School of Medicine, New Haven, CT, USA*
[2] *Division of Plastic and Reconstructive Surgery, Federal University of Paraná School of Medicine, 81.050-000 Curitiba, PR, Brazil*
[3] *Division of Plastic and Reconstructive Surgery, University of São Paulo School of Medicine, São Paulo, SP, Brazil*

Correspondence should be addressed to Renato da Silva Freitas, dr.renato.freitas@gmail.com

Received 3 August 2012; Revised 11 October 2012; Accepted 11 October 2012

Academic Editor: Luis Bermudez

Several authors have proposed classifications to analyze the quality over time of secondary alveolar bone grafting. However, little discussion has been held to quantitatively measure the secondary bone grafting for correction of nasal deformity associated to cleft palate and lip. Twenty patients with unilateral alveolar cleft, who underwent secondary alveolar bone grafting, were studied with 3D computer tomography. The height between the inferior portion of the pyriform aperture and the incisal border of the unaffected side (height A) and the affected side (height B) was measured using a software Mirror. A percentage was then obtained dividing the height B by the height A and classified into grades I, II, and III if the value was greater than 67%, between 34% and 66%, or less than 33%. Age, time of followup, initial operation, and age of canine eruption were also recorded. All patients presented appropriate occlusion and function. Mean time of followup was 7 years, and mean initial age for operation was 10 years old. 16 patients were rated as grade I and 4 patients as grade II. No cases had grade III. We present a new grading system that can be used to assess the success of secondary bone grafting in patients who underwent alveolar cleft repair.

1. Introduction

After initial cleft lip and palate repair, the residual bony defect is addressed with secondary bone grafting. This approach carries the following advantages: (1) maxillary stabilization; (2) effective closure of oronasal fistulae; (3) better support for the defective alar base, reducing nasal asymmetry and impairment of facial contour; (4) faster malocclusion correction with orthodontic treatment [1, 2]. Studies showed that the gap in the dental arch was closed orthodontically in 90%, and it was proposed that the ideal time for secondary bone graft is between 9 and 11 years of age [1, 2]. Abyholm et al. were the first to suggest the use of radiographic measure of interalveolar septum height as a grading system, which consisted of type I (height approximately normal), type II (at least 3/4 of normal height), type III (less than 3/4 of normal height), and type IV (failure), which was popularized by Bergland et al. in 1986, also known as the Oslo grading system [1]. Since then, multiple scales to assess the success of secondary alveolar bone graft have been proposed [1–4]. Kindelan et al. proposed the use of a 4-point scale that measured the degree of bony filling in the cleft area when compared to its initial bone graft site, which was radiographed after orthodontic treatment and prior to surgery. The scale ranged among grade I (more than 75% bony filling), grade II (50 to 75% bony filling), grade III (less than 50% bony filling), and grade IV (no complete bony bridge). Their scale seemed to be reliable and showed moderate to substantial intraobserver agreement and fair-to-moderate interobserver agreement [4]. Hynes and Earley proposed, in 2003, a modification for the Oslo grading system. Their mean followup between grafting and radiographic assessment was 4.5 years. They performed a 3×4 cm periapical dental radiograph. The occlusal level, the basal level, and the total height of the newly acquired bone in the alveolar cleft were graded using the Oslo system, and the bone graft height was compared with the expected height of normal interdental alveolar bone

Table 1: Literature review of major publications involving description of grading system to assess secondary bone grafting.

First author	Journal	Grading system
Abyholm 1981 [1]	SJPRS	Radiographical measurement of interalveolar septum height as a grading system: type I (height approximately normal), type II (at least 3/4 of normal height), type III (less than 3/4 of normal height), and type IV (failure)
Bergland 1986 [2]	CPJ	Popularized the Oslo grading system, which is described above
Long Jr 1995 [5]	CPCJ	Studied contours of the grafted bone, using ratios. The measurements included the amount of notching of the bone graft, the length of the proximal and distal segment anatomic root, the location of the alveolar crest, and the size of the most coronal attachment of the bone bilaterally
Kindelan 1997 [4]	CPCJ	4-point scale that measured the degree of bony filling in the cleft area when compared to its initial bone graft site. Grade I (more than 75% bony filling), grade II (50 to 75% bony filling), grade III (less than 50% bony filling), and grade IV (no complete bony bridge)
Witherow 2002 [6]	CPCJ	8-point scale to describe position of bone graft after secondary alveolar grafting in relation to the cleft roots. Depending on the positions of the bony bridge across the cleft, the X-rays were classified into one of six groups (A to F). May be used with mixed dentition.
Hynes 2003 [3]	BJPS	Modification for the Oslo grading system using periapical dental X-ray. The occlusal level, the basal level, and the total height of the newly acquired bone in the alveolar cleft were graded using the Oslo system, and the bone graft height was compared with the expected height of normal interdental alveolar bone in corresponding films

Journals: BJPS: British Journal of Plastic Surgery; CPCJ: Cleft and Palate Craniofacial Journal; CPJ: Cleft Palate Journal; SJPRS: Scandinavian Journal of Plastic and Reconstructive Surgery.

in corresponding films. Long Jr et al. studied contours of the grafted bone of 46 cleft sites, with a mean follow-up time of 3.1 years. They established a series of ratios of measurements obtained directly from the radiograph and were able to detect failure of the formation of a bony bridge. The measurements included the amount of notching of the bone graft, the length of the proximal and distal segment anatomic root, the location of the alveolar crest, and the size of the most coronal attachment of the bone bilaterally [5]. Witherow et al. analyzed radiographs of 87 cleft sites using an 8-point scale to describe position of bone graft after secondary alveolar grafting in relation to the cleft roots, and their scale can also be used in mixed dentition, as long as the roots can be divided into four, and the radiograph is directed through the cleft line. In addition, depending on the positions of the bony bridge across the cleft, the X-rays were classified into one of six groups (A to F) [6]. Nightingale et al. compared three methods for radiographic analysis proposed by Bergland et al, Kindelan et al., and Witherow et al. [2, 4, 6]. They found that none of the three radiographic scales showed superior reproducibility over the other two, and that each scale seemed to be more reproducible in the mixed dentition, that neither occlusal nor periapical X-rays were found to be more useful in assessing alveolar bone grafting success [7].

At this time, the traditional scales lack valuable information of how well the graft takes in the area between the incisal border and the inferior border of the pyriform aperture, an important region that constitutes the bony base for the nasal alae (Table 1). For this reason, our goal is to propose a new grading system that can be used to assess the success of secondary bone grafting, at the level of the pyriform aperture, in patients who underwent alveolar cleft repair.

Table 2: Description of new grading system to assess secondary bone grafting.

Grade	Percentage affected/unaffected side
I	Above 67%
II	34–66%
III	33% or less

2. Method

Twenty patients with unilateral alveolar clef underwent secondary alveolar bone grafting by a single experienced craniofacial surgeon using the same technique. They were studied with three-dimensional computed tomography. The height between the inferior portion of the pyriform aperture and the incisal border of the good side (height A) and the affected side (height B) was measured using a software Mirror (Figure 1). A percentage was then obtained dividing the height B by the height A and classified in grades I, II, and III if the value was greater than 67%, between 34 and 66%, or less than 33% (Table 2). Age, time of followup, initial operation, and age of canine eruption were also recorded.

3. Results

All patients presented appropriate occlusion and function. Mean time of followup was 7 years, and mean initial age for operation was 10 years old. Sixteen patients were rated as grade I (Figure 2), and 4 patients as grade II (Figure 3). No cases had grade III.

Interestingly, for the patient with grade II and partial result on the pyriform aperture, as demonstrated in Figure 4, it was still possible to perform dental implant in the area.

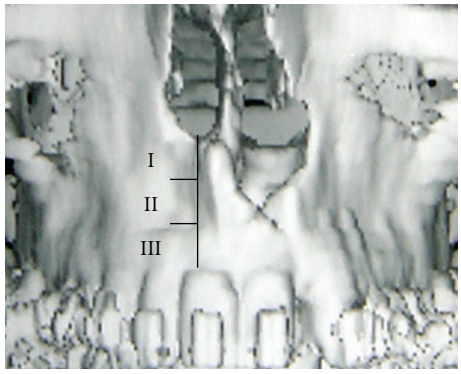
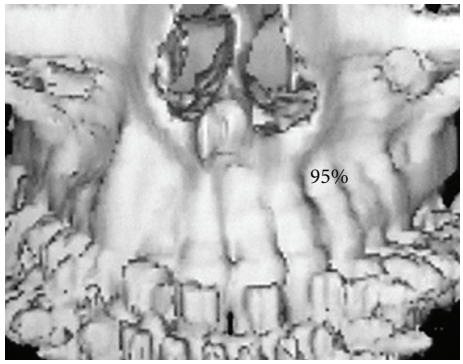


Figure 1: Classification based on pyriform aperture. Grade I: 67–100%; grade II: 34–66%; grade III: 0–33%.



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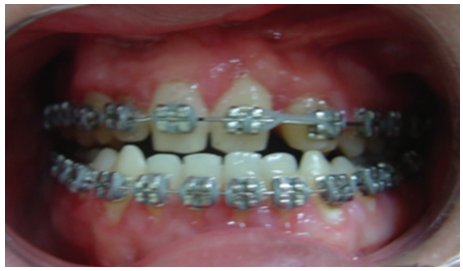

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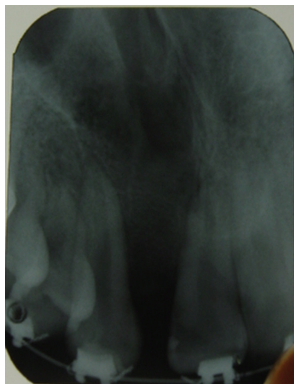
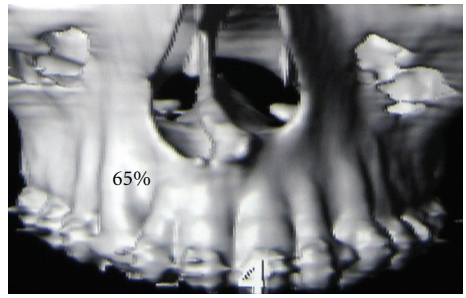


(c)

Figure 2: Patient with grade I. (a) CT scan view; (b) occlusal view; (c) dental X-ray.



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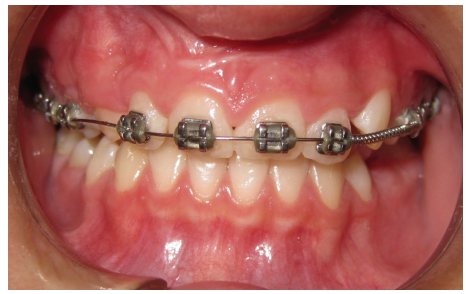

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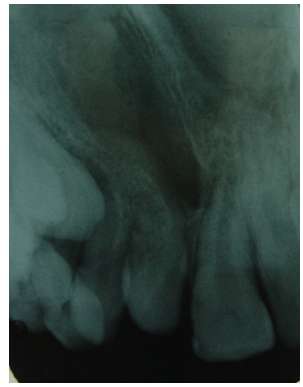


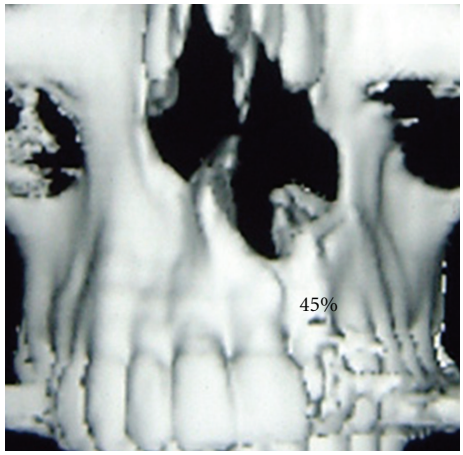
(c)

Figure 3: Patient with grade II. (a) CT scan view; (b) occlusal view; (c) dental X-ray.

In the other classifications, this case would be considered successful.

