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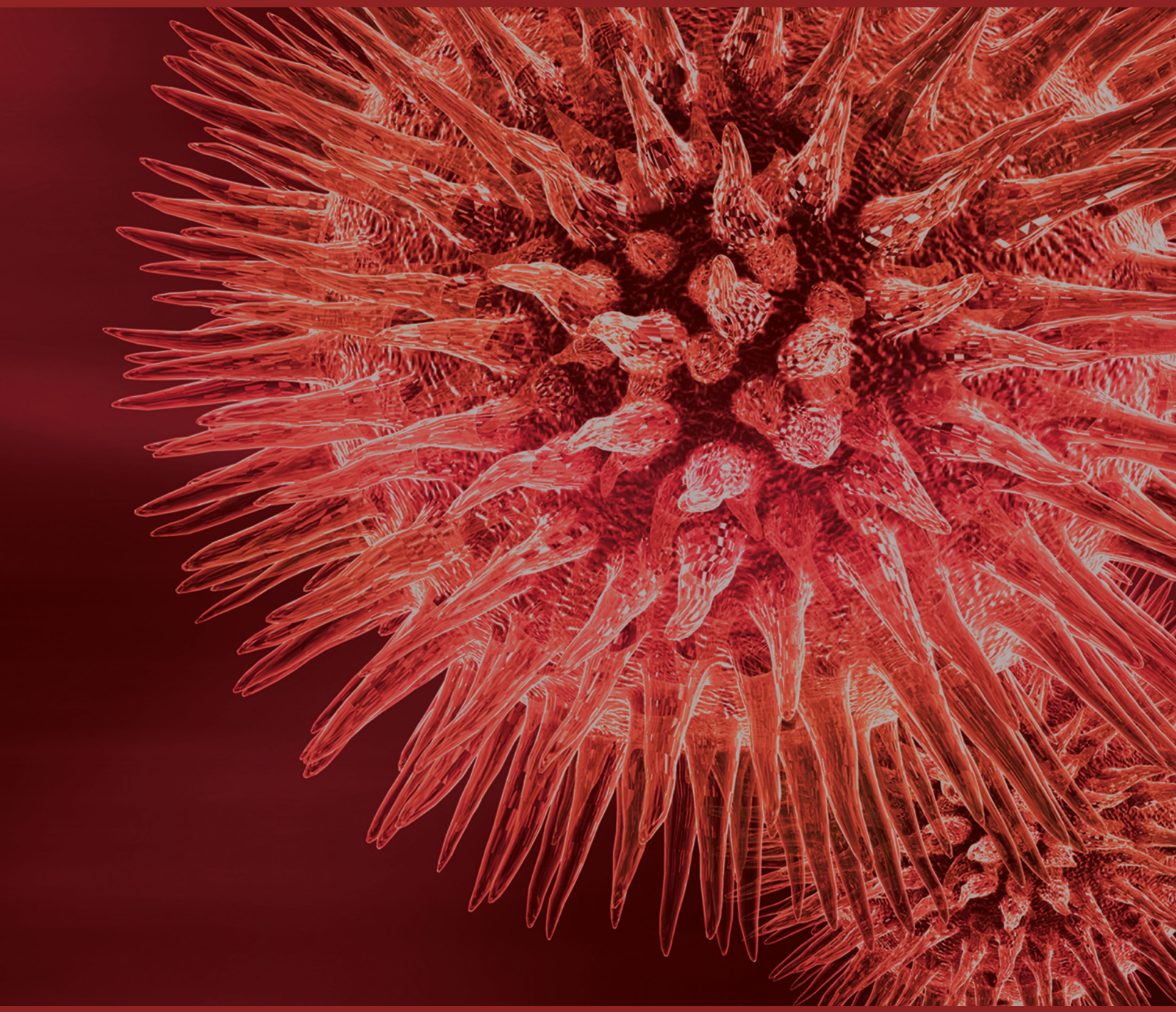
Cleft Palate, Interdisciplinary Diagnosis, and Treatment

Guest Editors: Pablo Antonio Ysunza, Maria Carmen Pamplona, and Gabriela Repetto



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Editorial

Cleft Palate, Interdisciplinary Diagnosis, and Treatment

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Cleft lip and palate is the 4th most common congenital malformation and the 1st most common craniofacial anomaly. The incidence of cleft lip and palate varies from 1 per 750 live births to 1 per 650 live births depending on the geographical area. Cleft palate is a feature of over 200 well defined syndromes of congenital malformations.

Although at the present time it is still not feasible to completely prevent the occurrence of cleft palate, the consequences of this major malformation on maxillary structure, esthetic appearance, speech, feeding, and swallowing can be appropriately addressed and corrected by the intervention of an interdisciplinary team.

A palatal cleft creates feeding difficulties and affects the function of the velopharyngeal sphincter during speech. The velopharyngeal sphincter is one of the most important valves of the vocal tract. Its function during speech is to keep a balanced nasal resonance and sufficient intraoral pressure by sealing and opening the communication between the nasal cavities and the rest of the vocal tract.

The velopharyngeal sphincter has 3 main components: the velum or soft palate, the posterior pharyngeal wall, and the lateral pharyngeal walls. All these structures show specific movements during speech and swallowing. Although the posterior and lateral pharyngeal walls are not affected by a cleft palate, the cleft palate disrupts the normal fusion of the velar muscles significantly affecting their movement during speech and swallowing. A vast number of scientific papers have focused on the diagnosis and management of cleft palate.

At the present time, it is universally accepted that patients with a cleft palate require the intervention of an interdisciplinary team. This special issue includes six papers addressing diverse aspects of the diagnosis and management of cleft palate.

One of the papers included in this special issue describes and discusses current controversies in the diagnosis and management of cleft palate and velopharyngeal insufficiency. Healthcare professionals from Chile, Mexico, and USA who work on cleft palate teams participated in this review. Imaging diagnosis and its importance for surgical planning and correction of velopharyngeal insufficiency, speech, and language pathology intervention for articulation disorders related with cleft palate and genetic aspects are reviewed in this paper.

The outcome of primary palatal surgery in children with cleft palate is addressed in another study from researchers from Korea. The differences between a syndromic and a nonsyndromic cleft palate are described. This study presents clinical outcomes of primary cleft palate surgery, including rate of oronasal fistula development, rate of velopharyngeal insufficiency, and speech outcomes. The results of this paper suggested that several factors, including cleft type, should be identified and comprehensively considered in order to

establish an optimal treatment regimen for patients with cleft palate.

Imaging diagnosis has become an indispensable tool for assessing the velopharyngeal sphincter during speech. In a study from a group of researchers from Japan, the differences in velopharyngeal structure during speech as revealed by 3-Tesla magnetic resonance imaging movie mode are analyzed. This study describes the use of MRI movie as a powerful and valuable method which can be useful for studying velopharyngeal structure and function.

As technology keeps advancing, it is predictable that new imaging procedures will be readily available for routine clinical diagnosis in patients with cleft palate.

A group of researchers from Brazil submitted a paper studying the outcome of infants with Pierre Robin sequence managed with nasopharyngeal intubation. The results demonstrate that children managed with the protocol described in this study improved respiratory and feeding difficulties and presented low morbidity and no mortality during the first year of life.

Another study by a single author from Peru addresses one of the most severe complications of palatal surgical repair: a flap necrosis. Different factors which can play a role in flap failure are studied, including anatomical variations, section of the pedicle, tension, vascular thrombosis, surgical technique, infection, and malnutrition. The management of fistulas as a consequence of necrosis is also analyzed including different surgical procedures.

The dimension of the velopharyngeal space following surgical maxillary advancement is studied in a paper from a group of researchers from Turkey. In this study, Le Fort I osteotomy is compared with Zisser segmental osteotomy. Cephalometric analysis was used for assessing the velopharyngeal space. The results suggest that Zisser segmental osteotomy seems to be a reliable procedure for maxillary advancement with the advantage of not significantly increasing velopharyngeal space.

In sum, this group of papers provides useful clinical information for healthcare professionals interested in the interdisciplinary diagnosis and management of patients with cleft palate.

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Clinical Study

Clinical Outcomes of Primary Palatal Surgery in Children with Nonsyndromic Cleft Palate with and without Lip

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This study presents clinical outcomes of primary cleft palate surgery, including rate of oronasal fistula development, rate of velopharyngeal insufficiency (VPI) requiring secondary surgery, and speech outcomes. We examined the effect of cleft type on the clinical outcomes. Retrospective analysis was performed using clinical records of all patients who received a primary palatoplasty at the Cleft Palate Clinic at Seoul Asan Medical Center, South Korea, between 2007 and 2012. The study included 292 patients with nonsyndromic overt cleft palate (±cleft lip). The results revealed that the rate of oronasal fistula was 7.9% and the incidence of VPI based on the rate of secondary palatal surgery was 19.2%. The results showed that 50.3% of all the patients had received speech therapy and 28.8% and 51.4% demonstrated significant hypernasality and articulatory deficits, respectively. The results of the rate of VPI and speech outcomes were significantly different in terms of cleft type. Except for the rate of oronasal fistula, patients with cleft palate generally exhibited better clinical outcomes compared to those with bilateral or unilateral cleft lip and palate. This study suggests that several factors, including cleft type, should be identified and comprehensively considered to establish an optimal treatment regimen for patients with cleft palate.

1. Introduction

Cleft palate is the most common type of innate craniofacial anomaly, which requires multidisciplinary treatment approach, including physical palatal correction, feeding management, orthodontic management, and speech-language services. Primary surgical correction of the cleft palate is typically performed by 12 months of age, and it ultimately aims to restore a mechanism for normal speech production. The criteria for successful primary palatal surgery include rates of occurrence of oronasal fistula, rates of persistent velopharyngeal insufficiency (VPI), and the achievement of normal speech. Over the past several years, advances have been made in surgical management of cleft palate in terms of surgical techniques and timing of palatal surgery [1–5], which has decreased the postoperative rate of oronasal fistula, decreased the rate of persistent VPI, and improved speech outcomes. Surgical palatal techniques have focused on a proper muscle repair (e.g., Furlow double-opposing Z-plasty), and the timing of palatal surgery has dramatically decreased from 18–24 months before the 1980s to 9–12 months in the present [6]. These changes in surgical management of cleft palate have led to improved clinical outcomes.

A number of studies reviewed cleft palate management employed by various centers worldwide. Clinical outcomes following primary palatal surgery tend to vary significantly, although the results have generally improved compared to those in the past. The incidence of oronasal fistula has been documented to range from 0% to 12.8% in the recent studies [5, 7–12]. A meta-analysis using 11 studies published between 2000 and 2012 comprising 2505 children found that the rate of fistula formation following primary palatal surgery was 4.9% [11]. The study also reported that patients with complete

bilateral clefts (Veau IV) would be more likely to develop a fistula. The reports of incidence of persistent VPI following primary surgery vary across the literature, with some studies reporting incidence as high as 30% [5–7, 13–15]. In general, the rate of VPI reportedly decreased in the condition using surgical palatal techniques with emphasis on a proper muscle, although the rate was higher in patients with more severe and wider clefts [7]. The relationship between the rate of VPI and cleft type was not statistically significant in some studies [5, 7, 16]. However, some other studies reported that VPI is more frequent in cleft lip and palate than in isolated cleft palate [16].