4. Discussion

The development of three-dimensional computed tomography enabled a better appreciation of volume that conventional two-dimensional plain radiographies are unable to provide. Feichtinger et al. prospectively studied twenty-four patients with complete unilateral cleft of lip and palate, measuring the cleft defect and bone bridges with three-dimensional computed tomography three years after the secondary alveolar bone graft with iliac crest. They concluded that conventional two-dimensional radiograph underestimates the amount of bone resorption in transversal dimension when compared to three-dimensional computer tomography [8]. CT offers better image quality and accuracy



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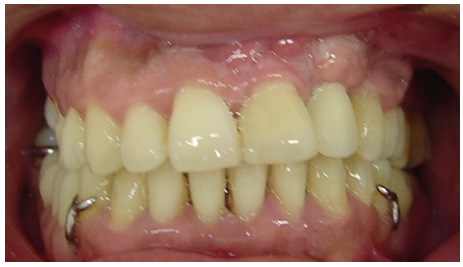

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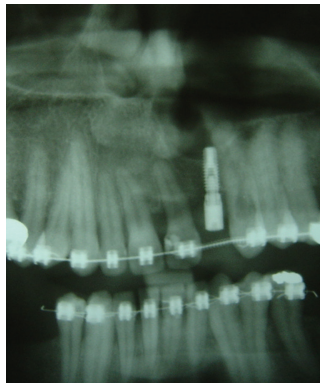

(c)

Figure 4: Patient with grade II. (a) CT scan view; (b) occlusal view; (c) panorex demonstrating dental implant.

without anatomic superimposition when compared with traditional X-rays [9].

Arctander et al. suggest that one should graft as much bone as possible to obtain adequate facial appearance. Their study examined 18 patients with complete unilateral cleft lip and palate using computed tomography 20 years after secondary cancellous bone graft from the iliac crest. They concluded that, even though all dental gaps were closed and patients were functionally intact, the amount of alveolar bone in the cleft side was less than that of the noncleft side [10]. Feichtinger et al. also showed that absence of adjacent teeth to the cleft site leads to mean bone volume loss of 95% [11].

Bergland et al. believe that nasal asymmetry, which is partially caused by skeletal malformation, can be to some degree corrected with filling in the alar base with cancellous chips [2]. The use of the current scales to measure bone graft size lacks valuable information regarding the portion of the graft that aims at correction of the pyriform aperture deformity and subsequent increase in nasal projection. Therefore, appropriate assessment of the area between the incisal border and the inferior border of the pyriform aperture is needed. Our study shows that the traditional grading systems classify as complete success bone grafts regardless of how properly they correct the nasal bone structure misshapenness. Hence, we would like to suggest the association of the traditional classifications and this new one in order to better evaluate the correction of facial bone structures affected by the cleft abnormality. Therefore, grade I would be considered success, grade II would be considered partial success, and grade III would require repeat procedure in future. In our experience, grafting success is best measured once maxillofacial growth is completed. It is also important to notice that this method is subject to limitations, such as asymmetrical pyriform aperture, dental crowding, and bilateral clefts. Also, this classification can be used even in cases of malocclusion, as long as the malocclusion is not caused by gross deformity of the dental arch around the canines.

In conclusion, we would like to propose a new grading system that can be used to assess the success of secondary bone grafting in patients who underwent alveolar cleft repair, using three-dimensional computed tomography and the inferior portion of the pyriform aperture as a bony landmark.

Conflict of Interests

The authors have no conflict of interests or disclosures.

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Hindawi Publishing Corporation
Plastic Surgery International
Volume 2012, Article ID 562892, 9 pages
doi:10.1155/2012/562892

Review Article

Protocols in Cleft Lip and Palate Treatment: Systematic Review

Pedro Ribeiro Soares de Ladeira[1] and Nivaldo Alonso[2,3]

[1] *School of Medicine, University of São Paulo, São Paulo, SP, Brazil*
[2] *Division of Burns and Plastic Surgery, Department of Surgery, School of Medicine, University of São Paulo, São Paulo, SP, Brazil*
[3] *Rua Afonso Brás, 473 cj 65 Vila Nova Conceição, 04511-000 São Paulo, SP, Brazil*

Correspondence should be addressed to Nivaldo Alonso, nivalonso@gmail.com

Received 27 June 2012; Accepted 24 September 2012

Academic Editor: Renato Da Silva Freitas

Objectives. To find clinical decisions on cleft treatment based on randomized controlled trials (RCTs). *Method*. Searches were made in PubMed, Embase, and Cochrane Library on cleft lip and/or palate. From the 170 articles found in the searches, 28 were considered adequate to guide clinical practice. *Results*. A scarce number of RCTs were found approaching cleft treatment. The experimental clinical approaches analyzed in the 28 articles were infant orthopedics, rectal acetaminophen, palatal block with bupivacaine, infraorbital nerve block with bupivacaine, osteogenesis distraction, intravenous dexamethasone sodium phosphate, and alveoloplasty with bone morphogenetic protein-2 (BMP-2). *Conclusions*. Few randomized controlled trials were found approaching cleft treatment, and fewer related to surgical repair of this deformity. So there is a need for more multicenter collaborations, mainly on surgical area, to reduce the variety of treatment modalities and to ensure that the cleft patient receives an evidence-based clinical practice.

1. Introduction

Orofacial clefts are the most prevalent craniofacial birth defects and the second most common birth anomaly, second only to clubfoot [1]. In the United States of America, it is estimated that $100,000 are spent to rehabilitate a child born with oral cleft [2].

The approach of the patient with cleft lip and palate is multidisciplinary, and the cleft team should be ideally composed by craniofacial surgeons, otolaryngologists, geneticists, anesthesiologists, speech-language pathologists, nutritionists, orthodontists, prosthodontists, and psychologists, and to be capable of treating even rare facial clefts with excellence, neurosurgeons, and ophthalmologists. In this manner, it is possible to provide long-term followup through the entire child's development and achieve all of the following treatment goals: normalized facial aesthetic, integrity of the primary and secondary palate, normal speech and hearing, airway patency, class I occlusion with normal masticatory function, good dental and periodontal health, and normal psychosocial development [3].

The most broadcast treatment modalities in the management of unilateral cleft lip and palate are listed in Table 1 (chronologic age) and Table 2 (dentofacial development).

The presented management of cleft lip and palate is not accepted exactly by all cleft centers, and there is a striking diversity of clinical practice in the area [4]. Evidence-based medicine should be the answer to the uncertainties in the treatment; however there is a paucity of high level of evidence (i.d. systematic reviews and randomized controlled trials [5]) on cleft lip and palate [6]. Therefore, many clinical decisions are made based on biased evidence, such as the decision of when to perform secondary bone graft, which is answered by many surgeons with the information of a retrospective study [7].

Aiming to find clinical decisions based on randomized controlled trials (RCTs), searches on cleft lip and/or palate were done in three main scientific databases: Cochrane Library, Embase, and PubMed [8]. Posteriorly, we selected articles that could validate or change the presented management.

Table 1: Treatment modalities in the management of unilateral cleft lip and palate which are often based on chronologic age.

Timing	Procedure
After 16 weeks of pregnancy	Cleft lip diagnosis by ultrasound images (palate is more difficult to acquire) [9]
Prenatal	Discussion with a craniofacial surgeon [10]
	Consultation with a geneticist/dysmorphologist [10]
Neonatal	If the child has cleft palate, specialized nipples and bottles are necessary to improve feeding after birth [11]
12 weeks of age	Cleft lip repair [12]
6–12 months of age	Cleft palate one-stage repair with intravelar veloplasty [13]
5 years	Secondary rhinoplasty [14]

Table 2: Treatment modalities in the management of unilateral cleft lip and palate which are often based on dentofacial development.

Timing	Procedure
Prior to cleft lip repair	Presurgical infant orthopedics [15]
Primary dentition	Orthodontic treatment for maxillary expansion [16]
Mixed dentition	Orthodontic treatment for maxillary expansion and maxillary protraction [16]
Before eruption of permanent dentition	Secondary alveolar bone graft with cancellous bone from iliac crest [10, 17]
Permanent dentition	Orthodontic treatment for dental arches alignment [18]
After fully eruption of permanent dentition, dental arches alignment, and end of the maxillofacial growth	Orthognathic surgery for maxillary advancement [16]
After orthognathic surgery	Postsurgical orthodontics for closure of residual spaces and occlusion final adjustments [19]
	Replacement of missing teeth by a prosthodontist [20]

2. Methods

On March 3, 2012, searches for RCTs were made in three databases (Cohrane Library, Embase, and PubMed) on cleft lip and/or palate. When appropriate, we used search strategies involving the MeSH descriptors and Emtree, Boolean logic operators, and free-text truncated with an asterisk.

The main descriptors used were as follows:

(i) MeSH: "cleft lip," "cleft palate";

(ii) Emtree: "cleft lip palate," "cleft lip," "cleft palate."

2.1. Cochrane Library. The searches in this database were made in "Search History," and the search strategy was assembled in "Search For."

We used MeSH descriptors when available, and free-text truncated with an asterisk. The following expression was added to the search strategy: "AND (randomized controlled trial*):ti,ab,kw." Only the results in "Cochrane Central Register of Controlled Trials" were considered.

2.2. Embase. The searches in this database were made in "Advanced Search," selecting the following items: "Map to preferred terminology (with spell check)," "Also search as free text," and "Include sub-terms/derivatives." In "Records from," we selected only "Embase."

We used Emtree descriptors and selected the item "Randomized Controlled Trial" in "Advanced Limits," option "Evidence Based Medicine."

2.3. PubMed. The searches in this database were made in "Search details."

We used MeSH descriptors when available, and free-text truncated with an asterisk. Additionally, we selected "Randomized Controlled Trial" in "Limits," option "Type of Article."

All abstracts provided by the databases in the searches were collected, resulting in a total of 170 different articles. From these abstracts, studies that clearly were not RCTs (e.g., reviews and case series) or not focused on cleft treatment were excluded. As a result, we were left with 88 papers. Posteriorly, we searched "Portal de Periódicos da CAPES" (http://www.capes.gov.br/) for the full-text articles. After meticulous reading of the studies, we verified that 53 of the 88 articles were really RCTs. Next, the approaches compared in each study were analyzed, in order to select articles in which the comparisons discussed appeared in two or more of the 53 studies. At the end of the selection, 28 articles were included for the analysis of the obtained conclusions. One paper on infant orthopedics was excluded since it emphasized a methodological fault on the study design (i.d. sample heterogeneity). The flowchart below (Figure 1) outlines the process of articles selection.

3. Results

The search results were recorded in Figure 2.

The issues discussed by the 28 selected articles were as follows:

(i) infant orthopedics: 15/28 = 53.57%;

(ii) postoperative pain relief: 5/28 = 17.86%;

(iii) management of the cleft maxillary hypoplasia: 4/28 = 14.28%;

(iv) perioperative steroids: 2/28 = 7.14%;

(v) alveoloplasty: 2/28 = 7.14%.

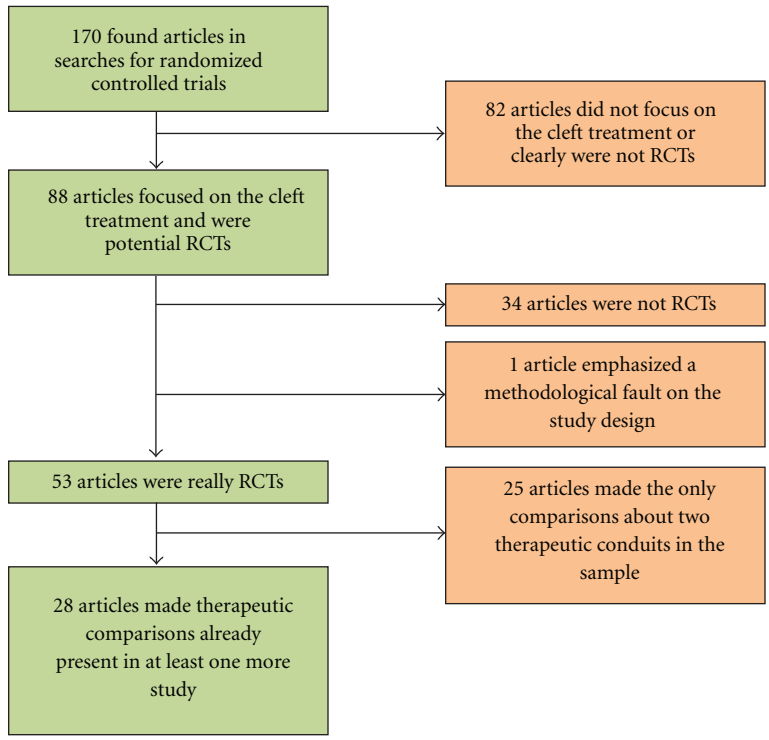

Figure 1: Flowchart outlining the selection process of the 28 articles.