Furthermore, the existing studies reported a wide range of speech outcomes following primary surgery in terms of different speech aspects and assessment methods. Most studies reported speech outcomes based on the presence or severity of hypernasal speech. Some studies also reviewed, in detail, articulatory issues that negatively affected many children with cleft palate. It is reported that up to approximately 25% to 30% of the children with cleft palate still tend to exhibit speech problems throughout most of their important formative preschool age and school-age years [17]. Hardin-Jones and Jones (2005) found that 37% of 212 preschoolers with repaired cleft palate demonstrated significant hypernasality or received secondary surgical management for velopharyngeal insufficiency. The study also reported that approximately two-thirds of the children demonstrated significant speech production problems and therefore were enrolled in direct speech therapy. In addition, the study indicated that a smaller percentage of children with clefts of the soft palate required speech therapy for articulatory problems and showed significant hypernasality compared to children with bilateral or unilateral cleft lip and palate and clefts of the hard and soft palate [6].

It is important to evaluate clinical outcomes of primary palatal surgery and to identify factors related to clinical outcomes in order to improve cleft care and achieve the ultimate goal of individuals with cleft palate, that is, to restore a mechanism for normal speech production. The purpose of the study was to investigate the clinical outcomes of primary palatal surgery in patients with nonsyndromic overt cleft palate (±cleft lip) treated in the cleft palate-craniofacial clinic of the Seoul Asan Medical Center, South Korea. The study presents an analysis of the results of cleft palate surgery, including postoperative rate of oronasal fistula development, rate of VPI necessitating secondary surgery, and speech outcomes. Moreover, we evaluate the effect of the cleft type on the clinical outcomes.

2. Materials and Methods

2.1. Participants. The Seoul Asan Medical Center Institutional Review Board approved this study. The study involved a retrospective analysis of 459 patients who received primary palatal surgery in the Cleft Palate-Craniofacial Clinic of the Seoul Asan Medical Center, South Korea, between 2007 and 2012. All patients had received primary palatal surgery performed by one plastic surgeon (the second author, K. S. Koh) in the clinic. Primary palatal surgery in the clinic is implemented at around 12 months of age using a Furlow double opposing Z-plasty, two-flap palatoplasty, intravelar veloplasty, or von Langenbeck flaps. A two-stage approach (soft palate closure at 9–12 months of age and hard palate closure around 18 months of age) has also been performed in some cases involving wide clefting of the palate. Choice of primary palatal surgical techniques was based on preoperative cleft anatomy. In addition, an orthodontist, a member of the cleft palate team at the medical center who works at a local dental clinic outside of the medical center, treated most babies born with unilateral or bilateral cleft lip and palate with preoperative nasoalveolar molding (NAM).

For inclusion in the current study, patients should be born with overt cleft palate, and they must have been seen for routine follow-up speech examinations at least until 36 months of age or for two years from the time of primary palatoplasty. Patients with submucous cleft palate were excluded from this study. None of the patients had demonstrated syndrome, other congenital anomalies, sensorineural hearing impairment, cognitive deficits, or neurological involvement. Two hundreds ninety-two patients with nonsyndromic overt cleft palate finally met the inclusion criteria. Of 292 patients in total, 41 patients had unilateral cleft lip and palate (UCLP), 94 had bilateral cleft lip and palate (BCLP), and 157 had clefts of palate only (CPO).

2.2. Procedures. The data on cleft type, sex, age at palatal surgery, and postoperative complications (e.g., oronasal fistula, VPI), along with secondary palatal surgery rates and the results of follow-up speech examinations, were obtained from patients' electronic medical records. This study included only clinically significant oronasal fistula developed at the anterior part of the hard palate (i.e., the hard palate anterior or posterior to incisive foramen) and in the region at the junction of the soft and hard palate according to the medical records. The follow-up speech examinations were administered to each participant at 12 (one month after primary palatoplasty), 15, 24, and 36 months of age. For the purpose of this study, the data from the 36-month follow-up examination were considered as clinical decisions (i.e., speech therapy and/or secondary palatal surgery, or termination of routine speech examination due to normal speech-language development) made around 36 months of age or 2 years after the time of primary surgery. At the follow-up speech examination, the presence and type of resonance problems and articulatory proficiency were determined based on patients' speech samples. A speech-language pathologist in the clinic measured perceptual judgments of the severity of hypernasality and articulatory proficiency on a seven-point rating scale (1 = normal; 2 = minimal; 3 = mild; 4 = mild to moderate; 5 = moderate; 6 = moderate to severe; 7 = severe).

2.3. Statistical Analysis. Dependent variables included (1) rate of occurrence oronasal fistula, (2) percentage of patients who had received secondary palatal surgery for VPI, (3) percentage of patients receiving speech therapy as recommended, (4) percentage of patients demonstrating significant hypernasality above mild to moderate, and (5) percentage

Table 1: Clinical outcomes by type of cleft.

Results	UCLP		BCLP		CPO		Total		χ^2	P
	n	%	n	%	n	%	n	%		
Total	41	14.0	94	32.2	157	53.8	292	100		
Oronasal fistula	3	7.3	5	5.3	15	9.6	23	7.9	1.5	.479
2nd palatal surgery	11	26.8	26	27.7	19	12.1	56	19.2	11.0	.004
Speech therapy	28	68.3	58	61.7	61	38.9	147	50.3	18.4	<.001
Hypernasality	15	36.6	42	44.7	27	17.2	84	28.8	29.3	<.001
Articulatory deficits	29	70.7	52	55.3	69	43.9	150	51.4	17.5	.002

UCLP: unilateral cleft lip and palate; BCLP: bilateral cleft lip and palate; CPO: cleft palate only.

of those exhibiting articulatory problems above mild to moderate requiring speech therapy. Chi-square analyses were performed to examine the effect of cleft type on the dependent variables.

3. Results

3.1. Total Patients. This study included 292 patients with nonsyndromic overt cleft palate (±cleft lip) who received primary palatal surgery at the Seoul Asan Medical Center between 2007 and 2012. The patients included 147 boys and 145 girls and ranged in age from 36 months to 19 years 4 months (mean = 72.48 months) at the time of data collection. Fourteen percent of the total patients had UCLP, 32.2% had BCLP, and 53.8% had CPO. The patients ranged in age at primary palatal surgery from 9 months to 5 years and 3 months, with the mean age of 11.97 months.

Table 1 shows the rate of oronasal fistula following primary palatal surgery, the percentage of patients who had received secondary palatal surgery for VPI, the percentage of patients who received speech therapy as recommended, and speech outcomes at 36-month follow-up for all patients by type of cleft. The retrospective analysis showed that 7.9% ($n = 23$) of all patients developed oronasal fistula following primary palatal surgery. Furthermore, 19.2% ($n = 56$) of the total group had received secondary palatal surgery for VPI, and the mean age for the surgery was 63.7 months (range = 35 months to 14 years and 9 months). Finally, 50.3% ($n = 147$) of all patients were enrolled in or had previously received speech therapy. Regarding speech results at 36-month follow-up, 28.8% ($n = 84$) of the total group demonstrated significant hypernasality, obtaining a score of 4 points or greater on 7-point scale. In addition, 51.4% ($n = 150$) showed significant articulatory deficits of a degree of severity greater than mild, requiring direct speech therapy.

3.2. The Effect of Cleft Type on Clinical Outcomes. Patients with CPO appear to have a slightly higher rate of oronasal fistula development following primary palatal surgery (9.6%) compared to patients with UCLP or BCLP (7.3% and 5.3%, resp.). However, Chi-square analyses revealed that the rate of oronasal fistula was not significantly different among the three groups of cleft type. The relationship between cleft type and percentage of patients who had received secondary palatal surgery was significant ($\chi^2 = 11.0$, $P = .004$). A relatively higher percentage of patients with UCLP or BCLP (26.8% and 27.7%, resp.) received secondary palatal surgery for VPI compared to patients with CPO (12.1%). A significant relationship was also evident between cleft type and percentage of patients who were currently enrolled in or had previously received speech therapy ($\chi^2 = 18.4$, $P < .001$). The percentage of the patients with UCLP or BCLP (68.3% and 61.7%, resp.) who received speech therapy was higher compared to that of patients with CPO (38.9%). The results showed a significant relationship between cleft type and percentage of patients demonstrating a degree of hypernasality greater than mild ($\chi^2 = 29.3$, $P < .001$). Consistent with the results of secondary palatal surgery for VPI, a relatively higher percentage of patients with UCLP or BCLP (36.6% and 44.7%, resp.) demonstrated significant hypernasality compared to patients with CPO (17.2%). In addition, a significant relationship was evident between cleft type and percentage of patients showing significant articulatory deficits of a degree of severity greater than mild ($\chi^2 = 17.5$, $P = .002$). The percentage of patients with UCLP and BCLP who demonstrated significant articulatory deficits (70.7% and 55.3%, resp.) was higher compared to that of patients with CPO (43.9%), which was consistent with the results of the relationship between cleft type and percentage of patients who were currently or previously enrolled in speech therapy.

4. Discussions

This study performed retrospective analysis of clinical outcomes of 292 patients with nonsyndromic overt cleft palate (±cleft lip) who received primary palatal surgery at the Seoul Asan Medical Center between 2007 and 2012. This study focused on three postoperative outcomes, the rate of oronasal fistula and the rate of VPI based on the percentage of secondary palatal surgery as well as speech outcomes related to hypernasality and articulatory proficiency. This review indicated that 7.9% of all patients developed oronasal fistula following primary palatal surgery. The literature has reported various rates of oronasal fistula, ranging from 0% to 12.8% in the recent studies [5, 7–12]. These results could be attributed to different inclusion criteria for oronasal fistula found in the literature. In addition, the incidence of oronasal fistula may be closely related to several factors, including cleft type, width of cleft, surgical techniques, and preoperative orthopedics.

Among the influential factors, this study examined the effect of cleft type on the incidence of oronasal fistula. We found no significant effect of cleft type on the rate of oronasal fistula. In general, the literature reports that patients with complete bilateral clefts (Veau IV) are more likely to develop a fistula [10, 11]. In this study, patients with UCLP or BCLP had a relatively lower rate of oronasal fistula development following primary palatal surgery compared to patients with CPO, although the results did not reach statistical significance. The low incidence of oronasal fistula in patients with UCLP or BCLP in this study might be related to preoperative NAM. Approximately 90% of babies born with UCLP or BCLP in our institution were treated with preoperative NAM, but only few babies with CPO underwent preoperative procedure. Recently, preoperative orthopedics, such as the NAM procedure, was reported to contribute to the narrowing of the cleft width and therefore reducing the rate of oronasal fistula developed following primary palatal surgery [10, 17, 18]. However, we could not obtain valid medical records on NAM, as the preoperative procedure was performed at a local dental clinic outside the institution. Future research should use objective and systematic data to examine whether patients who received the preoperative orthopedic procedure show better clinical outcomes after primary cleft repair.

The study also reported that 19.2% of the total group had received secondary palatal surgery for VPI. The incidence rates of persistent VPI following primary surgery also vary in the literature, being as high as 30% [5–7, 13–15]. Such varied outcomes concerning VPI following primary surgery might be associated with several factors, including variability in the definition of or criteria defining VPI, different surgical techniques, cleft type, and extent of clefting. Although many studies used mainly secondary corrective surgery as inclusion criteria of VPI, some studies included results evidenced by perceptual assessment of hypernasal speech and assessments using nasoendoscopy and/or videofluoroscopy. Regarding hypernasality, which is a speech problem associated with VPI, 28.8% of the total group demonstrated significant hypernasality requiring secondary palatal surgery or speech therapy. In general, secondary palatal surgery has been performed at our institution in cases where anatomic deficits of the velopharyngeal mechanism following primary repair appear to show persistently moderate or severe degrees of hypernasality. Patients who exhibit a mild to moderate degree of hypernasality and simultaneous articulatory deficits are referred to speech therapy. Therefore, this clinical decision-making process results in differences between the percentage of patients demonstrating significant hypernasality and the rate of secondary palatal surgery. In addition, the results showed that cleft type has a significant effect on the incidence of VPI, that is, the percentage of patients who had received secondary palatal surgery. A relatively higher percentage of patients with UCLP or BCLP received secondary palatal surgery for VPI compared to patients with CPO.

The percentage of patients enrolled in speech therapy or demonstrating significant articulatory deficits requiring speech therapy was high in this study. Approximately half of all the patients had enrolled in or received speech therapy, and 51.4% showed significant articulatory deficits. These results of speech outcomes in this study were consistent with the previous study [6], which examined speech production of preschoolers with cleft palate. Hardin-Jones and Jones concluded that the majority of preschoolers with cleft palate continue to demonstrate speech problems that require direct speech therapy, despite advances in management of cleft palate [6]. A significant relationship was also found between cleft type and speech outcomes. More patients with UCLP and BCLP were enrolled in speech therapy and more demonstrated significant articulatory deficits compared to patients with CPO. This result might be associated with the relatively higher rate of VPI in patients with UCLP and BCLP compared to those with CPO. That is, more patients with UCLP and BCLP showed significant hypernasal speech and articulatory problems due to VPI and therefore needed to receive speech therapy.

To implement a better clinical service approach, it is important to evaluate complications and surgical outcomes. It is also necessary to identify factors that influence surgical outcomes and successful clinical management of individuals with cleft palate. Clinical outcomes of primary cleft palate repair are related to several factors, including cleft type, the extent of innate clefting, surgical repair techniques, expertise of the operating surgeon, preoperative orthopedics, and timing of primary palatal repair. This study examined the effect of only one influential factor on clinical outcomes. Future research should investigate the relationship between several influential factors and clinical outcomes comprehensively.

A final comment on the limitations of this study appears warranted. Several limitations arose in the retrospective review of patient records, which is subject to confounding factors. Especially, the limitation was evident in classifying cleft type and comparing the results with those of previous studies. We found that the cleft classification system of patients' electronic medical records was not consistent and sometimes insufficient, as several junior doctors were involved in recording patients' cleft type. Information on cleft type generally appeared to be described using the terms such as unilateral (right or left sides), bilateral, complete, and incomplete. However, to classify all patients in the study using the existing medical records, we had to use simple cleft classification system, which does not accurately reflect the magnitude of the defect and does not guarantee the homogeneity of each cleft type group. The classification system in this study, by the nature of its simplicity, may reduce the sensitivity for the analysis of the effect of cleft type on clinical outcomes. More detailed cleft classification system should be used or the exact size or width of clefting should be estimated in future research so that a large degree of heterogeneity in cleft type group can be reduced and the effect of cleft type on clinical outcomes can be sensitively detected. Furthermore, continuous research efforts using prospective analysis should attempt to identify presurgical risk factors for clinical outcomes in primary palatal surgery.

5. Conclusion

This study represents clinical outcomes of primary cleft palate repairs based on large data gathered from a single institution

and reflects a single surgeon's intensive experience over a 5-year period. This makes it possible to rule out influential and confounding factors, such as expertise of surgeons. The study showed that the incidence of oronasal fistula and the incidence of VPI following cleft palate surgery are comparable to those of other cleft centers worldwide, although care needs to be taken when interpreting the results due to lack of standard definitions used for oronasal fistula and VPI in the literature and the weakness of retrospective analyses. The study also suggests that approximately half of patients show speech problems following primary palatal surgery and require direct speech therapy. This result highlights the importance of routine follow-up speech examinations and multidisciplinary team approach for this population. In addition, the study suggests that cleft type is one of the important factors related to clinical outcomes. This audit provides a retrospective quality review of primary palatal surgery at the Seoul Asan Medical Center and a basis for ongoing research efforts to establish an optimal treatment regimen for patients with cleft palate.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Flap Necrosis after Palatoplasty in Patients with Cleft Palate

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Palatal necrosis after palatoplasty in patients with cleft palate is a rare but significant problem encountered by any cleft surgeon. Few studies have addressed this disastrous complication and the prevalence of this problem remains unknown. Failure of a palatal flap may be attributed to different factors like kinking or section of the pedicle, anatomical variations, tension, vascular thrombosis, type of cleft, used surgical technique, surgeon's experience, infection, and malnutrition. Palatal flap necrosis can be prevented through identification of the risk factors and a careful surgical planning should be done before any palatoplasty. Management of severe fistulas observed as a consequence of palatal flap necrosis is a big challenge for any cleft surgeon. Different techniques as facial artery flaps, tongue flaps, and microvascular flaps have been described with this purpose. This review article discusses the current status of this serious complication in patients with cleft palate.

1. Background

Severe complications in patients after cleft palate surgery are not common.

Severe defects are characterized by extended deficiency of tissues usually wider than the primary cleft and presented as severe fistulas or absence of palatal tissue in worst cases (Figures 1 and 2).

These defects are commonly in relation with loss of palatal tissue after palatal flap necrosis. The extent of functional impairment is great and they have psychological, social, and developmental consequences.

This condition permits a free flow of food into the nasal cavity in a volume large enough that it may exit through the naris. In addition, the nasal secretion seeps into the mouth producing bad taste, malodorous breath, and poor oral hygiene.

Furthermore, these sequels affect speech and resonance with hypernasality, audible nasal scape, and weakness of pressure consonants.

Preservation of the mucoperiosteal flaps after palatoplasties guarantees the closure of the cleft and the functional outcomes of these surgeries (speech, feeding).

Few studies have addressed this disastrous complication and the prevalence of this problem remains unknown.

Prevalence of palatal flap necrosis in three centers in Peru was 0.34% (Table 1) [1].

Two cases were bilateral cleft palates and two incomplete cleft palates. Three of them were children and one adult.

Studied prevalence in a study made by Diah et al. from Chang Gung University of Taiwan was 64/2 (3.1%) [2].

Another study from Nigeria observed two cases of flap necrosis (1%) in patients with bilateral cleft palates [3].

A multivariate analysis made in 709 patients by Deshpande et al. found low rate of total or partial flap necrosis (less than 1%) [4].

Management of severe fistulas observed as a consequence of palatal flap necrosis is a big challenge for any cleft surgeon. Different techniques as facial artery flaps, tongue flaps, and microvascular flaps have been described with this purpose.

This review article discusses the current status of this serious complication in patients with cleft palate.

2. Anatomy

The palate has a rich blood supply.

Table 1: Analysis of patients with cleft palate operated by three centers in Lima, Peru, who developed palatal flap necrosis 1994–2013.

	Center A	Center B		Center C	Total
	Case 1	Case 2	Case 3	Case 4	
Age*	1	2	24	1	
Sex					
Male	1	0	0	0	1
Female	0	1	1	1	3
Type of cleft					
Veau I	0	0	0	0	0
Veau II	0	1	1	0	2
Veau III	0	0	0	0	0
Veau IV	1	0	0	1	2
Prevalence	155/1 (0.64%)	325/2 (0.61%)		694/1 (0.14%)	1,174/4 (0.34%)

* Age at the time of the surgery.

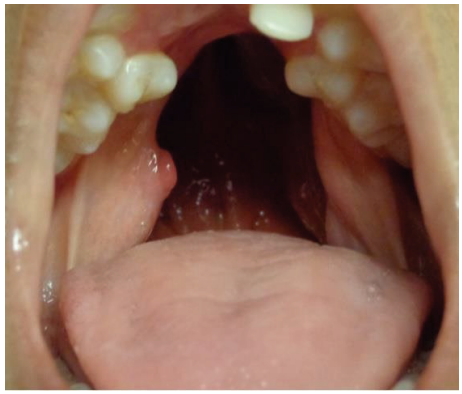


Figure 1: Patient with bilateral cleft palate and large palatal defect after mucoperiosteal flap necrosis. The extent of the defect is bigger than the original cleft size.

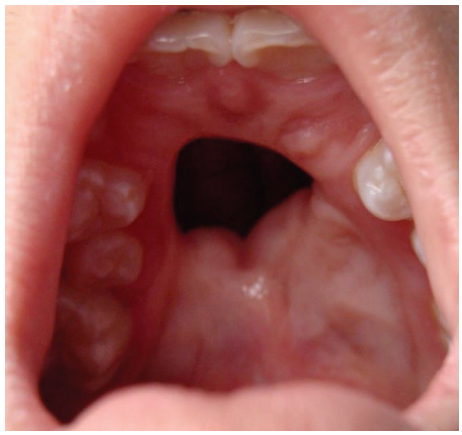


Figure 2: Patient with isolated cleft palate and severe fistula after mucoperiosteal flap necrosis.

Blood supply of the palate is carried by branches of the external carotid artery: greater palatine, ascending palatine, infraorbital, alveolar, superior labial arteries, and branches of the ascending pharyngeal artery [5] (Figure 3).

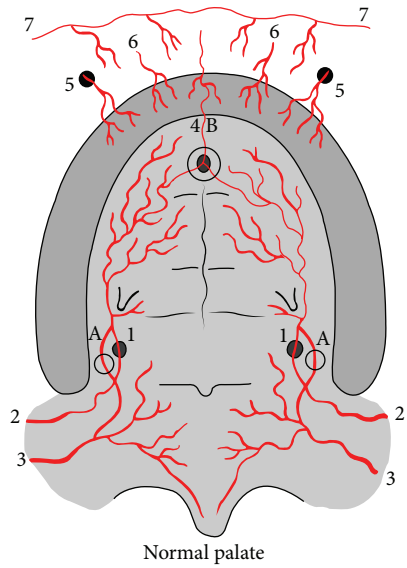


Figure 3: Noncleft palate vascularization. 1: greater palatine artery; 2: descending palatine artery; 3: ascending palatine artery; 4: anterior palatine artery; 5: branches from infraorbital artery; 6: superior alveolar artery; 7: branches superior labial artery. A: Vascular anastomoses between descending palatine artery and ascending palatine artery through lesser palatine vessels; B: vascular anastomoses between greater palatine artery and anterior palatine artery.

Vascularization of the mucoperiosteum of the hard palate comes mainly from the greater palatine vessels (branch of descending palatine artery from the maxillary artery) which emerge from the greater palatine foramen [6, 7].

Location of the greater palatine foramen during the surgery let us prevent the injury of this artery (Figure 4).

Main location of greater palatine foramen was located at the level of the second molar (35.7%), interproximal to the second and third molars (35.7%) in women, and at the level of the second molar in men (65%) as described by Klosek and Rungruang in 2009 [8].

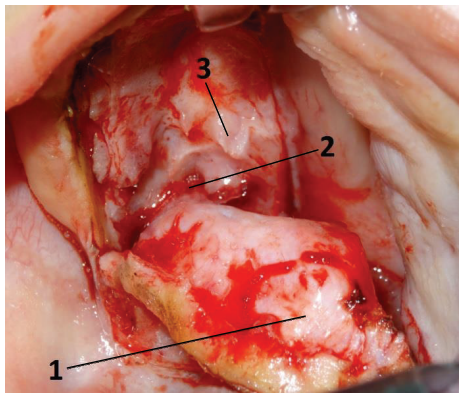


Figure 4: Anatomical relations of the greater palatine vessels: 1, mucoperiosteal flap; 2, greater palatine vessels coming from greater palatine foramen; 3, palatal spine.