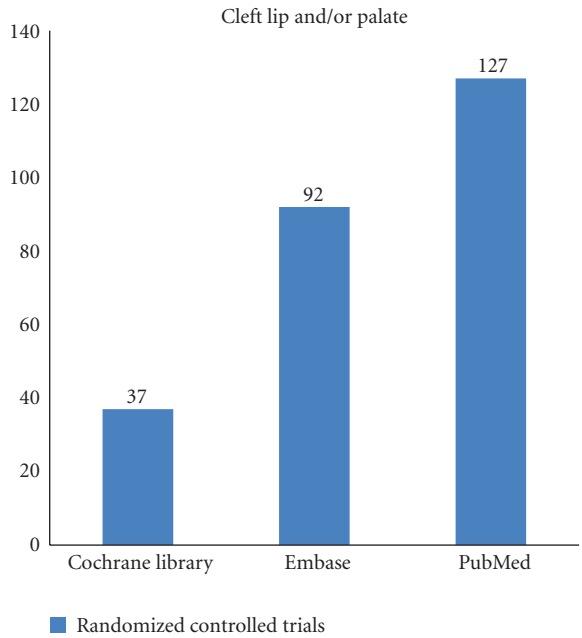

Figure 2: Results of searches on "Cleft Lip and/or Palate" in the three databases.

The conclusions of the 28 papers are presented by issue addressed in Tables 3, 4, 5, 6, and 7, where the signs "<," ">," and "=" mean, respectively, that experimental approach is "less recommended than," "more recommended than," and "equivalent to" control.

4. Discussion

RCTs and systematic reviews of these studies are considered the best levels of evidence to conduct clinical practice [49]. For this reason, we searched for RCTs that could orientate the cleft lip and/or palate treatment, which is marked by a great number of approaches [10]. To find the RCTs we used two main databases proposed by World Health Organization (i.d. PubMed and Embase) [8] and the Cochrane Library, reference of studies for evidence-based medicine practice [50]. Therefore, from the 170 articles found in the searches for RCTs, we reached 28 final studies that approached therapeutic practices on cleft patient. The issues of these 28 articles were collected together with their conclusions.

During this study, a scarce number of RCTs were found approaching cleft treatment. This fact is confirmed by the literature, which showed in 2004 that only 6% of RCTs in "Plastic and Reconstructive Surgery," "British Journal of Plastic Surgery," and "Annals of Plastic Surgery" approached cleft lip and/or palate [51]. In an article of 2007, it is possible to observe that the lack of studies with high level of evidence is a problem present in the whole plastic surgery, resulting in the following distribution of articles from the 16 leading journals in the area: case report, 80%; RCTs, 2%; and meta-analysis, <1% [52].

In the final sample of 28 articles, we verified the presence of five issues, arranged here in descending order by number of studies that addressed them: infant orthopedics, postoperative pain relief, management of the cleft maxillary hypoplasia, and perioperative steroids and alveoloplasty. The issues of the selected articles are consistent with

Table 3: Conclusions of articles that addressed "infant orthopedics".

Infant Orthopedics			
Experimental group	Conclusion	Control	Explanation for the conclusion
Patients who had infant orthopedics	=	Patients who did not have infant orthopedics	Cephalometric outcomes at ages 4 and 6 were not relevant [21]; no long-term (age 6 [22]) or short-term (18 months [23]) outcomes on facial appearance; no influence on mother's satisfaction [24]; no improvement on feeding efficiency or general body growth within the first year [25, 26]; no long-term outcomes on the maxillary arch dimensions (age 6 [27]), on deciduous dentition (age 6 [27, 28]), or on the occlusion (age 6 [28]); no short-term outcomes on the maxillary arch dimensions (18 months) [29, 30]; no long-term outcomes on language development (age 6) [31]; no improvement on the intelligibility at 2.5 years [32].
Patients who had infant orthopedics	>	Patients who did not have infant orthopedics	Acceptable cost effectiveness based on speech development at 2.5 years [33]; better speech development between 2 and 3 years [34]; higher ratings for intelligibility at 2.5 years [35].

Table 4: Conclusions of articles that addressed "postoperative pain relief".

Postoperative pain relief*			
Experimental group	Conclusion	Control	Explanation for the conclusion
Rectal Acetaminophen	>	Rectal placebo	In children who underwent palatoplasty, acetaminophen (40 mg/kg administered in the operating room at the end of surgery, and 30 mg/kg every 8 hours until 48 hours) was more effective in pain control than placebo [36].
Rectal Acetaminophen (40 mg/kg)	=	Rectal placebo	Acetaminophen and placebo were equivalents in regards to nauseas and vomits, the most frequent adverse effects [36]. Rectal acetaminophen (administered at anesthesia induction) did not result in analgesic plasma concentrations and it was not effective in pain control after palatoplasties [37].
Bilateral Palatal Block with Bupivacaine (0.5 mL of 0.25% solution at greater palatine, lesser palatine, and nasopalatine foramina)	=	Plain saline (0.5 mL at each point)	Bupivacaine and saline were effective in the palatal block and provided good parental satisfaction. Both provided better postoperative analgesia than the no block group [38].
Bilateral Infraorbital Nerve Block with Bupivacaine	>	Plain saline	In children who underwent cleft lip repair, the injection of 1.5 mL of 0.25% bupivacaine (extra-oral approach) [39] or 1–1.5 mL of 0.5% bupivacaine (intraoral approach) [40] in the area of infraorbital foramen provided safe and prolonged postoperative pain relief (at least 8 hours [39]).

* All the alveoloplasties used iliac crest bone graft.

Table 5: Conclusions of articles that addressed "management of the cleft maxillary hypoplasia".

Management of the cleft maxillary hypoplasia			
Experimental group	Conclusion	Control	Explanation for the conclusion
Osteogenesis distraction	=	Le Fort I osteotomy	No significant differences were found in development of velopharyngeal insufficiency postoperatively [41, 42] and patient morbidity (infection and occlusion disturbance) [43].
Osteogenesis distraction	>	Le Fort I osteotomy	Better skeletal stability in maintaining the maxillary advancement in the long term [43, 44].

Table 6: Conclusions of articles that addressed "perioperative steroids".

Perioperative steroids			
Experimental group	Conclusion	Control	Explanation for the conclusion
Intravenous dexamethasone sodium phosphate	>	Intravenous dextrose solution	In patients who underwent primary palatoplasty, intravenous dexamethasone sodium phosphate 0.25 mg/kg before surgery and every 8 hours (two doses after surgery) lowered the risks of postoperative airway distress and fever [45], and no adverse sequelae were verified [46].

Table 7: Conclusions of articles that addressed "alveoloplasty".

Alveoloplasty			
Experimental group	Conclusion	Control	Explanation for the conclusion
Cleft repair with BMP-2 (bone morphogenetic protein-2)	>	Iliac crest bone graft	Increased bone regeneration and lower patient morbidity: oral wound quality, pain, infection, paresthesia, and donor area wound healing [47]; infection, paresthesia, neuropathy, and donor area wound healing [48].

the importance given by the literature, because of the following: the infant orthopedics efficacy is debatable since its creation, nearly six decades ago [53, 54]; postoperative pain relief for children has become a necessary practice recently, about two decades ago, on account of several myths on pediatric pain and lack of scientific knowledge in the area [55]; the question whether to use or not osteogenesis distraction instead of the conventional Le Fort I osteotomy on cleft maxillary hypoplasia divides opinions in the scientific community [56, 57]; perioperative steroids are a common practice in craniofacial surgery; however it has several documented side effects [58, 59] and few well designed studies [46]; alveoloplasty is a highly debated intervention, especially with the advent of bone substitutes [60].

From the five issues, only two approached the surgical act, resulting in 21.43% (6/28) of the selected articles. This fact reflects the lack of RCTs on surgical procedures itself. A survey of 2003 supports this affirmation, which estimates that only 3.4% of the publications on the main surgical journals were RCTs [61].

From the final sample, 53.57% were composed by articles approaching infant orthopedics. That was due to the fact that 14 of the 15 studies on this issue were part of the Dutch Intercenter Study (Dutchcleft), a great effort to analyze the effects of presurgical infant orthopedic treatment in complete unilateral cleft lip and palate [32].

No study in the selected sample analyzed specifically a cleft patient with a syndrome or congenital abnormality. That explains the difficulty of treating orofacial clefts related to over 300 syndromes [62], and the twenty percent of all children with a cleft that have other congenital abnormality, part of a known syndrome or not [63].

From the 15 studies approaching infant orthopedics, only 3 found a benefit of this treatment, an improvement of the patient speech at nearly 2.5 years old [33–35]. However, when the language development was evaluated in the long term, at nearly 6 years old, there were no differences between experimental group and control [31]. On the other hand, all of the 14 Dutchcleft studies used only the Zurich approach to treat their patients whereas the other articles applied a passive and an active maxillary orthopedic treatment. So, in our systematic review we did not find RCTs about nasoalveolar molding therapy, a promising practice in presurgical infant orthopedics [54]. Non-RCTs studies have been appointing to the benefits of nasoalveolar molding therapy: long-term aesthetic outcomes [64–66] and better nasal symmetry [67].

Four distinct comparisons were found on postoperative pain relief: rectal acetaminophen versus placebo, bilateral nerve block with bupivacaine versus plain saline, continuous bupivacaine infusion through iliac crest catheter versus plain saline, and intravenous ketorolac with morphine versus morphine alone. There was a divergence between the conclusions of the two RCTs found on the first comparison; one appointed an effective pain control and equivalence in regards to nauseas and vomits (rectal loading dose of 40 mg/kg followed by 30 mg/kg 8 hourly) [36], whereas the other one did not observe effective pain control (single prophylactic dose of 40 mg/kg) [37], emphasizing the fact that both analyzed palatoplasties. These results are in concordance with the standard clinical practice that states a postoperative rectal loading dose (30–40 mg/kg) followed by regular maintenance doses (20 mg/kg 6 hourly or 30 mg/kg 8 hourly) [68–70]. Besides the difficulties associated with rectal administration (e.g., delayed and erratic absorption), an RCT done in patients undergoing craniosynostosis repair verified a higher efficacy than oral administration [68].

On the comparison of bilateral nerve block with bupivacaine versus plain saline, there were one article approaching palatal block [38] and two approaching infraorbital nerve block [39, 40]. Prabhu et al. proved with a randomized, double blind, prospective clinical trial that bilateral infraorbital nerve block with bupivacaine is more effective than periincisional infiltration in postoperative pain relief after cleft lip repair [71], and it became a standard clinical practice in cleft care [72, 73]. However, the scientific literature does not clarify which volume should be used to make this block,

so there is evidence defending 0.5 mL of 0.5% bupivacaine in each side [74], 3 mL of 0.5% bupivacaine [75], and 0.5–1 ml of 0.5% bupivacaine [73]. Since very small doses of bupivacaine have serious side effects, such as cardiac dysrhythmias and neurotoxicity [76], more studies need to be done to standardize this technique. In regards to the article that analyzed palatal block, there were no differences between experimental group (0.5 mL of 0.25% bupivacaine at each point) and control (0.5 mL of plain saline at each point), with both resulting in postoperative analgesia. Besides the extensive use of palatal block [77], including in Smile Train [78], the results of the selected RCT led us to conclude that the analgesic effects are results from the liquid pressure, not from the anesthetic solution. Such results appeared in a similar manner with Van Gheluwe and Walton, explaining the analgesic effect of intrapulpal saline injection with the pressure that it exerts [79].