A study made by Fu et al. in 2011 [9] observed that the most frequent greater palatine foramen location was between the second and third molars (66.6%) and similar results were observed by studies made in Chinese skulls by Wang et al. in 1988 [10] and Ajmani in Nigerian and Indian skulls [11].

Other important anatomical landmarks of the greater palatine foramen are distance from the foramen to the posterior border of the hard palate (approximately 3 mm), perpendicular distance of the foramen to the midline maxillary suture (about 14 mm) [12], 0.3 cm from the inner border of the alveolar ridge [13], 10.72 mm from the alveolar crest, and 4.38 mm from the surface of the palatal mucosa in the palatal region between the first premolar and the first molar [14].

Differences in relation with age were not considered in these studies since they were made in adult skulls. Therefore, application of these findings in primary cleft palate surgery is limited and should be studied.

Some ethnic variations about the greater palatine foramen have been found in different studies and the bilateral symmetry of greater palatine foramen on both sides of each skull is remarkable [11].

Another point of reference of the hard palate to locate the greater palatine artery is bony prominences named as palatine spines (Figure 4).

These are small projections that arise from the middle, posterior margin of the maxilla near their junction with the palatine bone and divide the medial and lateral grooves.

These prominences project a few millimeters over the greater palatine vessels as they pass forward on the inferior surface of the palate and can be easily identified during the cleft palate surgery (Figure 3).

Palatal spines were frequently observed as bony prominences (66.3%, 57 sides) and were located at 6.49 ± 1.76 mm from the greater palatine foramen, with a length of 10.42 ± 2.45 mm [15].

In my personal experience, palatine spines are the most important point of reference to locate the greater palatine vessels during the surgery.

These bony prominences may be absent or small in 14.7% of cases (mostly in syndromic patients) [16].

The greater palatine artery reaches the mucoperiosteum of the hard palate and runs anteriorly, in the lateral portion of the palate near its junction with the alveoli.

The artery emerged in the posterior lateral section of the greater palatine foramen and it continued its pathway into an osseous groove until it reached the retroincisive zone.

The artery is divided into two or three branches at the exit of the foramen [17].

The most common greater palatine artery branching pattern was the one which gave off the medial and canine branches after the palatal spine (41.7%) [15].

In the same study made by Klosek and Rungruang, they observed that the greater palatine artery was branching most frequently at the level of first premolar (38%) and at first and second molars together (43%) in women [8].

In cleft patients, additional vascularization is provided by multiple branches passing both medially from the nasal mucosa and laterally toward the alveolus [18].

There are numerous arterial connections between nasal and palatal mucosa with connections made at bony margins and by perforating osseous arteries [18, 19].

These branches are divided by medial and lateral incisions and subperiosteal dissection during conventional palatoplasty.

The descending palatine artery provides additional branches, named as lesser palatine arteries, which enters the palate through the lesser palatine foramen to supply the soft palate [19, 20] (Figure 1).

The soft palate is supplied by the following arteries: (a) ascending palatine artery (from facial artery mainly), (b) tonsillar (branch of the ascending palatine artery), (c) ascending pharyngeal artery (from external carotid artery), (d) lesser palatine arteries (from the greater palatine artery), and (e) recurrent pharyngeal artery (from the external carotid artery) [18, 21].

Facial artery provides additional blood supply to the hard palate by the ascending palatine artery (Figures 3 to 7).

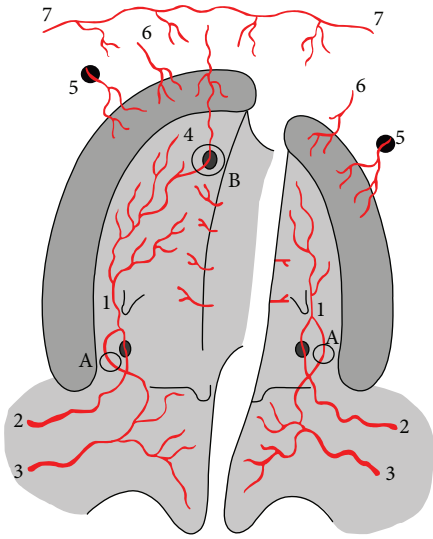
This artery supplies mainly the superior pharyngeal constrictor and the soft palate.

There is a large network of anastomoses between the vessels that supply the hard palate and soft palate [21] (Figures 3 to 7).

The most important are the anastomoses between the ascending palatine and lesser palatine arteries and acquire importance when the greater palatine artery is sectioned accidentally during palatoplasty.

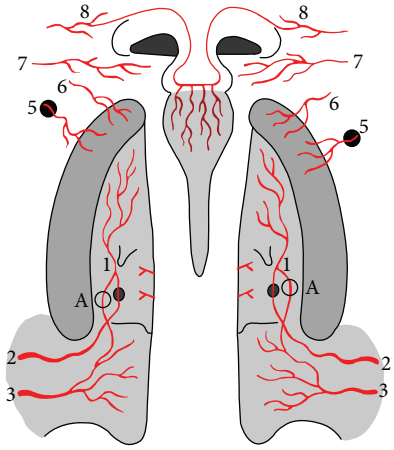
Few studies have been published reporting anatomical variation of these vessels and its relation with some nondesirable outcomes after cleft palate repair.

Maher in 1977 described position and variations of the arteries of the palate in cleft patients and observed in cleft and noncleft fetuses arterial anastomoses between the greater palatine artery and infraorbital, superior alveolar, sphenopalatine branches from the maxillary artery, and superior labial branches from the facial artery [5, 18] (Figures 5, 6, and 7).



Unilateral cleft palate

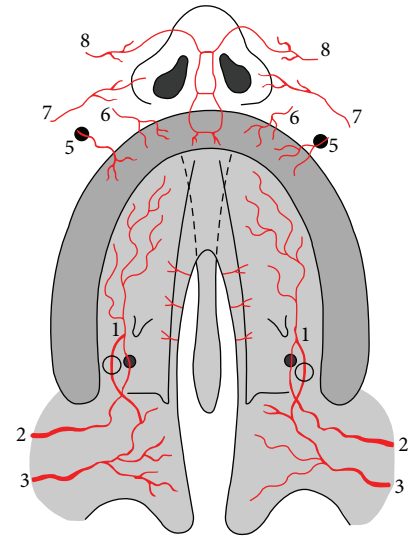
FIGURE 5: Unilateral cleft palate vascularization. 1: greater palatine artery; 2: descending palatine artery; 3: ascending palatine artery; 4: anterior palatine artery; 5: branches from infraorbital artery; 6: superior alveolar artery; 7: branches superior labial artery. A: vascular anastomoses between descending palatine artery and ascending palatine artery through lesser palatine vessels; B: vascular anastomoses between greater palatine artery and anterior palatine artery.



Bilateral cleft palate

FIGURE 6: Bilateral cleft palate vascularization. 1: greater palatine artery; 2: descending palatine artery; 3: ascending palatine artery; 5: branches from infraorbital artery; 6: superior alveolar artery; 7: branches superior labial artery; 8: dorsal nasal artery. A: vascular anastomoses between descending palatine artery and ascending palatine artery through lesser palatine vessels.

Gauthier et al. (2002) published a study performing ligation of both descending palatine arteries (in setting of Le Fort osteotomies); subsequent colored latex injection demonstrated perfusion of the hard palate mucosa via anastomoses between the greater palatine and ascending palatine arteries



Incomplete cleft palate

FIGURE 7: Incomplete cleft palate vascularization. 1: greater palatine artery; 2: descending palatine artery; 3: ascending palatine artery; 5: branches from infraorbital artery; 6: superior alveolar artery; 7: branches superior labial artery; 8: dorsal nasal artery. A: vascular anastomoses between descending palatine artery and ascending palatine artery through lesser palatine vessels.

through the lesser palatine arteries and another soft palate collateral from ascending pharyngeal artery [6].

This study demonstrates the existence of vascular anastomoses between hard and soft palates and confirms that the section of the vascular pedicle of the flap is not necessarily related to flap necrosis [6].

In order to guarantee the blood supply of the hard palate through this anastomosis, the vascular connection should be preserved and the surgical dissection of the soft palate should be limited if the greater palatine artery is sectioned.

These findings support the concept described by Wardill and Dorrance in their techniques which include the section of both greater palatine pedicles in order to obtain proper length and closure of the palate with success, without any report of palatal necrosis in their group of patients [22, 23].

Traditional anatomical descriptions in noncleft humans consider the presence of an anterior palatine artery (from the sphenopalatine artery coming through the incisive foramen) and a vascular connection with the greater palatine artery, and this anastomosis has been observed only in unilateral cleft palates (noncleft side) and some incomplete cleft palates [5, 18] (Figure 8).

Maher in 1977 [18] developed an anatomical study with arteriographic examination in three human fetuses with cleft palate, based on Spriestersbach's theory who said that the aberrant craniofacial morphogenesis implies commensurate aberrant vascular supply [24].

During our surgical experience, we observe duplication, malposition, hypoplasia, and absence of the greater palatine foramen.

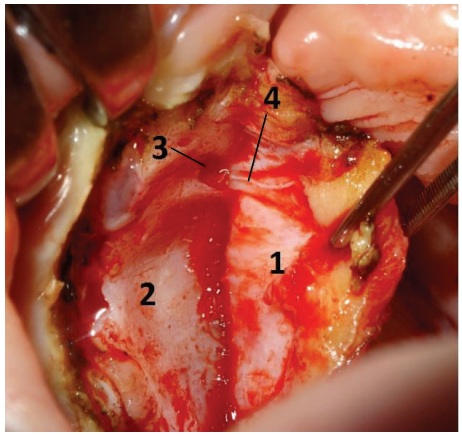


Figure 8: Anterior anastomosis of the palate. 1: mucoperiosteal palatal flap; 2: hard palate. 3: anterior palatine vessels and nerve coming through the anterior palatine foramen.

Vascular hypoplasia or absence is more common to observe in bilateral and incomplete cleft palates. Almost all cases of palatal necrosis evaluated during our practice belong to these types of cleft palates and seem to be the most probably related factor to the mucoperiosteal flap necrosis.

The growth of the nasal septum (vomer) outstrips the growth of other skeletal and soft tissues in the midface to such an extent that it is the pacemaker for growth of the face and anterior portion of the skull [25, 26].

The abnormal development of the nasal septum and nonattachment to the maxilla can be observed in bilateral and isolated (included submucous type) cleft palate [27, 28].

The role of this variations in the development of palatal flap necrosis remains unclear actually.

3. Etiology

Different etiologies have been described for the development of large defects after cleft palate repair like tension of the wound closure related to the surgeon's performance and cleft width, infection, and hematoma formation; however, it appears that necrosis of the mucoperiosteal flap is the most common cause of this complication [29].

The precise pathophysiologic events occurring in a failing flap are not totally understood.

To date there have been no major directly investigating the pathophysiology of conventional palatal mucoperiosteal flap failure after palatoplasty.

Palatal flap necrosis can be attributed to different causes.

These include mainly local causes (compression, tension, stretching, or section of the pedicle, vascular thrombosis, bleeding and hematoma, and surgical damage during the intervention).

In most cases, these causes can be minimized by careful perioperative management.

The association between use of local anesthesia with epinephrine and palatal flap necrosis was not studied yet; however, the use of lidocaine with epinephrine used before the surgery was found to have no harmful effect on the survival of nondelayed skin flaps.

This was the conclusion of an experimental study developed by Reinisch and Myers [30].

Compression of the pedicle is not a common event after palatoplasty.

Orientation of the greater palatine foramen and limited medial mobilization of the pedicle during the surgery make the compression of the greater palatine vessels difficult.

However, 2 factors may cause the compression of the palatal flap's pedicle: the use of islanded flaps and the severity of the cleft.

The utilization of islanded flaps, because of the section of the vascular anastomoses and the compression of the vascular pedicle over the greater palatine foramen due to the extended mobilization of the islanded flap.

Furlow [31] described before a relation between the use of island mucoperiosteal flap in association with his technique. He had 2 cases of flap necrosis in 100 operated cases.

Severe forms of cleft palate may affect the palatal flap's pedicle because of the tension and compression of the pedicle observed in these cases due to the extended mobilization of the flaps.

Wider cleft palates usually require extended dissection of the palate, mobilization of monopedicled flaps (based on hypoplastic vessels without additional blood supply from peripheral anastomoses), and surgical closure under some stretching and tension.

A study developed by Kuwahara and Yoshimoto found that older children and adults are more likely to develop hard palate mucoso-periosteal flap necrosis than infants in an investigation of 26 cleft palates in 13 patients aged 15 years or older that revealed that a number of anatomical differences were found when compared with infants [32].

Of these, abnormal bone protrusion appeared to be a factor that produced vascular compression and flap necrosis.

Stretching of a palatal mucoperiosteal pedicle flap also stretches vessels contained within it causing narrowing of their lumina and possible vascular occlusion and/or thrombosis.

The surgical injury of the pedicle (partial or total) is a rare event during the cleft palate repair. Its role in developing of palatal flap necrosis is not well studied.

Section of the vascular pedicle during the surgery has been associated with necrosis of the mucoperiosteal flap by some authors [2, 4].

However some authors concluded (based on previous observations) that the involuntary section of the greater palatine artery during the surgery is not necessarily in relation with flap necrosis [18, 20].

Controversy exists regarding the possible role of the artery's injury since authors like Dorrance and Wardill used the ligation of the vascular pedicle as a regular procedure during their surgical techniques for primary cleft palate repair without flap necrosis [22, 23].

This situation would be explained because of the vascular anastomoses between the greater palatine artery and the ascending palatine artery mentioned before.

Abnormal development of palatal vessels associated with the tissue's hypoplasia seems to be a probably related factor to the mucoperiosteal flap necrosis.

The growth of the nasal septum (vomer) outstrips the growth of other skeletal and soft tissues in the midface to such an extent that it is the pacemaker for growth of the face and anterior portion of the skull.

The abnormal development of the nasal septum and nonattachment to the maxilla can be observed in bilateral and isolated (included submucous type) cleft palates [27, 28].

Palatal flap necrosis is more common in these types of palatal clefts [1–3].

Other considerations related to the surgical technique and surgeon's performance are sutures too tightly secured and stitches inadvertently placed around the primary nutritional sources of a flap causing strangulation necrosis.

In addition, excessive manipulation of the pedicle may alter its blood supply causing ischemia and necrosis or atrophy.

Infection is a serious complication after palatoplasty because it may progress to flap necrosis [33, 34].

Ischemic or necrotic flaps may become infected secondarily and this condition is more commonly observed.

The extension of tissue necrosis may be increased by the presence of infection.

Zhang et al. have reported 9 cases of wound infection after cleft palate repair in 2100 patients [33] and Frolova et al. have found 13 cases with infectious inflammations of the wound from a sample of 153 babies after cleft palate surgery [34].

Primary infection of the surgical wound is rare and may be in relation to patient's immunodeficiency (mainly associated with severe chronic malnutrition).

Palate necrosis as a consequence of a palate infection has been reported by Sancho et al. in a 6-month-old child who presents this complication in relation to a suppurative medical otitis that involved hard and soft palates. The culture was positive for *Pseudomona aeruginosa* [35].

Careful examination and diagnosis of middle ear status and blood tests are recommended before cleft palate surgery in order to avoid this complication.

A study published by Maine et al. [36] observed a probable relation between the development of palatal fistulas after cleft palate repair and nutritional status of the patients; however, this association is not well demonstrated yet.

Additional studies are required in order to establish the association between the nutritional status and the development of fistulas or palatal necrosis.

A prospective study to evaluate possible pathogenic organisms associated with wound complications in the form of wound infections, wound breakdown, and the formation of oronasal fistulas was performed by Mÿburgh and Bütow and found that a group of organisms that originated from the colon/perineum is mostly associated with these postoperative complications [37].

The antibiotic resistance profile showed a high resistance to antibiotics such as ampicillin, amoxicillin-clavulanic acid, and first- and second-generation cephalosporins.

Frolova et al. [34] have found (on day 3 after the operation) Gram-negative Bacilli isolated from the majority of patients with postoperative wound infection coursing in the presence of marked dysbacteriosis.

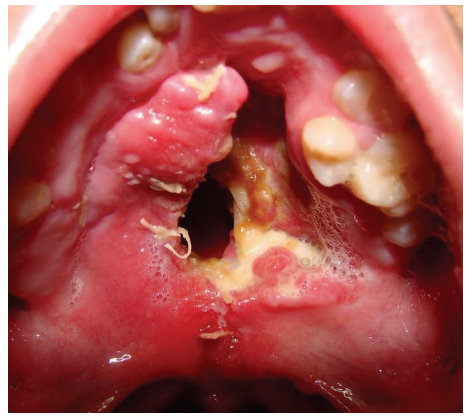


Figure 9: Twenty-one-year-old patient with incomplete cleft palate. After one week the patient returns and the repaired cleft palate showed necrotic tissue and dehiscence of the palate closure.

Chuo and Timmons [38] in a retrospective study found that children with unrepaired cleft lip and palate have a significant risk of carrying *S. aureus* and a small risk of carrying beta-hemolytic *Streptococci*.

However, colonization by *S. aureus* decreased significantly following surgical repair of the cleft lip and palate [39].

A prospective study published by Cocco et al. [40] observed a direct relation between palatal dehiscence and the presence of beta-hemolytic *Streptococci* and recommend a screening for *Streptococci* prior to surgery routinely.

All these studies did not evaluate association between pathogenic organisms and palatal necrosis.

Finally, the association between bleeding (hematoma) and mucoperiosteal flap necrosis is not well establish and additional studies are required.

Hematoma related necrosis of palatal flaps does not occur only because of the internal pressure. A toxic effect of the mass of blood on skin flaps has been demonstrated by Mulliken and Healey in an experimental rat model [41].

The role of bleeding as risk factor for flap necrosis could be related to the minimal incision technique because of the absence of lateral raw surfaces.

4. Diagnosis

This complication is characterized by early signs after palatoplasty which are change in a flap color (initially pale and then dark) associated with bad odor during the first days.

Signs of infection may be present and include swelling of the palate, irritability, raised temperature, and loss of appetite.

After 5 to 7 days, dehiscence of the surgical wound closure, loss of necrotic tissue, and some bleeding appear (Figure 9).

Then, the exposed palatal bone is resorbed leaving a defect which is characterized by large dehiscence or fistulas (bigger than the initial congenital defect) (Figures 10 and 11).

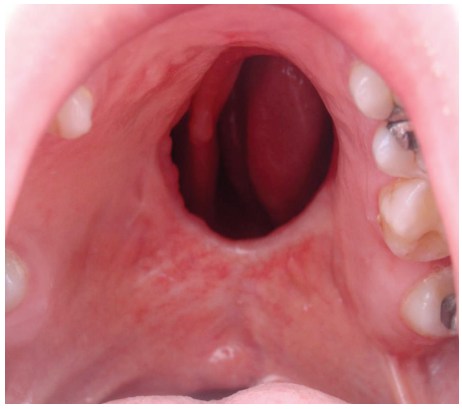


Figure 10: Large fistula after cleft palate repair in a 28-year-old patient with incomplete cleft palate.

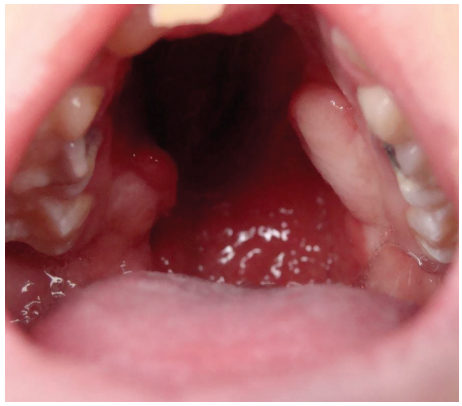


Figure 11: Large defect after cleft palate repair in a 12-year-old patient with bilateral cleft palate. The surgery developed bilateral palatal flap necrosis and the wound healed leaving a large defect in the hard and soft palate.

Blood tests are necessary in order to establish the diagnostic of infection associated with the necrotic tissue and the requirement of antibiotics.

5. Prevention

In most cases, causes of flap necrosis can be minimized by careful preoperative planning and prevention is possible.

Nutritional status of the patient, associated diseases as middle ear infections, knowledge of the vascular anatomy of the palate, and type of the cleft should be considered during the preoperatory evaluation.

Based on the reviewed information we may consider the following recommendations in order to prevent palatal flap necrosis.

Cleft palate's degree of hypoplasia should be estimated before the surgery in order to design a proper surgical planning and prevent nondesirable outcomes.

Most of the reported cases of palatal necrosis are clefts with more tissue's hypoplasia.

We design a predicting scale for mucoperiosteal flap necrosis after primary palatoplasty to evaluate cleft palate's degree of hypoplasia.

This scale evaluates degree of hypoplasia and is based on the following items.

(a) Type of Cleft. It is based on Veau's classification for cleft palate deformity [42]:

(1) soft palate (score: 1),

(2) soft and hard palates (score: 4),

(3) unilateral soft and hard palates (score: 2),

(4) bilateral soft and hard palates (score: 4).

(b) Index of the Cleft Palate. It is based on the palatal index description for cleft palate deformity (proportion between the width of the cleft (cleft's severity) and the summary of the width of the two palatal segments (tissue deficiency)) measured at the level of the hard and soft palates junction [43]:

(1) mild index: less than 0.2 (score: 1),

(2) moderate index: 0.2 to 0.4 (score: 2),

(3) severe index: greater than 0.4 (score: 4).

(c) Length of Soft Palate. It is based on Randall's classification for cleft palate deformity [44].

(1) Uvula reaches the posterior pharyngeal wall (score: 1).

(2) Uvula reaches the posterior half of the adenoid pad (score: 2).

(3) Uvula is located at the anterior half of the adenoid pad (score: 3).

(4) Uvula is located anteriorly to the adenoid pad (score: 4).

5.1. Grading Scale Score

Low risk is total score 3–5.

Moderate risk is total score 6–8.

High risk is total score 9–12.

Based on the cleft palate's degree of hypoplasia scale we may propose the following surgical protocol:

(a) *mild (risk score 3–5)*

unipedicled flaps (two-flap palatoplasty),

(b) *moderate (risk score 6–8)*

bipedicled flaps (Von Langenbeck technique),

(c) *severe (risk score 9–12)*

soft palate closure + vomer flap (delayed hard palate closure).