In regards to the studies that addressed the management of cleft maxillary hypoplasia [41–44] there was only one comparison, distraction osteogenesis versus Le Fort I osteotomy. There were no divergences in the studies conclusions, leading to a possible superiority of distraction osteogenesis over the conventional technique. However, the scientific literature induces us to conclude that the choice between distraction osteogenesis and conventional orthognathic surgery is dependent on advancement length. Baek et al. published a controlled clinical trial comparing these techniques in which they realize this fact [80]. Scolozzi, in a review of 80 scientific articles, concludes that distraction osteogenesis should be applied for displacements larger than 6 mm in cleft patients [81]. On the other hand, as a meta-analysis on the issue concludes, there is little high-level evidence to safely guide the surgeon in this decision [82].

On the issue "perioperative steroids," both selected articles [45, 46] conclude in favor of intravenous dexamethasone sodium phosphate perioperative administration in palatoplasties. Since there is a substantial risk of postoperative airway obstruction after palatoplasties (one of the most common postoperative problems) [83] and other craniofacial surgeries [84], perioperative steroids became a standard practice in many craniofacial centers [45, 84, 85]. However these two RCTs did not report relevant side effects; the samples were too small (45 [45] and 20 [46] patients) to analyze, without a high bias, steroids complications, such as psychosis [58, 59] and hypertension [86].

The use of bone substitutes is one way to avoid the morbidities associated with performance of autogenous bone graft in alveoloplasties, and one of the most promising is the bone morphogenetic protein-2 (BMP-2) [87]. The two RCTs found on alveoloplasties [47, 48] concluded that BMP-2 is superior to the conventional technique, with an increase in bone regeneration and reduced patient morbidity. However, since the samples used were small (16 [48] and 21 [47] patients), we still can not assure its safety in relation to theoretical risks: non-small-cell lung cancer; pancreatic and oral cancer; heterotopic ossification and undesirable bone growth, even in the malignant form [87]. The lack of larger studies has been highlighted by a Cochrane review on the issue [60].

This systematic review found RCTs in favor of the following: rectal acetaminophen 40 mg/kg administered in the operating room at the end of the palatoplasty, and 30 mg/kg every 8 hours until 48 hours; bilateral infraorbital nerve block with bupivacaine in children who will undergo cleft lip repair; osteogenesis distraction in the cleft maxillary hypoplasia treatment; intravenous dexamethasone sodium phosphate 0.25 mg/kg before palatoplasty and every 8 hours (two doses after surgery); alveoloplasty with BMP-2. However, a far from ideal number of non-Dutchcleft RCTs (14 articles) proved to be of high quality, which can be verified by the following parameters [88]: 57.14% (8/14) explicit the randomization mode; 21.43% (3/14) report allocation concealment; 21.43% (3/14) made clear how they calculated the sample size. In regards to Dutchcleft studies, all of them explicit in some way the randomization mode and allocation concealment. These high-quality RCTs proved that infant orthopedics with Zurich approach is not recommended to the cleft patient. More collaborations such as Dutchcleft need to be done to safely guide cleft teams around the world, and to decrease the huge variety of practices in this area in the long term.

5. Conclusion

Few randomized controlled trials were found approaching cleft treatment, and fewer related to surgical repair of this deformity. From the found articles, only a small percentage reported the study with known quality parameters. However, one consistent conclusion could be verified due to fourteen Ducthcleft RCTs; there is no high-level evidence supporting the use of infant orthopedics by Zurich approach. So there is a need for more multicenter collaborations, mainly on surgical area, to reduce the variety of treatment modalities and to ensure that the cleft patient receives an evidence-based clinical practice.

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Hindawi Publishing Corporation
Plastic Surgery International
Volume 2012, Article ID 782821, 11 pages
doi:10.1155/2012/782821

Review Article

Genetics and Management of the Patient with Orofacial Cleft

Luciano Abreu Brito, Joanna Goes Castro Meira, Gerson Shigeru Kobayashi, and Maria Rita Passos-Bueno

Human Genome Research Center, Institute of Biosciences, University of São Paulo, 05508-090 São Paulo, SP, Brazil

Correspondence should be addressed to Maria Rita Passos-Bueno, passos@ib.usp.br

Received 4 August 2012; Accepted 1 October 2012

Academic Editor: Renato Da Silva Freitas

Cleft lip or palate (CL/P) is a common facial defect present in 1 : 700 live births and results in substantial burden to patients. There are more than 500 CL/P syndromes described, the causes of which may be single-gene mutations, chromosomopathies, and exposure to teratogens. Part of the most prevalent syndromic CL/P has known etiology. Nonsyndromic CL/P, on the other hand, is a complex disorder, whose etiology is still poorly understood. Recent genome-wide association studies have contributed to the elucidation of the genetic causes, by raising reproducible susceptibility genetic variants; their etiopathogenic roles, however, are difficult to predict, as in the case of the chromosomal region 8q24, the most corroborated locus predisposing to nonsyndromic CL/P. Knowing the genetic causes of CL/P will directly impact the genetic counseling, by estimating precise recurrence risks, and the patient management, since the patient, followup may be partially influenced by their genetic background. This paper focuses on the genetic causes of important syndromic CL/P forms (van der Woude syndrome, 22q11 deletion syndrome, and Robin sequence-associated syndromes) and depicts the recent findings in nonsyndromic CL/P research, addressing issues in the conduct of the geneticist.

1. Introduction

Cleft lip or palate (CL/P) is a common human congenital defect promptly recognized at birth. Despite the variability driven by socioeconomic status and ethnic background,the worldwide prevalence of CL/P is often cited as 1 : 700 live births; nevertheless, the different methods of ascertainment may lead to fluctuations in the prevalence rates [1]. Essentially, CL/P results from failure of fusion of the maxillary processes or palatal shelves, which occur between the 4th and 12th weeks of embryogenesis (as reviewed by Mossey et al. [2]). Cellular processes of proliferation, differentiation, and apoptosis, which are essential for appropriate lip and palate morphogenesis, are regulated by complex molecular signaling pathways; therefore, genetic and environmental factors that dysregulate those pathways are subject of intensive research as it is expected that their understanding will accelerate the development of preventive measures. Maternal alcohol intake or exposure to tobacco and several chemicals, such as retinoic acid and folate antagonists (e.g., valproic acid), among others, has been shown to be teratogenic, thus representing risk factors to embryos during the first trimester of pregnancy (reviewed by Bender [3] and by Dixon et al. [4]). Despite their etiological importance as environmental predisposition factors to CL/P,we will focus in this paper on the genetic causes of CL/P.

Within CL/P, cleft lip with or without cleft palate (CL ± P) is considered a distinct entity from cleft palate only (CP), based on the different embryonic origin when palate development occurs, that is, the closure of the palatal shelves occurs between 8th and 12th weeks of the human gestation [5] while lip formation is concluded at the 7th week [6]. Accordingly, this subdivision is clearly supported by epidemiological findings [4]; however, in some syndromic forms of CL/P, both entities may segregate in the same family [7–10]. CL/P can occur as the only malformation (nonsyndromic (NS), representing 70% of CL ± P cases and 50% of CP cases) or associated with other clinical features (syndromic, 30% of CL ± P and 50% of CP cases; [11]), a classification that we will consider in the next topics.

The majority of children affected by CL/P require a lasting and costly multidisciplinary treatment for complete rehabilitation. The precise clinical diagnosis of CL/P patients, which is not always simple, is crucial for an accurate genetic counseling, patient management, and definition of surgical strategies, as reviewed below.

2. Genetic Factors

2.1. Syndromic CL/P. Mutations in single genes and chromosomal abnormalities are the most common mechanisms underlying syndromic CL/P. The Online Mendelian Inheritance in Man database (OMIM) describes more than 500 syndromes with CL/P as part of the phenotype. Furthermore, several cases of trisomy of chromosomes 13, 18, and 21 associated with CL/P were described, as well as partial deletions and duplications of other chromosomes [12]. These findings suggest that there may be several genomic regions containing loci which, in excess or in insufficiency, may lead to CL/P.

In this paper, we highlight van der Woude syndrome (VWS) and Velocardiofacial syndrome (VCFS), due to their high frequency among CL/P cases, together with Robin sequence (RS), a clinical feature that may be associated with other syndromes, including VCFS.

2.1.1. Van der Woude Syndrome (VWS). Van der Woude syndrome (VWS; OMIM 119300), the most frequent form of syndromic CL/P, accounts for 2% of all CL/P cases [13]. VWS is a single gene disorder with an autosomal dominant pattern of inheritance. Its penetrance is high (89–99%; [14]) and it is clinically characterized mainly by CL ± P or CP, fistulae on the lower lip, and hypodontia [15]. There is a wide spectrum of clinical variability, in which patients lacking fistulae are indistinguishable from individuals affected by nonsyndromic forms. Kondo et al. [16] showed that missense and nonsense mutations in interferon regulatory factor 6 (IRF6) were responsible for the majority of VWS cases. Although the pathogenic mutations may occur in any region of the gene, about 80% of them have been found in exons 3, 4, 7, and 9 (reviewed by Durda et al. [17]). It is predicted that the pathogenic mutations leading to SVW cause loss of function of the protein encoded by the gene [16].

Although we can estimate that the recurrence risk for future children of affected patients is 50%, it is still not possible to predict the severity of the disease in a fetus with a pathogenic mutation in *IRF6*, as there is no clear genotype-phenotype correlation. The pathogenic mutations in *IRF6* seem to play its major harmful effect during embryonic development, indicating that *IRF6* plays a critical functional role in craniofacial development. However, *IRF6* also seems to act after birth, as children with VWS have an increased frequency of wound complications after surgical cleft repair than children with NS CL ± P [18].

The spectrum of clinical variability of VWS has recently been expanded by the demonstration that mutations in *IRF6* are also causative of the Popliteal Pterygium Syndrome (PPS; OMIM 119500), an allelic, autosomal dominant disorder that presents, besides the facial anomalies typical of VWS, bilateral popliteal webs, syndactyly, and genital anomalies [17]. Most of the pathogenic mutations causative of PPS are located in exon 4 of the *IRF6* gene [16]. There are a strong genotype-phenotype correlation associated with VWS and PPS, but how the different mutations lead to PPS or VWS is still uncertain [19].

Since most of the VWS and PPS cases can be diagnosed by clinical evaluation, the necessity of genetic testing should be evaluated in each case.

2.1.2. Velocardiofacial Syndrome or 22q11.2 Deletion Syndrome. Velocardiofacial syndrome (VCFS; OMIM 192430) is an autosomal dominant disorder mainly characterized by the presence of cardiac anomalies (conotruncal defects, predominantly tetralogy of Fallot and conoventricular septal defects), CP or submucosal CP, velopharyngeal incompetence, facial dysmorphia, thymic hypoplasia, and learning disabilities [20]. The major known mutational mechanism causative of VCFS is a submicroscopic deletion at 22q11.2, usually spanning 1.5 Mb to 3 Mb. The spectrum of clinical variability is very wide, with the mildest cases presenting only two clinical signs of the syndrome in contrast to the full blown phenotype of the syndrome. Patients with DiGeorge syndrome (DGS; OMIM 188400), a condition with a great clinical overlap with VCFS, is also caused by deletions at 22q11.2, and thus represents a single entity; the term "22q11.2 deletion syndrome" is now commonly used to refer to all these cases. The clinical diagnosis for this group of patients is usually difficult, and genetic tests are often recommended in the presence of at least two clinical features of the syndrome, such as velopharingeal insufficiency and cardiac defects [21]. Moreover, patients may develop late onset psychosis or behavior disturbances, such as schizophrenia or bipolar disorders [22]. The severity of the syndrome is not dependent on the size of the deletion [23, 24] and several studies have pointed loss of one copy of *TBX1* as the major etiological agent within 22q11.2 leading to the phenotypic alterations [25, 26]. However, other environmental or genomic factors may also influence phenotype manifestation. Therefore, identification of 22q11.2 deletion patients is important for genetic counseling purposes as well as for discussing prognosis and surgical intervention, as the choice of surgical procedure depends upon the presence of abnormal and misplaced internal carotid arteries, which is relatively common in these patients (reviewed by Saman and Tatum [27]) The recurrence risk is high (50%) for carriers of the 22q11 deletion and it is still not possible to predict the severity of the disorder in fetuses with this alteration.