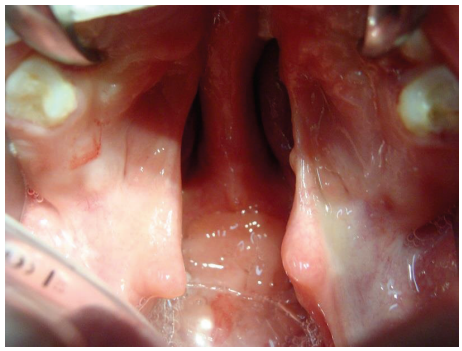


Figure 12: A one-year-old girl with a history of bilateral cleft lip and palate. The cleft palate was classified as Veau 4, Randall 4, and severe palatal index (0.48) with high risk score for palatal necrosis.

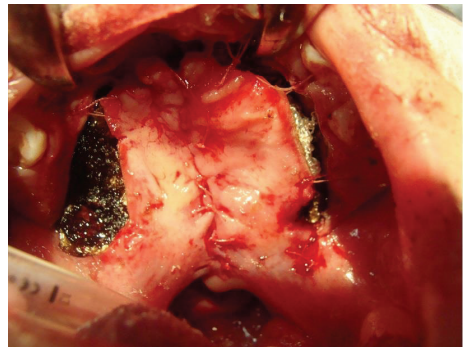


Figure 13: The cleft palate was closed using the two-flap palatoplasty at on year old.

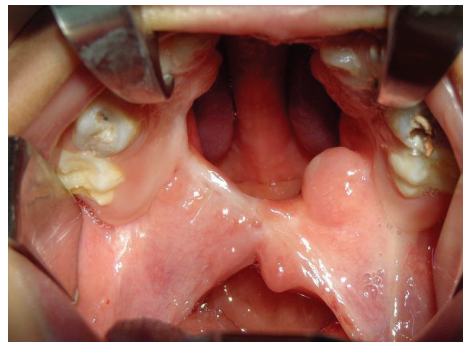


Figure 14: The surgery developed bilateral palatal flap necrosis and the wound healed leaving a large defect in the hard and soft palate.

This scale has not been validated before and will be studied in the near future.

Surgical design should be based on the anatomical considerations described before and the surgical technique should be carefully selected based on the type of repair, type of cleft, and its severity.

During cleft palate surgery all the vascular anastomoses are sectioned using flaps based in one pedicle (two-flap technique) (Figures 5 to 7).

This technique has an increased risk of palatal flap necrosis and should be avoided in cleft palates with hypoplastic vessels (bilateral and incomplete cleft palates).

Unipedicled flaps are used in our program only in the noncleft side of unilateral cleft palates because the arteries are well developed.

Anterior vascular anastomoses (branches coming from infraorbital, alveolar, and superior labial arteries) are preserved using the Von Langenbeck method.

However, these vascular connections may be affected by the lip surgery previously done in special branches from infraorbital and superior labial arteries. The labioalveolar sulcus incision during cheiloplasty should be limited in order to preserve these vessels.

This technique is recommended in cleft palates with hypoplastic vessels (incomplete and bilateral cleft palates).

Severe forms of incomplete and bilateral cleft palate require a careful surgical design to prevent this devastating complication (Figures 12, 13, and 14).

Bipedicled flaps (based on Von Langenbeck's concept) are recommended for these types of clefts. In severe bilateral cleft palates, we use the delayed hard palate closure without elevation of mucoperiosteal flaps.

Variations in palatal arterial distribution cannot be determined before surgery.

However, changes in position and hypoplasia or absence of these vessels can be identified during the surgery if the procedure is performed with caution avoiding damage of these structures and taking decisions to preserve vascular anastomoses.

Injury of the greater palatine artery is not necessarily related to flap necrosis; however, this situation requires a special management in order to prevent this complication.

Our protocol under this scenario includes first the compression of the greater palatine foramen using some resorbable material in order to control the hemorrhage.

Then the surgical dissection should be stopped at the side of the injured vessel preserving the vascular anastomosis between the mucoperiosteal flap and the soft palate.

The cleft palate surgery can be continued doing an extended dissection of the tissues in the opposite side in order to obtain a surgical closure with minimal tension.

Similar proceeding is recommended in case of injury of the greater palatine vessels with the cautery or surgical needle.

Finally, in relation to the wound infection. Frolova et al. suggest a method for wound infection prevention in uranoplasty, consisting in irrigation of the operative wound with acilact suspension (a biopreparation) and shortening of antibiotic prevention course to just 48–72 [34].

However, this method required additional studies to evaluate its efficacy.

The data obtained in a study developed by Savenkova et al. [45] show that the development of intercurrent diseases and postoperative complications (not specifically palatal necrosis) can be prevented by the parenteral application of cephalosporins of the III and IV generations as well as by oral administration of cefixime and protected aminopenicillins.

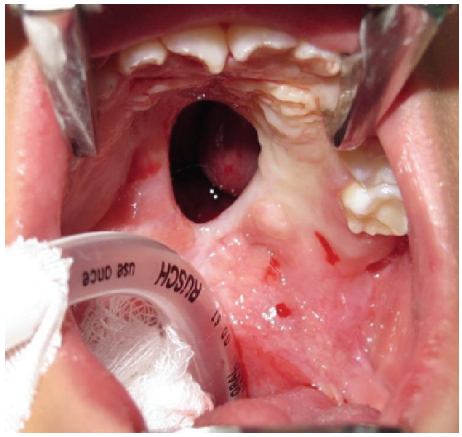


Figure 15: Nine-year-old patient with diagnosis of incomplete cleft palate and a severe fistula after cleft palate repair complicated with flap necrosis.

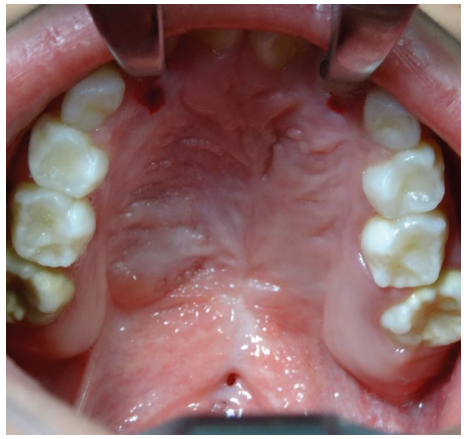


Figure 16: Postoperative view of the palate after one year. The defect was closed using two mucoperiosteal flaps.

This antibiotic prophylaxis protocol requires scientific validation.

6. Management

Initial management of this complication may require surgical debridement of the necrotic tissue; however, most of the patients presented for follow-up few days after surgery had an autolytic debridement of the necrotic flap and irrigation of the wound and antibiotics during 5 days are only necessary to prevent any infection (Figure 9).

As some bleeding may be associated, if this is moderate or severe, reoperative hemostasis is required in surgical room.

Treatment of the sequels especially when the defects are wide and scarred is a challenge for both patients and plastic surgeons, with high rate of recurrence.

Large defects after cleft palate repair produce various symptoms, including regurgitation of fluid into the nasal cavity, hearing loss, and velopharyngeal insufficiency.

In these cases, the palatal tissue around the fistula can be quite scarred and in short supply.

A variety of reconstructive options are commonly employed, using local and distant flaps or combination of both.

The first option in our protocol of management is the use of local flaps (Figures 15 and 16).

The availability of healthy tissue from palatal mucosa should be evaluated and identification of greater palatal artery patency using Doppler is necessary.

However, at times the site and the size of the fistula make use of local flaps for its repair a remote possibility.

The combination of buccal mucosa and buccinator muscle as an axial myomucosal flap based on the facial artery has been described by Pribaz et al. [46].

This flap consists of mucosa, submucosa, part of the buccinator and orbicularis muscles, and the facial artery with its venous plexus.

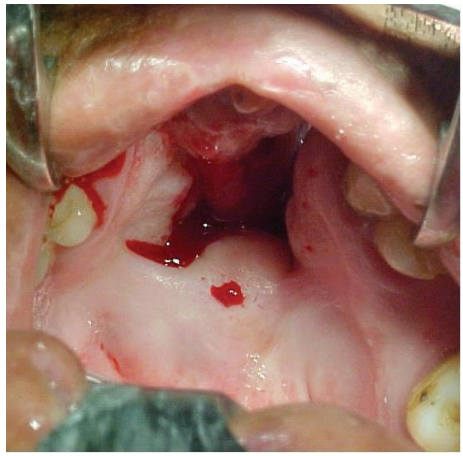


Figure 17: Severe anterior fistula after cleft palate repair in a 32-year-old patient with bilateral cleft palate. Surgery was complicated with distal flap necrosis.

This is known as the facial artery musculomucosal (FAMM) flap and is one of the most used flaps for intraoral defects (Figures 17 and 18).

Partial flap necrosis has been described in 18% of cases using this flap [47].

Some described limitations of this flap are as follows: surgical elevation can be technically challenging and its pedicle may interfere with the dental occlusion and eruption of permanent molars. Close to 26% of cases required further surgery to divide the bridge segment of the flap usually after 3 weeks [48].

Bite block may be required postoperatively in order to prevent an injury of the flap.

The author of this paper described a variation of this flap including an island of skin (named as FAMMC (facial artery myomucosal cutaneous) flap) to be used when the amount of nasal mucosa is not enough [49].

We observed partial necrosis in one case (8.3%) and one dehiscence (8.3%) using this flap.

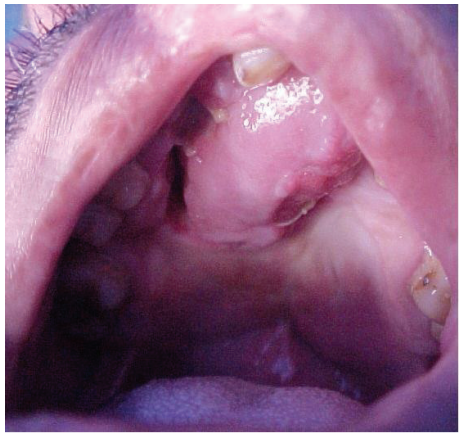


Figure 18: The fistula was closed using the FAMM flap.

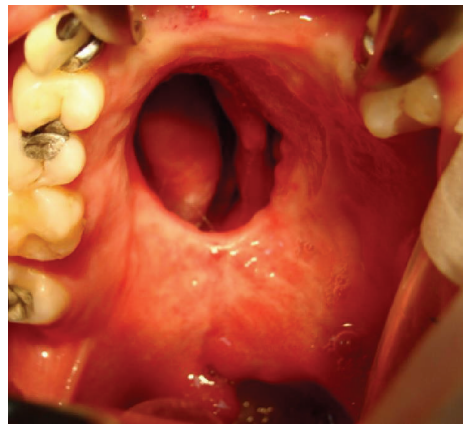


Figure 19: Large fistula after cleft palate repair in a 28-year-old patient with incomplete cleft palate. The surgery developed extensive flap necrosis and the wound healed leaving a large defect in the palate.

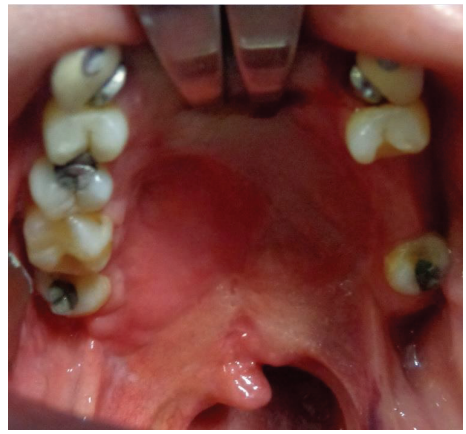


Figure 20: The defect was repaired using a combination of local mucoperiosteal flap and FAMM flap.