2.1.3. Robin Sequence and Associated Syndromes. Robin sequence (RS), also referred as Pierre Robin sequence, is characterized by the presence of micro or retrognathia, respiratory distress, and glossoptosis, with or without CP [28, 29]. It is also associated with high morbidity secondary to a compromised airway, feeding difficulties, and speech problems. It can occur isolatedly (called NS RS), but most of the time it is associated with a genetic syndrome [30].

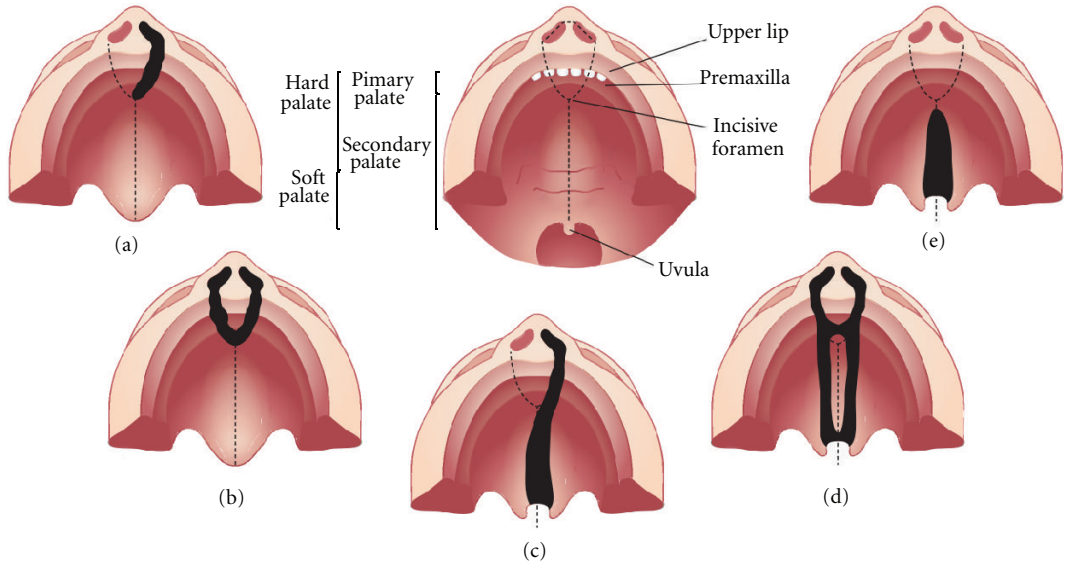

Figure 1: Representation of the most common types of cleft affecting the palate. (a) Unilateral cleft lip with alveolar involvement; (b) bilateral cleft lip with alveolar involvement; (c) unilateral cleft lip associated with cleft palate; (d) bilateral cleft lip and palate; (e) cleft palate only.

Therefore, RS must not be regarded as a definitive diagnosis, and defining the presence of an associated syndrome has implications for future case management and determination of recurrence risks [30]. The most common syndromes associated with RS are Stickler syndrome and VCFS, both with an autosomal dominant pattern of inheritance and with several additional clinical complications that are not present in NS RS.

The pathogenesis of NS RS is heterogeneous and not well defined. NS RS has been considered the result of intrauterine fetal constraint where extrinsic physical forces (e.g., oligohydramnios, breech position, or abnormal uterine anatomy) inhibit normal mandibular growth. Micrognathia in early fetal development may in turn cause the tongue to remain between the palatal shelves, thus interfering with palate closure [29, 31]. However, this mechanism has been challenged by the identification of several genetic alterations associated with RS, including chromosomal deletions such as 2q24.1-33.3, 4q32-qter, 11q21-23.1, and 17q21-24.3 [32] and microchromosomal deletions involving regulatory elements surrounding *SOX9* [33]. NS RS usually occurs as the unique case in the family and the recurrence risk for future pregnancies of the couple with one affected child is low [34].

2.2. Nonsyndromic CL ± P (NS CL ± P). NS CL ± P includes a wide spectrum of clinical variability, from a simple unilateral lip scar to bilateral cleft lip and cleft of the palate, as partly represented in Figure 1. Different epidemiological evidence, as familial recurrence, observed in 20–30% of the cases [35, 36] and twin concordance rates (40–60% for monozygotic and 3–5% for dizygotic; [37]), suggest an important genetic component in NS CL ± P etiology. High heritability rates have been estimated in several studies (reaching 84% in Europe [38],78% in China [39] and 74% in South America [40]; in Brazil, our group found estimates ranging from 45% to as high as 85%, depending on the population ascertained [36]). The most accepted genetic model for NS CL ± P is the multifactorial, in which genetic and environmental factors play a role in phenotype determination.

Researchers have conducted different approaches to seek for genetic NS CL ± P susceptibility *loci*. Linkage analysis and association studiesof candidate genes were, initially, the most popular approaches, and the first gene suggested to be associated with NS CL ± P was transforming growth factor alpha (TGFα), by Ardinger et al. [41]. Thereafter, linkage analyses raised some other genomic regions as possible susceptibility factors, as 6p24-23 [42] (recently studied by Scapoli et al. [43]), 4q21 [44], 19q13 [45], and 13q33 [46]. Additional studies, however, faced a lack of reproducibility of the emerged genomic *loci*, as reviewed in detail by others [4, 47], suggesting the existence of a strong genetic heterogeneity underlying the predisposition to the disease (i.e., different causal *loci* might be acting in the different studied families).

Candidate genes analyzed through association studies emerged not only from initial findings by linkage analysis, but also from: (1) the gene role in lip or palate embryogenesis, as suggested by animal model studies (e.g., *TGFα*, in the pioneer study by Ardinger et al. [41] and *MSX1* [48]); (2) gene role in the metabolism of putative environmental risk factors (e.g, *MTHFR*, involved in folate metabolism and firstly tested by Tolarova et al. [49], and *RARα*, which encodes a nuclear retinoic acid receptor, tested initially by Chenevix-Trench et al. [50]); (3) from the identification of chromosomal anomalies in patients (as *SUMO1* [51]), and (4) from their role in syndromic CL/P, such as van der Woude (*IRF6*, its causal gene, was firstly associated with NS CL ± P by Zucchero et al. [52]), Cleft Lip/Palate Ectodermal Dysplasia Syndrome (caused by mutations in *PVRL1* [53], firstly associated with NS CL ± P by Sözen et al. [54]) and EEC and AEC (both caused by mutations in *TP63* [55], associated with NS CL ± P by Leoyklang et al. [56]), among others.

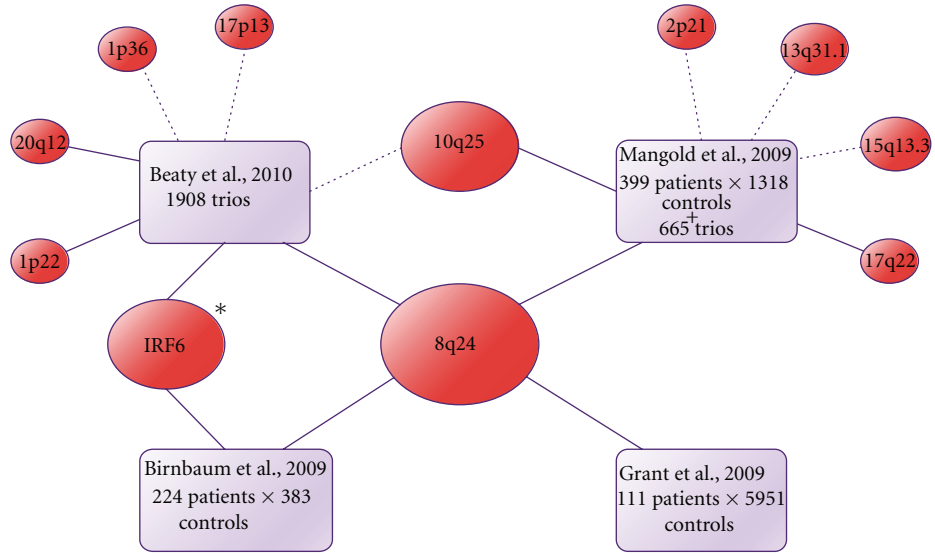

Figure 2: Diagram depicting the main lociassociated with NS CL ± P in the GWAS performed by Birnbaum et al. [72], Grant et al. [73], Mangold et al. [65], and Beaty et al. [64], which mixed case-control and trios (probands and their parents) approaches. Dotted lines represent borderline associations, whereas solid lines represent significant associations at the commonly accepted GWAS threshold ($P < 10E - 7$). (*) Mangold et al. [65] found evidence of interaction between IRF6 and GREM1, a gene located in 15q13.3 region, in NS CL ± P susceptibility.

Among all *loci* that arose through linkage and candidate gene association studies, the *IRF6* gene was the only *locus* to be consistently associated with NS CL ± P, as first shown by Zucchero et al. [52]. Rahimov et al. [57] identified a common nucleotide variant (namely rs642961) in an *IRF6* regulatory sequence conferring risk to NS CL ± P that could potentially dysregulate *IRF6* transcription levels and consequently dysregulate other signaling pathways. The variant rs642961 has been repeatedly associated in other studies in Europe [58, 59], Latin America [60, 61], and Asia, [62, 63]. Nevertheless, the role of rs641961 in embryonic development and how it predisposes to NS CL±P remains to be elucidated.

With the advent of high-throughput genotyping technologies, which allowed for a deeper investigation at the genomic level without prior hypothesis of candidate regions to be tested, the landscape changed substantially. Genome-wide association studies (GWASs) came up from these advances, providing remarkable contribution to the understanding of NS CL ± P etiology. Four large GWASs were performed on NS CL ± P so far, and their main findings are summarized in Figure 2. Markers within a gene desert in the chromosomal region 8q24 were unequivocally implicated in NS CL ± P susceptibility, since they shared similar results. A second promising locus that emerged from these studies is the region 10q25. Other minor association studies have replicated association for both 8q24 and 10q25 [59, 60, 66–69]. Therefore, the *IRF6* gene and the chromosomal regions 8q24 and 10q25 are, to date, the most corroborated *loci* implicated in NS CL ± P. However, contrary to *IRF6* association, for which a punctual susceptibility variant has been identified, finding the functional causative mutations and the molecular pathogenesis beneath the associations observed for 8q24 and 10q25 regions remains a challenge; Table 1 summarizes the main candidate genes proposed by these studies. Recently, a GWAS performed in 34 consanguineous families from a Colombian isolated population suggested that the *loci* 11p12, 11q25 and 8p23.2 may harbor recessive genes underlying NS CL ± P etiology [70]; these results, however, will need further replication. A recent linkage analysis applying high-throughput genotyping also suggested a role for the region of FOXE1 (9q22-q33) in NS CL ± P susceptibility [71]; nevertheless, this locus lacks reproducibility in other studies.

The difficulty of replication of the investigated *loci* may be a consequence of the genetic heterogeneity in NS CL ± P, that is, susceptibility variants differing from patient to patient; also, susceptibility variants may be different across unrelated populations. Beaty et al. [64] highlighted a stronger evidence for 8q24 in Europeans compared to Asians. Ethnic heterogeneity was also observed by Blanton et al. [67]; we have observed differences even across the Brazilian country populations [69], and a study with a Kenyan population failed in finding this association [74]. On the other hand, the Asians in the study reported by Beaty et al. [64] presented the most solid association for 20q12 and 1p22, compared to the European sample. It is possible that such differences may be a consequence of low statistical power in the subsample of a given ethnicity, as observed by Murray et al. [75]. Anyhow, these findings stress the value of testing non-European populations in order to identify the risk factors of NS clefting for each population, and to better understand the genetic architecture of the disease.