Two-layer method of fistula repair is recommended in any technique to avoid recurrences.

In conventional fistula repair, the fistula margins are dissected 2 to 3 mm around the fistula as a turndown flap from oral mucosa closing the nasal layer of the palate.

However, this procedure is not adequate to close the nasal layer in larger fistulas.

Use of FAMMC flap and utilization of pharyngeal flaps or mucosal grafts are indicated in these cases [49–51].

Main limitations for facial artery flaps are requirement of an open dental arch for passage (anteriorly based type), width of the flap limited to 1.5 to 2 cm, and the inclusion of facial muscles, which could interfere with speech development.

In addition, these local axial flaps are hampered by a need for scrupulous postoperative patient compliance.

The pedicle buccal fat pad flap is another option as combined method when the nasal mucosa is repaired and there is deficiency of tissues from oral mucosa [52].

Similar use has been described for amniotic membrane allograft and a cellular dermal matrix [53, 54].

Combination of local flaps and facial artery flaps can is recommended when the defect is too large (Figures 19 and 20).

Use of temporoparietal-galeal flap and temporalis muscle flap has been described for palatal fistula repair too [55, 56].

This technique has been described as being able to cover palatal defects; however, it usually leaves a temporal hollow as a donor-site deformity and in children might not be sufficiently developed for transposition [57].

In addition, for adequate transposition and sufficient length, an osteotomy of the zygomatic arch might be necessary, with the dissection procedure endangering the frontal arch of the facial nerve.

Tongue flaps were introduced for intraoral reconstruction by Lexer in 1909 [58].

The excellent vascularity and the large amount of tissue that tongue flaps provide have rendered the flaps appropriate for the repair of large fistulas in operated cleft palates.

The central position in the floor of the mouth, mobility, and the diversity of positioning the flaps make it a method of choice for closure of anterior palatal fistula especially (Figures 21 and 22).

Complications include hematoma, sloughing, epistaxis, dehiscence, loss of tongue taste and sensation, narrowing of the tongue, and flap necrosis with recurrence of fistulas [59–61].

Described intraoral flaps are actually the standard of care; however, the donor-site morbidity, multistage operative protocols, and the use of nasogastric tube for patient's feeding during some days required for many of these flaps make them less than ideal.

Microvascular tissue transfer may be indicated for more severe cases with large defects, extensive scar tissue around the fistula, and repeated failure of conventional methods.

With experienced hands and proper teamwork, free-tissue transfer has achieved a success rate of 95 percent [62].

First dorsal metatarsal artery dorsalis pedis flap, angular scapular flap, radial forearm flap, anterolateral thigh flap, and the temporal parietal flap were described with this purpose [62–66].

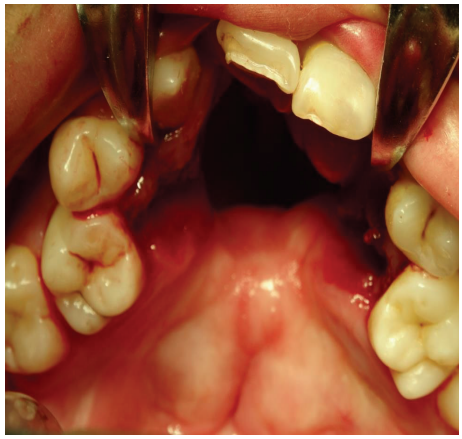


Figure 21: Fifteen-year-old patient with bilateral cleft lip and palate who has a large anterior palatal fistula after distal mucoperiosteal flap necrosis.

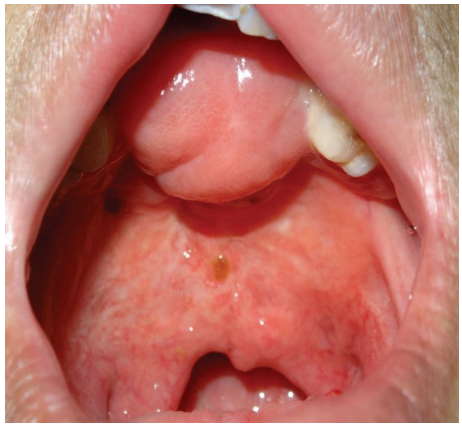


Figure 22: Fistula was closed using an anteriorly based tongue flap. After 2 weeks the flap was divided.

Use of free flaps requires competence in microsurgery, longer operative time, and prolonged hospitalization.

It may also lead to donor site morbidity and esthetically unsatisfactory results [62].

Donor site morbidity should be well considered for flap selection.

Use of tissue expanders has been described in palatal fistula repair; however, its utilization is not widespread and additional studies are required [67, 68].

Use of platelet rich plasma mixed with autologous bone graft seems to be an effective, safe, and low-cost technique for the closure of recurrent cleft palate fistulas [69].

The rehabilitation using obturator prosthesis is an option to surgical treatments [70].

In cases where the surgical treatment is contraindicated, the prosthetic rehabilitation becomes a definitive treatment [71, 72].

However, patients using obturator prostheses often present complications as ulcerations and stomatitis related to *Candida albicans* [73].

The presence of large oronasal communications alters the normal oral environment and different results are expected in this situation.

Reconstruction of the velopharyngeal sphincter is usually required in these cases.

7. Summary

Palatal necrosis after cleft palate repair is a rare but significant problem.

The extent of functional impairment is great and has psychological, social, and developmental consequences. Sequels affect feeding and speech of these patients.

Vascular anatomical variations including hypoplasia or absence of greater palatine vessels, injury of the pedicle, cleft type, surgeon's performance, and used surgical technique may be in relation to this complication.

Other risk factors such as nutritional status, associated anomalies, and concomitant infection should be evaluated and further prospective studies are necessary.

In most cases, causes of flap necrosis can be minimized by careful preoperative planning and prevention is possible.

Surgical techniques used for treatment of the sequels should be carefully selected based on sized and location of the defect and patient's condition.

Conflict of Interests

The author has no financial interests in any of the products, devices, or drugs mentioned in this paper.

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Clinical Study

Dimensions of Velopharyngeal Space following Maxillary Advancement with Le Fort I Osteotomy Compared to Zisser Segmental Osteotomy: A Cephalometric Study

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The objectives of this study are to assess the velopharyngeal dimensions using cephalometric variables of the nasopharynx and oropharynx as well as to compare the Le Fort I osteotomy technique to Zisser's anterior maxillary osteotomy technique based on patients' outcomes within early and late postoperative follow-ups. 15 patients with severe maxillary deficiency treated with Le Fort I osteotomy and maxillary segmental osteotomy were assessed. Preoperative, early postoperative, and late postoperative follow-up lateral cephalograms, patient histories, and operative reports are reviewed with a focus on defined cephalometric landmarks for assessing velopharyngeal space dimension and maxillary movement (measured for three different tracing points). A significant change was found between preoperative and postoperative lateral cephalometric measurements regarding the distance between the posterior nasal spine and the posterior pharyngeal wall in Le Fort I osteotomy cases. However, no significant difference was found between preoperative and postoperative measurements in maxillary segmental osteotomy cases regarding the same measurements. The velopharyngeal area calculated for the Le Fort I osteotomy group showed a significant difference between the preoperative and postoperative measurements. Le Fort I osteotomy for advancement of upper jaw increases velopharyngeal space. On the other hand, Zisser's anterior maxillary segmental osteotomy does not alter the dimension of the velopharyngeal space significantly.

1. Introduction

Patients with cleft lip and palate have changes of the maxilla concerning anatomical dimension, position, and function with diverse prevalence of these changes, which are caused by genetic, developmental, and treatment-associated determinants [1, 2]. In planning secondary orthognathic surgery, the jaw and occlusal relations must be considered in addition to the functional aspects of the pathology [3, 4].

(1) Velopharyngeal Function. Length and position of the velum may lead to speech impairment or borderline compensated speech [5].

(2) Reduced Maxillary Length (Shortened Maxilla). It lacks space in the dentate area for prosthodontic treatment (bridges, implants) [6].

(3) Maxillary Retrognathia. It may lead to esthetical and functional complaints [7].

(4) Velopharyngeal Flap (Velopharyngoplasty). It, completed at an early stage of growth, may result in a reduced anterior growth of the maxilla [8].

Frequency of maxillary osteotomy for advancement is correlated with the spectrum of severity of labiopalatal clefting [9]. Advancement of the maxilla by a Le Fort I

osteotomy carries the risk of increased velopharyngeal space and deterioration of speech function, ending up in hypernasal resonance [10–12], advancement of a short maxilla without gaining new space for prosthodontic treatment, and prevention of sufficient anterior movement caused by the velopharyngeal flap.

Maxillary segmental osteotomy, first described by Zisser (1969) [13, 14], advances the anterior maxillary segment without disturbing nasopharyngeal function. Several modifications of segmental osteotomy such as transpalatal or segmental osteotomy have been described for the maxilla [15, 16]. It seems that using a segmental osteotomy may prevent foreseen problems of conventional maxillary osteotomy for advancement such as disturbance of nasopharyngeal function. However, it is important to define specific indications for when each treatment should be utilized.

In this study, a cephalometric analysis was conducted to evaluate and compare the position of the maxilla, the length of the maxilla, and dimension of the velopharyngeal space after Le Fort I and segmental osteotomy.

2. Patients and Methods

After having an approval from local ethics committee in 2013, patient charts were reviewed with the key words "maxillary osteotomy" between 1997 and 2012 in the surgical records of one surgeon in order to make comparison between different surgical procedures without any effect of surgeon's personal preferences. After exclusion of syndromic cases, patients who had maxillary osteotomy previously and had additional systemic disorders, 38 maxillary osteotomy patients were identified initially. Subsequently, 15 were excluded due to lack of records, four patients were excluded due to a setback procedure, and five patients were excluded due to less than 4 mm of advancement or multiple pieces of osteotomy. Therefore, seven patients who had the Zisser operation (named the Zisser group) and seven patients who underwent Le Fort I osteotomy (named the Le Fort group) were included in the study. Patient's characteristics and lateral cephalograms were recorded digitally and numbered by a different author (Susanne Jung) to deidentify cephalograms and ensure blinded measurements by the observer (another author, Furkan Erol Karabekmez). Preoperative cephalograms, taken at the closest date to the surgical procedure, were used for preoperative evaluation and were grouped as T1. Early postoperative cephalograms taken at closest date to the surgical procedure were named T2. The late postoperative cephalograms taken on the latest follow-up of the patient were named T3. Complications and date of the removal of elastics were also recorded.

2.1. Cephalometric Evaluation. The standard lateral cephalometric radiographs were transferred to digital images using a digital camera (DSC-W90, Sony Corp., Tokyo, Japan). The landmarks on the lateral cephalometric radiographic images were traced using Image J software (National Institutes of Health, http://rsbweb.nih.gov/, USA). After calibration with the scale, the following were measured using the "measure" tools of the program: posterior nasal spine (PNS) to posterior pharyngeal wall (PPW) distance parallel to the palatal plane (PP), PNS to PPW distance perpendicular to the PPW, tip of the uvula (U) to PPW distance parallel to the PP, U to PPW distance perpendicular to the PPW, anterior nasal spine (ANS) to PNS distance (for the maxillary dental arch length), PNS to U distance, sella-nasion plane (SN) PP angle (SN-PP), ANS to SN distance, and PNS to SN. The area located superior to the U-PPW line parallel to the PP was calculated. Points, distances, and areas used in the study are showed in Figure 1. Each measurement was calculated for T1, T2, and T3 time points by the same blinded observer. Different author performed the cephalometric tracings and the surgery.