Regardless of the success of GWAS in identifying new susceptibility *loci*, those consistently implicated in NS CL ± P fail in explaining the complete genetic contribution proposed. This "failure" has been a common observation in many other traits, such as type 2 diabetes, height, and early onset myocardial infarction [76], and there is a current debate on where the remaining genetic causes

Table 1: Main GWAS hits and genes possibly involved according to the authors.

Region	Possible gene involved	Function*
8q24	No know gene	
10q25	VAX1 [64]	Transcription factor, apparently involved in the development of the anterior ventral forebrain.
1p22	ABCA4 [64]	Transmembrane protein expressed in retinal photoreceptors. Mutations are involved with retinopathies.
17q22	NOG [65]	Secreted protein; binds and inactivates TGFβ[1] proteins. Mutations are involved with bony fusion malformations, mainly in head and hands.
20q12	MAFB [64]	Transcription factor, acts in the differentiation and regulation of hematopoietic cell lineages. Mutations cause multicentric carpotarsal osteolysis syndrome.
1p36	PAX7 [64]	Transcription factor. Plays a role during neural crest development. Defects cause a form of rhabdomyosarcoma.
2p21	THADA [65]	Unclear function. Defects are related with thyroid tumors.
13q31.1	SPRY2 [65]	Citoplasm protein, colocalized with cytoskeleton proteins. Possibly acts as antagonist of FGF[2].
15q13.1	FMN1 [65]	Peripheral membrane protein plays a role in cell-cell adhesion.
	GREM1 [65]	Secreted protein; BMP[3] antagonist, expressed in fetal brain, small intestine, and colon.
17p13	NTN1 [64]	Extracellular matrix protein, mediates axon outgrowth and guidance. It may regulate diverse cancer tumorigenesis.

*According to OMIM database.
[1]Transforming growth factor beta.
[2]Fibroblast growth factor.
[3]Bone morphogenetic protein.

could be hidden. One hypothesis is that gene-gene and gene-environment interactions may represent a substantial additional risk; however, their evaluation is still difficult with the current research tools. It is also possible that a combination of rare mutations per individual can be responsible for a large proportion of cases. New technologies to perform exome and genome sequencing are promising approaches to bridge this gap, and have potential to bring out new susceptibility variants. The use of other approaches, such as expression analysis, can also bring new insights into the causative pathways behind this malformation. In this respect, we have recently shown that dental pulp stem cells from NS CL ± P patients exhibit dysregulation of a set of genes involved in extracellular matrix remodeling, an important biological process for lip and palate morphogenesis [77].

2.3. Nonsyndromic CPO (NS CPO). Cleft palate only is also a common malformation with a wide variability spectrum, comprising mildest phenotypes involving only uvula bifida to more severe cases, the majority of which include cleft of the soft and hard palates (Figure 1). The higher recurrence risk observed for close relatives compared to the general population [78, 79], and the higher concordance in monozygotic compared to dizygotic twins [80, 81] evidence the presence of genetic components in the etiology of NS CPO. Akin to NS CL ± P, NS CPO is believed to result from a combination of genetic and environmental factors [78]. However, in contrast to NS CL ± P, only a few studies on the genetic basis of NS CPO have been conducted, probably because of its lower prevalence and difficulty of ascertainment.

A first linkage genome scan to find NS CPO susceptibility loci was performed in 24 Finnish families by Koillinen et al. [82], which suggested 1p32, 2p24-25, and 12q21 as candidate regions; all of them, however, reached only borderline significance. Recently, Ghassibe-Sabbagh et al. [83] demonstrated the involvement of the Fas-associated factor-1 gene (*FAF1*) with NS CPO and provided insights into the gene's function in facial chondrogenic development, using a combination of an association study in a large multiethnic sample, gene expression analysis and animal model. Beaty et al., [84] performed a GWAS in 550 trios (proband and parents) of mixed ancestries and, although they did not find significant results by testing the associations of genetic markers with phenotype, they obtained interesting results when they performed the association tests conditioning on environmental variables (maternal smoking, alcohol consumption, and vitamin supplementation): association of TBK1, ZNF236, MLLT3, SMC2, and BAALC was suggested. None of the *loci* raised in these studies were in common with those emerged for NS CL ± P. Similarly, in search of a possible common etiology between NS CL ± P and NS CPO, many researchers tested the involvement of NS CL ± P candidate loci with NS CPO, but negative or conflicting results were reported for TGFα, TGFβ3, MSX1, SUMO1, BCL3, IRF6 and 8q24 [57, 72, 85–90].

A number of studies in mice has shown that defects in several genes lead to cleft palate, often accompanied by a set of other defects, as reviewed by Cobourne [91].

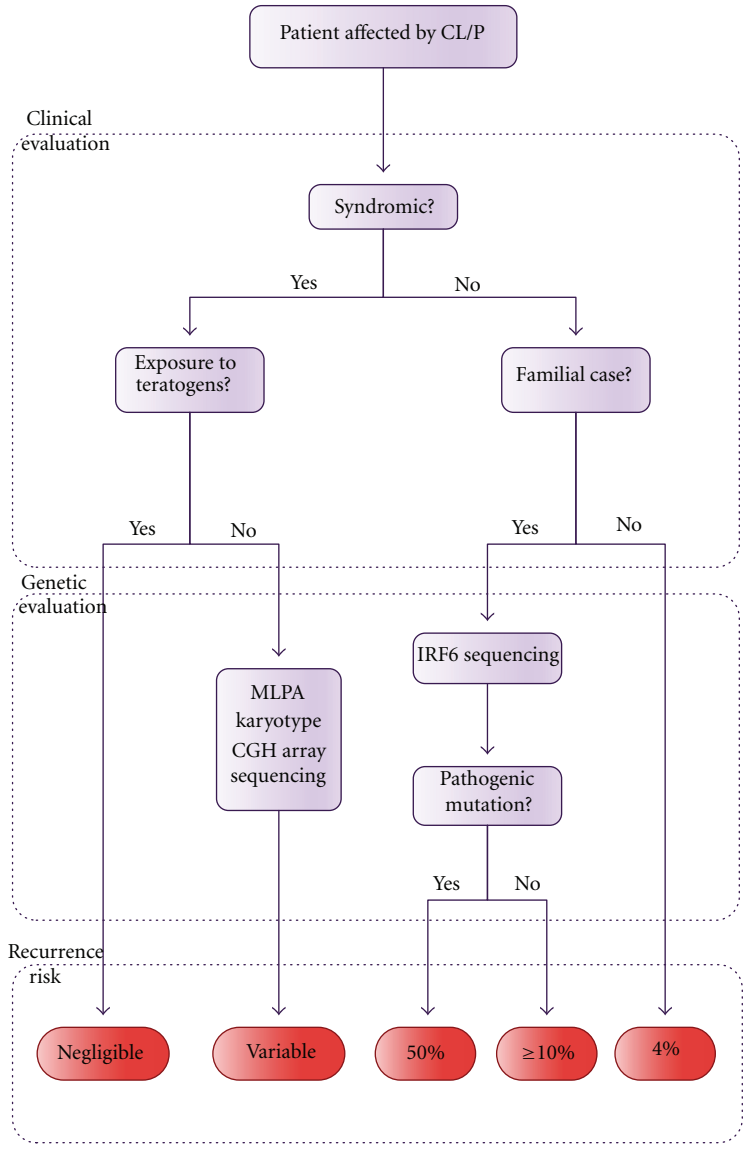

Figure 3: Flowchart depicting the genetic evaluation of a CL/P patient.

Among those genes, the *MSX1* was the most penetrant, that is, alterations in *MSX1* led to CPO more frequently than alterations in other genes. Some authors have also reported chromosomal duplications, deletions and rearrangements in NS CPO patients [92–94]. Nonetheless, the genes located within those chromosomal regions lack confirmation with regards to their pathogenic role.

3. Genetic Management of the Family with CL/P-Affected Children

The clinical evaluation of a CL/P patient, outlined in Figure 3, starts with his/her classification in syndromic and nonsyndromic cases, based on the presence or absence of other dysmorphisms or malformations, together with an investigation of the occurrence of relatives with similar features.

Among the syndromic cases, it is first necessary to investigate the possibility of non-genetic causes, for example, exposure to teratogens during the first trimester of gestation. In cases of CL/P arising from the action of teratogenic agents during embryogenesis, the recurrence risk is negligible since exposure to teratogens in a next pregnancy does not recur. Once the possibility of a teratogenic origin for CL/P is ruled out, the geneticist should raise the diagnostic hypothesis of genetic syndromes and recommend the most adequate test (however, these tests might also be useful in the cases of teratogenic exposure, in order to refute chromosomal abnormalities). The most commonly performed tests are the karyotype, Multiplex Ligation-dependent Probe Amplification (MLPA), Comparative Genomic Hybridization array (CGH-array), gene target sequencing, and exome sequencing. Whilst the karyotype is a cytogenetic technique which allows for detection of large structural and numeric chromosomal

anomalies in a low resolution, MLPA and CGH-array are quantitative molecular tests that enable the investigation of gain or loss of genetic material at the submicroscopic level. MLPA is applied to investigate specific targets in the genome while CGH-array can be used to screen the whole genome with a very high resolution. MLPA or CGH-array are the recommended tests to be used for a first screening, depending on the available resources [95, 96].

Gene target sequencing is recommended when one or more genes are known to be causative of the disorder. There is a trend towards the use of next generation sequencing particularly in diseases associated with genetic heterogeneity, as this approach permits the simultaneous testing of several genes, thus resulting in a more cost-effective test in the long run. Recurrence risk estimates for future children of the parents of one affected patient is dependent on the definition of the etiological mechanisms of the disease, evidencing the importance of selecting the appropriate test, combined with the clinical evaluation, for the establishment of the diagnosis.

In nonsyndromic cases, due to our full lack of understanding with regards to their etiological mechanisms, the recurrence risks have been empirically determined by epidemiological studies. As expected for a multifactorial model of inheritance, these risks can be influenced by several factors, such as gender of the affected propositus, severity of the orofacial cleft, and number of affected relatives [97]. The recurrence risk among families with one first-degree affected relative has been estimated as 4% for NS CL ± P and 2% for NS CPO [98]. These estimates may vary depending on the population. In Brazil, the recurrence risk has been estimated at only 2% among families with one first-degree NS CL ± P affected relative [36].

In NS cases, the identification of other individuals with CL/P in the family should be always interpreted with caution. Due to genetic heterogeneity associated with NS CL/P, a family with several affected individuals can actually represent the segregation of a single-gene disorder, which would not be promptly recognized based solely on clinical evaluation. For example, among 102 families with at least two individuals affected by NS CL/P, we identified 4 families with pathogenic mutations in *IRF6*, which actually represented VWS cases. Due to the high prevalence of VWS, we thus recommend *IRF6* genetic testing in familial cases of NS CL/P [99].

CL/P is a complex group of disorders and the adequate genetic management of the family requires evaluation by a trained group of geneticists in order to best define the diagnosis of the affected propositus, evaluation of prognosis, surgery indications, and, finally, recurrence risk estimates for the individuals at risk. With the advance of genomic technology, we expect that new advances and understanding of the genetic mechanisms leading to CL/P will be achieved in the upcoming years.

Glossary

Association Analysis: correlates the occurrence, in two groups of individuals (e.g., affected and unaffected), of one genetic variant with the phenotype. If the frequency difference of one genotyped variant is statistically significant between the two groups, the genomic region harboring the variant will be associated with the trait. This approach is better suited to identify common and low impact genetic variants of shared origin.

Exome Sequencing: sequencing focused on the 2% of the genome which constitutes the protein-coding genes (exome). Despite the low proportion of the genome, 85% of the high-impact mutations already identified rely on the exome [100], which makes this approach highly promising.

Genetic Marker: any polymorphism loci of known location which is suitable for gene mapping. Single nucleotide polymorphisms (SNPs), which involve one nucleotide substitution, are the most used for this purpose (e.g., in GWAS). A large number of SNPs can be analyzed simultaneously through the use of semi-automated equipments and microchips.

GWAS: association analysis at the genomic level. Requires the genotyping of thousands or millions of genetic markers, and has been made possible after advances in the characterization of the human genome (e.g., the Human Genome Project and the HapMap Project (http://www.hapmap.org/)) and automation of genotypic analysis. This strategy is suitable for identifying common low-effect variants without prior hypothesis. Finding association of the trait with a genetic marker does not necessarily mean that the marker is directly involved with the disease; most likely, the chromosomal region harboring this marker also comprises one or more susceptibility factors. Finding the real cause behind the association signal is currently a challenge.

Heritability: fraction of phenotypic variance in a population attributable to genetic factors.

Linkage Analysis: approach that searches for genomic regions which cosegregate among affected individuals within a family, by genotyping known genetic markers spread throughout the genome. Powerful to detect genes of high impact, but loci of small or moderate effect are usually missed. Large families with many affected individuals are required.

Polymorphism: genomic locus that admits two or more variants in the population and its rarest variant has a populational frequency greater than 1%.

Whole-Genome Sequencing: sequencing analysis of the whole genome, including coding and noncoding regions.

Acknowledgments

The authors are grateful to Regina de Siqueira Bueno for the assistance with the images, and all the colleagues and patients involved with cleft research. The authors are funded by CEPID/FAPESP and CNPq/CAPES.

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Hindawi Publishing Corporation
Plastic Surgery International
Volume 2012, Article ID 185725, 6 pages
doi:10.1155/2012/185725

Research Article

Effectiveness of International Surgical Program Model to Build Local Sustainability

William P. Magee, Haley M. Raimondi, Mark Beers, and Maryanne C. Koech

Research and Outcomes Department, Operation Smile, Inc., 6435 Tidewater Drive, Norfolk, VA 23509, USA

Correspondence should be addressed to Haley M. Raimondi, haley.raimondi@operationsmile.org

Received 31 August 2012; Accepted 2 October 2012

Academic Editor: Luis Bermudez

Background. Humanitarian medical missions may be an effective way to temporarily overcome limitations and promote long-term solutions in the local health care system. Operation Smile, an international medical not-for-profit organization that provides surgery for patients with cleft lip and palate, not only provides surgery through short-term international missions but also focuses on developing local capacity. *Methods*. The history of Operation Smile was evaluated globally, and then on a local level in 3 countries: Colombia, Bolivia, and Ethiopia. Historical data was assessed by two-pronged success of (1) treating the surgical need presented by cleft patients and (2) advancing the local capacity to provide primary and ongoing care to patients. *Results*. The number of patients treated by Operation Smile has continually increased. Though it began by using only international teams to provide care, by 2012, this had shifted to 33% of patients being treated by international teams, while the other 67% received treatment from local models of care. The highest level of sustainability was achieved in Columbia, where two permanent centers have been established, followed by Bolivia and lastly Ethiopia. *Conclusions*. International missions have value because of the patients that receive surgery and the local sustainable models of care that they promote.

1. Background

Humanitarian medical missions often utilize international surgical teams to provide specialized surgical care to a large number of patients in a short period of time. It is an effective way to temporarily overcome limitations of the local health care system in order to deliver immediate care to patients in need. Despite some obvious benefits to the patients, short-term international surgical missions receive ample criticism. Some primary concerns include the failure of this model to provide sustainable solutions or ongoing access to care for appropriate medical followup. This paper examines whether the model of short-term international teams may be valuable on two different levels. It not only illustrates how this model meets a surgical need, but it examines whether this model of short-term international teams is effective in providing opportunities towards long-term, sustainable solutions in that locality and in the overall field of global health.

2. Introduction

Operation Smile, Inc. (OSI) is an international not-for-profit organization that specializes in treatment of patients with cleft lip and cleft palate. The organization was founded in 1982 by Bill and Kathy Magee. Since this time, Operation Smile has provided millions of patient evaluations and hundreds of thousands of free surgeries for children and young adults born with craniofacial deformities. The number of procedures performed annually by Operation Smile has grown exponentially from several hundred patients in 1985, three years after its founding, to more than eighteen thousand during the last fiscal year (2011-2012). The organization, which began in the Philippines, now has a presence in over 60 countries.

At its inception, OSI programs were limited to short-term international missions using USA medical volunteers; however, the organization has continually concentrated on

establishing local foundations to build sustainability in their countries. After receiving an invitation from a country, OSI first establishes medical missions within that country and then works to build a relationship with local medical and nonmedical volunteers. OSI aims to develop local foundations that can recruit volunteers, obtain resources, manage local missions according to local needs, and advocate with governmental and nongovernmental organizations to elevate the quality of life of cleft patients. OSI also places great importance on interacting with local business to build sustainability as evidenced in the composition of their boards—where both business professionals and physicians work together to achieve local capacity.

After thirty years of working toward sustainability, there are now nearly 7,000 local and international specialized volunteers from over 82 countries, over half of whom volunteer locally. Globally, OSI has established 9 cleft care centers and 34 local foundations in other countries and has performed missions at 308 different local sites throughout the world. Education programs such as the Physicians Training Program, medical specialty workshops, and American Heart Association Life Support training have provided additional knowledge and skills to local volunteers, improving the care provided on and off missions. An outcomes system and evaluation process have also been developed to track patient outcomes, audit surgical performance, and provide feedback to surgeons. Formal resident and fellowship education programs have been developed thanks to the generosity of the Regan family and the Stryker Corporation. Since the founding of Operation Smile, high school and college students have been given opportunities to attend missions. There are now more than 700 students clubs in existence in the USA alone, with many more throughout the world. These students are instrumental in raising awareness and support. In the midst of this growth, international missions remain a core aspect of OSI's mission and vision as they serve as a gateway to the creation of local capacity building.

3. Methods

The history and evolution of Operation Smile has been evaluated, first globally, and then on a local level in 3 countries: Colombia, Bolivia, and Ethiopia. This was accomplished by looking at historical data for the past two decades. The total number of local and international missions was calculated, and the total number of patients operated on during local and international missions was compared.

(i) Local missions are defined as either missions of which over 50% of the volunteers are local and/or missions of which are planned and executed by local foundations. (Missions that occur at the comprehensive cleft care centers are thus considered local missions.)

(ii) International missions are defined as either missions of which over 50% of volunteers are international and/or missions of which are planned and executed by OSI.

Selection criteria for the three specified countries were based on the level of sustainability of the country foundation, the number of years the local foundation has been in existence, the number of locally based trained volunteers, and the number of patients annually operated on in the country. The three countries represent three different phases of self-sufficiency as determined by the number of local volunteers and by the capacity of the local foundation to plan and to execute missions effectively.

Historical data was assessed to measure a two-pronged success of (1) treating the surgical need presented by cleft lip and palate patients and (2) advancing the local capacity to provide primary and ongoing care to cleft patients moving forward.

The surgical need was established by approximating the number of individuals living with cleft lip and/or cleft palate at the time of the first Operation Smile program in that country. UNICEF and the World Bank provided the population estimate and the total births per year for each country. An approximation of individuals living with clefts and of the number of children born with clefts each year was then calculated for each country. Because of the lack of birth registries and of research investigating cleft incident rates, these estimates were calculated using the approximation that cleft lip and/or cleft palate affects 1 in 700 live births [1]. This established the total number of possible clefts that exist in the country. Secondly, the World Health Organization (WHO) provided the per capita total expenditure on health, the number of hospital beds, and the number of physicians for each country. These numbers were used to explain the local medical infrastructure and the countries' varying capability to establish local capacity. The number of surgeries provided by Operation Smile during five-year increments was also calculated to show how the organization has been effectively treating children with clefts.

The advancement of local capacity was assessed by comparing the number of Operation Smile patients cared for by international volunteers to those cared for by local nationals and how that ratio has changed over the history of Operation Smile's existence. The progression of local capacity within each of the three selected countries was assessed by documenting the establishment of local programs and systems as each foundation developed.

4. Results

4.1. Global Analysis. The first measure of success was determined by looking at the number of surgeries provided since the organization's inception. The average cleft lip repair surgery can take 45 minutes to an hour to complete, and the average palate repair can last between 1 and a half to 2 hours. An international surgical mission has 5 to 6 operating tables with 1 primary surgeon and 1 anesthesia provider for each table, plus a floating surgeon and a floating anesthesia provider. This translates to an average of 150 surgeries in 5 days of surgery. While other local and international medical organizations also provide reconstructive surgery to patients with clefts, it is inevitable

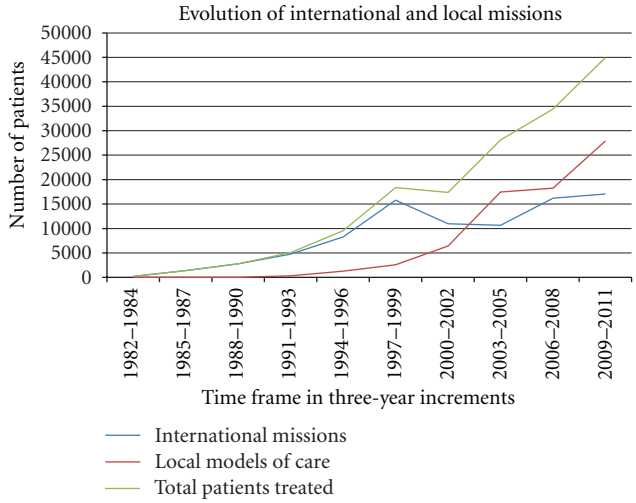

Figure 1: Evolution of International and Local Missions throughout History of OS.

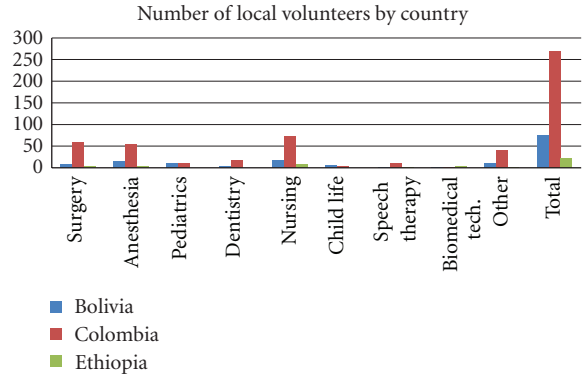

Figure 2: Number of local volunteers by country.

that developing countries will have many untreated patients. Operation Smile originally established specific sites to which they would return annually in order to reduce the prevalence of cleft lip and palate. Analyzing the historical numbers of Operation Smile missions globally, Figure 1 shows that the number of patients treated has increased consistently over time, providing one measurement of success. Figure 1 also illustrates the increase of patients on local missions versus international missions, highlighting Operation Smile's growth toward local sustainability.

4.2. Country Analysis. Colombia has a population of approximately 46,295,000 people, and approximately 914,000 births per year [2]. Based on the aforementioned incident rate, the country is approximated to have 6,6136 individuals living with clefts in various stages of repair. Each year, about 1,306 more children are born with clefts in Colombia. Operation Smile has operated on 14,034 of these patients during cleft missions. The country has roughly 7,198 physicians, ten hospital beds per 10,000 people, and a per capita total expenditure on health of $713 [3].

On the other hand, Bolivia, which has a population of approximately 10,090,000 and 161,440 births per year [4], has about 14,414 individuals with cleft lip and/or cleft palate and 231 newborns each year with the deformity. Of those individuals with clefts, Operation Smile has treated 2,438 patients. Approximately 10,329 physicians live in Bolivia where 11 hospitals beds exist per every 10,000 people and a per capita total expenditure on health of $233 [3].

The third country, Ethiopia, has a population of 84,730,000 and 1,779,339 births per year [5]; thus, about 121,043 individuals live with clefts, and 2,541 children are born per year with the craniofacial anomaly. Operation Smile has treated 1,466 total patients in Ethiopia. Approximately 1,806 physicians live in Ethiopia where there are 2 hospitals beds per 10,000 and $51 per capita total expenditure on health [3].

Preliminary evidence was also found to support the second measure of success, advancing the local capacity to provide primary and ongoing care for cleft patients. Over the past thirty years, OSI has shifted from 100% of patients receiving care from international teams to, in 2012, only 33% of patients being treated by visiting international teams, while the other 67% receive treatment from local models of care. The organization currently has 124 local missions scheduled for the current fiscal year 2012-2013, in comparison to 58 international missions. In the fiscal year 2008-2009, 62% of surgeries were performed during local missions [6] increasing to about 67% this past fiscal year (2011-2012). Figure 2 illustrates the number of local volunteers that OS currently has in each of the three countries.

The three countries that were evaluated presented three different levels of growth towards achieving local sustainability. The highest level of sustainability was achieved in Columbia, where two permanent centers have been established, and a total of 270 volunteers provide care to patients on a continuous basis. Just in the last fiscal year, 1,041 patients received free reconstructive surgery, and local programs provided over 10,000 individual and group consultations in nutrition, dental, speech, ENT, anesthesia, plastic surgery, and psychology. Operation Smile Colombia held its first local mission in 1993, and in 2002, international missions were phased out altogether. Then in 2006, OSI began holding an annual international mission with Operation Smile Colombia for the purpose of educational exchange. OSI has been active in Colombia for 24 years.

Operation Smile has 14 years of history in Bolivia and has not reached the same level of self-sufficiency seen in Columbia. The foundation has 122 nonmedical and 23 medical volunteers, with 21 more currently in the process of being credentialed. From 2007 to 2011, OSI held surgical education modules to provide local surgeons and anesthesiologists with hands on training and mentorship. These resulted in the credentialing of 15 additional medical volunteers, enabling Operation Smile Bolivia to hold its first local mission in June, 2012.

Operation Smile began in Ethiopia in 2005 and has seen very little in the way of sustainable growth. With only six

locally credentialed volunteers, medical programs continue to depend almost entirely on international teams. Basic Life Support certifications and pulse oximetry training are a few of the education programs that have been offered. The most significant initiative to promote local capacity began in March 2012 with the first of many surgical education rotations, where international surgeons, anesthesiologists, and nurses will provide hands on training to local providers. Figure 3 highlights the major landmarks and progression toward sustainability in these three countries.

5. Discussion

International medical missions can serve as a valuable tool for reducing the burden of surgical disease by treating patients, while at the same time providing the opportunity to establish long-term solutions and to build local capacity. However, to build local sustainability and capacity, an organization must explore and adapt its model to the specific country's environment. Operation Smile has had to develop unique strategies to overcome various challenges which countries face. The effectiveness of a surgical program model to establish sustainability is dependent on a variety of factors, as evidenced in the following discussion of Colombia, Bolivia, and Ethiopia.

Operation Smile Colombia has been exemplary as its growth and success continue to impact cleft patients and their communities. Having a substantially higher number of physicians and per capita total expenditure on health, Colombia has a stronger medical infrastructure than the other two countries, which has aided in its growth toward self-sustainability. Two comprehensive care centers were established in 2002 in the cities of Bogota and Duitama. Not only do the centers provide reconstructive surgery to patients, but they also offer ongoing treatment and provide resources to patients. This multidisciplinary type of care permits the centers to have the opportunity to provide specialty services to patients. Reaching such a large population would not be feasible without the local volunteer base and the establishment of the centers. In fact, local volunteers are now participating in "El Caribe Sonrie," a project created to provide postoperative care to patients in other regions of the country. This new program, which aims to widen the impact of actions taken, increase resource management efficiency, and create local and regional autonomy in treating clefts, was locally developed and remains locally driven. Focusing on capacity building in Colombia, the program engages local health care workers and trains them in areas of psychology, speech, and oral health. The local volunteers can then provide access to rehabilitation process in social and communicational skills and adequate oral health care prevention to cleft patients. The first year of the pilot program was completed in May 2012 and has proven to be an exemplary model of how local professionals can train other locals to treat patients within their communities. OS Colombia has also witnessed the formation of other similar organizations which can be expected given the visible and inspirational nature of this type of work.

Operation Smile Bolivia was officially established in February 2000, soon after its first inaugural mission in 1999. OS Bolivia, which holds ongoing international medical programs each year, has a weaker medical infrastructure than Colombia as evidenced in the disparity between number of physicians and money spent on health care. Given the difference in total physicians in Bolivia and Colombia, it can be assumed that Bolivia has far too few plastic surgeons to meet the country's need. In 2008, the foundation began implementing regular education models which focused on training local volunteers, and thus, improving the local medical infrastructure. These modules have enabled 15 additional credentialed volunteers to join OS Bolivia's base, which is now comprised of 40 medical volunteers. The number of credentialed surgeons has also grown from one, in 2008, to three, in 2012. Additionally, the foundation now provides speech therapy through weekly workshops, monthly dental evaluations, and psychological counseling for patients and their families. OS Bolivia and OSI have worked together to provide medical professionals with Pediatric Advanced Life Support (PALS), Advanced Cardiac Life Support (ACLS), and Basic Life Support (BLS) training, in accordance with the American Heart Association's (AHA) protocols. As of June 30, 2012, 127 medical professionals have been certified in BLS, 78 in PALS, and 78 in ACLS. Because of these education initiatives, OS Bolivia has been able to grow its local volunteer base, and many local professionals have been trained in critical care. The first local mission, completed in June of 2012, marked a significant step in the history of Operation Smile Bolivia.

Since its inaugural mission in Ethiopia in December 2005, Operation Smile has conducted 16 medical missions and has provided surgery to 1,466 patients. Additionally, Operation Smile started to conduct medical education programs in various hospitals throughout the country. Over 500 Ethiopian health care professionals have completed American Heart Association (AHA) Basic Life Support (BLS) training conducted by Operation Smile. While Ethiopia has experienced some growth since its inception, the lack of infrastructure and medical personnel has impeded the organization from experiencing the local growth exhibited in countries like Colombia. This lack of medical infrastructure is evidenced in the low number of physicians, hospitals beds, and per capita income spent on health care. Because of the seriously low number of physicians in Ethiopia, the number of plastic surgeons in this country can be assumed to be much too low to treat the number of individuals with cleft. In Ethiopia, OSI aims to help build local infrastructure and also provide expertise to train local health care workers. For example, OSI has partnered with LIFEBOX, a not-for-profit organization that provides pulse oximeters and training to hospitals where this crucial monitoring tool is not currently available. OSI has developed a strong relationship with Jimma University Specialized Hospital (JUSH) and has committed to supporting the building of a new surgical center where two-week-long rotations in plastic surgery,

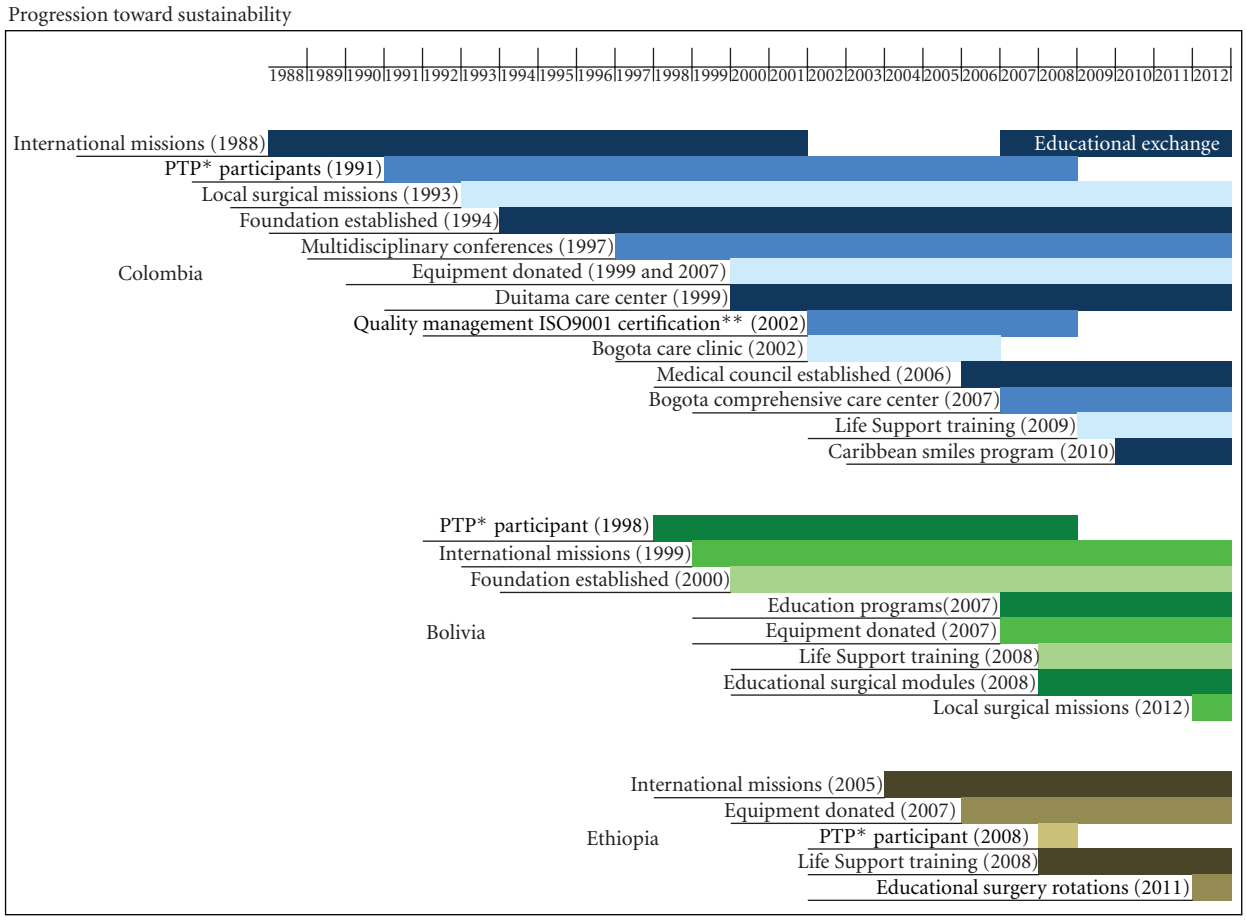

Figure 3: Major landmarks and progression toward sustainability. *PTP: the physicians training program involved training foundation's medical volunteers in USA hospitals. **ISO9001: International Organization for Standardization Certificate which is awarded when reaching and maintaining quality management systems requirements.

anesthesia, and nursing will provide local health care workers with the opportunity to receive training and mentorship in small focused rotations. One such rotation, which included 49 surgeries, was completed in March, 2012.

Operation Smile has evolved its large-scale international team mission model to one of local management and ownership. Not only has Operation Smile, in conjunction with local governments, nonprofits, and health care professionals, established nine comprehensive cleft care centers operating in seven countries, but it also has established some weekly clinics in other countries to aid in the backlog of cleft patients. The organization has treated 161,096 patients, reducing the backlog of clefts, but it has also built a solid local volunteer base with the medical knowledge, skills, and passion to continue evolving local models of care. Local foundations have engaged local businesses and hospitals to amass resources, raise awareness, and provide patient care. Involvement of international medical volunteers on missions raises awareness and establishes a link to the academic, professional, and financial resources available in more developed countries. In fact, the OSI resident programs, which promote international surgical volunteerism, have increased participants' appreciation for the burden of disease in the developing world, the participants' perspectives on global disparities regarding health care access, and the participants' "personal sense of social responsibility" [7].

6. Conclusion

The momentum that Operation Smile has experienced during the past 30 years has enabled the organization to impact the lives of children and communities exponentially. Building local capacity and sustainability is essential to reaching a larger population of patients. Operation Smile has created a long-standing, well-respected, effective organization whose sustainable model may aid other similar organizations in their path toward local capacity building. While the surgical interventions accomplished by short-term international teams are the most easily showcased success, in Operation Smile's history, international missions have in many cases preceded the establishment of local capacity that has a greater impact. It is the authors' belief that international missions served a substantial role in paving the way for that capacity.

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