2.2. Surgery. For Le Fort I surgery, patients are induced with nasotracheal hypotensive general anaesthesia and prepared for a standard intraoral Le Fort I procedure. Rigid skeletal fixation using a couple of 2.0 mm miniplates and screws to both sides was performed in all patients.

For surgery with the Zisser technique, presurgical orthodontic treatment includes the preparation of space for vertical interdental osteotomies between the second premolar and first molar on the upper jaw (between 15-16 and 25-26, according to the Palmer Notation Method). Surgery was performed following the standard procedure.

In the case of the distractor application, after the Le Fort I or segmental osteotomy, fixation was performed by using a bone born distractor (Medartis, Modus MDO 2.0, Basel, Switzerland) (Figure 2). The maxilla was advanced at a rate of 0.5 mm twice a day after a five-day latency period. The vector of the distractor was planned according to the vertical deficiency, if it existed. The amount of distraction was also determined according to the need of each patient.

2.3. Statistical Analysis. The angular, linear, and area measurements were compared using a Wilcoxon signed ranks test to assess the changes between T1 and T2 (as the surgical change); T2 and T3 (as the postsurgical change); and T1 and T3 in both Le Fort I and Zisser groups. Differences between surgical and postsurgical movements of the Le Fort I and Zisser groups' measurements were also compared with Mann-Whitney tests. Distractions versus nondistraction and cleft versus noncleft comparisons were also completed with Mann-Whitney tests.

Correlations between cleft palate history, distraction, and the measured parameters were investigated with the Spearman correlation coefficient test.

The intraobserver reliability was tested with the intraclass correlation coefficient test. Measurements were repeated 1 month later by the same observer. Statistical analyses were performed with PASW (version 18) software (SPSS Inc., Chicago, IL). The results are shown as the mean and the standard deviation; $P < 0.05$ was considered as significant.

3. Results

Mean follow-up time for the late postoperative lateral cephalogram (T3) was 20.5 months. T1 cephalograms were obtained mean 28.3 days preoperatively. T2 cephalograms were obtained mean 19.5 days postoperatively. Of the

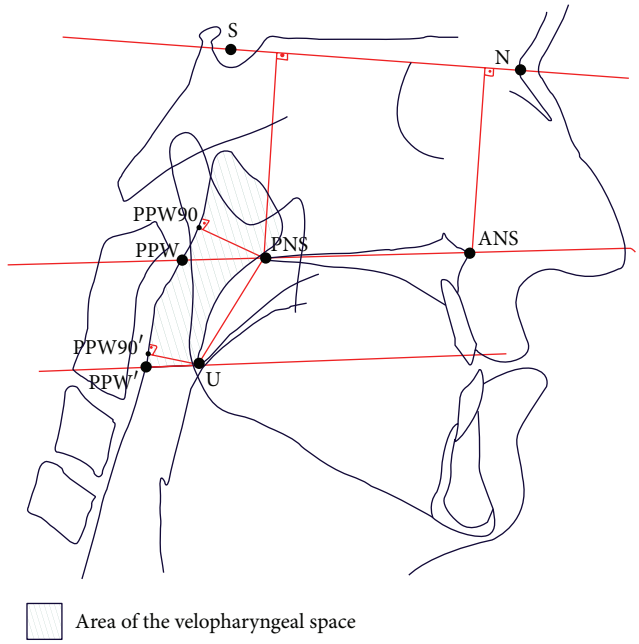

Figure 1: Variables used for cephalometric evaluations: *points*: ANS, most anterior point of anterior nasal spine; PNS, posterior nasal spine; PPW, posterior pharyngeal wall; U, tip of the uvula; S, midpoint of hypophyseal fossa; N, most anterior point of frontonasal suture. *Planes*: SN, sella-nasion plane; PP, palatal plane. *Distances*: PNS-PPW, distance measured parallel to the PP from PNS to PPW; PNS-PPW90, distance measured with line drawn perpendicular from PNS to PPW90; U-PPW′, distance measured parallel to the PP from U to PPW′; U-PPW90′, distance measured with line drawn perpendicular from U to PPW90′; ANS-PNS, distance measured ANS to PNS (for the maxillary dental arch length); PNS-U, distance measured from PNS to U; ANS-SN, distance measured with line drawn perpendicular from ANS to SN; PNS-SN, distance measured with line drawn perpendicular from PNS to SN. *Angle*: SN-PP, angle between SN and PP. *Area*: area of the airway located above the line drawn parallel to the PP and passing through U point.

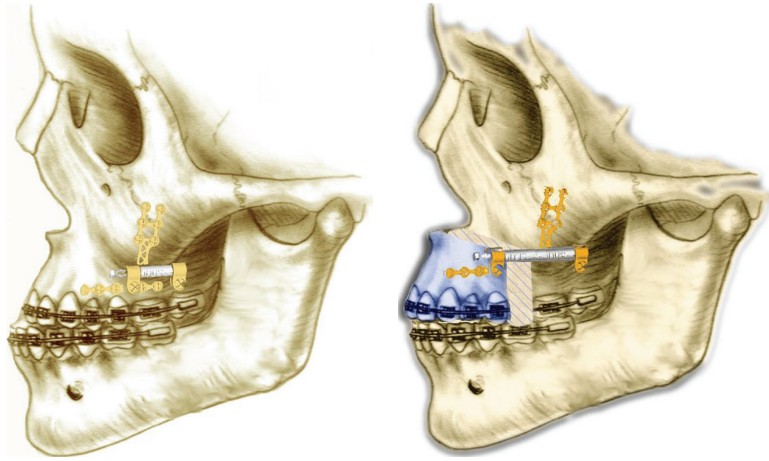

Figure 2: Vertical interdental osteotomies between second premolar and first molar on upper jaw according to Zisser technique followed by distractor application and activation.

14 patients, 8 were females and 6 were males. The age at the time of surgery was 15–36 years (mean 21 years). Six of the seven patients in the Zisser group and three of the seven patients in the Le Fort group have cleft lip palate. Four of the seven patients in the Le Fort group and three of the seven in the Zisser group had distraction osteogenesis. Patients' characteristics were summarized in Table 1. Variables used for cephalometric evaluations, including velopharyngeal soft tissue points, are shown in Figure 1.

Comparisons between T1 and T2 within the Zisser group for all measurements with Wilcoxon signed ranks test revealed no significant difference, except PNS-ANS distance ($P = 0.02$) (Table 2, Figure 3). Comparisons between T1 and T2 within the Le Fort I group for all measurements with

Table 1: Patient characteristics.

Group	Age	Advancement (left/right)	Distraction	Cleft	Follow-up (month)	Mandibular setback
Le Fort	16	11 mm	+	+	21	−
Le Fort	23	5 mm	−	−	1	−
Le Fort	36	7.5 mm/9.5 mm	−	−	11	+
Le Fort	20	9.5 mm	+	−	13	−
Le Fort	15	10 mm	+	+	24	−
Le Fort	17	7.5 mm	+	+	7	−
Le Fort	32	4 mm	−	−		+
Zisser	16	5.5 mm	+	−	1	−
Zisser	21	4 mm	−	+	1	−
Zisser	19	9 mm/7 mm	+	+	62	−
Zisser	17	7 mm	−	+	23	−
Zisser	20	8 mm	−	+	47	−
Zisser	25	4 mm	−	+	1	−
Zisser	16	9.5 mm/10.5 mm	+	+	28	+

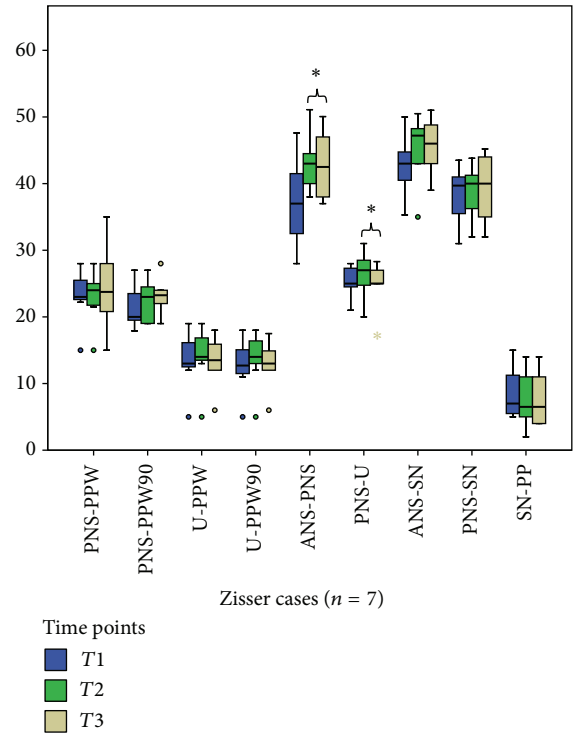

Figure 3: A statistically significant difference found between preoperative (T1) and postoperative (T2) ANS-PNS distances and postoperative (T2) and late postoperative (T3) PNS-U distances in the Zisser group. (Box plots show the median, interquartile range, 95% percentile, and outliers as circles. ∗ indicates significant difference.)

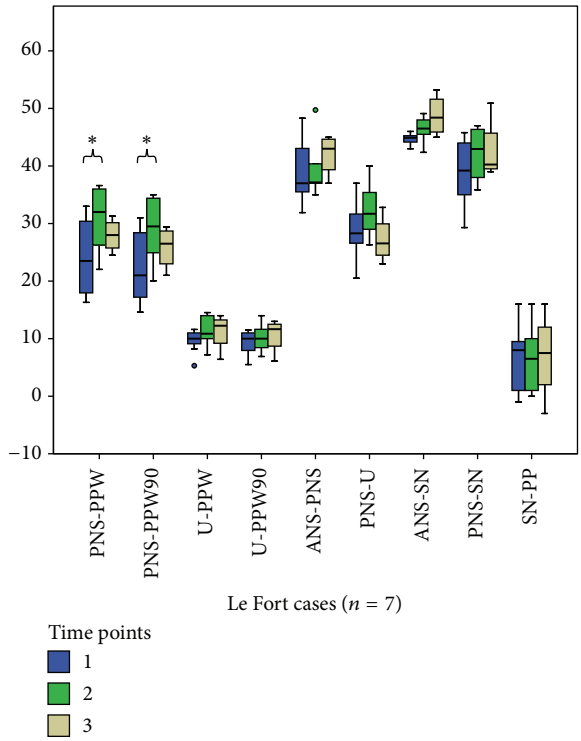

Figure 4: A statistically significant difference was found between T1 and T2 measurements for PNS-PPW and PNS-PPW90 in the Le Fort group. (Box plots show the median, interquartile range, 95% percentile, and outliers as circles. ∗ indicates significant difference.)

the Wilcoxon signed ranks test revealed significant differences concerning PNS-PPW distance, PNS-PPW90 distance, and velopharyngeal area ($P = 0.03$, 0.03, and 0.03, resp.) (Table 2, Figure 4).

Comparisons between T2 and T3 within the Zisser group for all measurements with the Wilcoxon signed ranks test revealed no significant difference, except PNS-U distance ($P = 0.03$) (Table 3, Figure 3). The comparison between T2 and T3 within the Le Fort group for all measurements with the Wilcoxon signed ranks test revealed no significant differences (Table 3, Figure 4).

Le Fort I group's patients' velopharyngeal area measurements, however, showed a significant change between T1 and T2 but not between T2 and T3 ($P = 0.03$ and 1.0, resp.)

Table 2: Surgical movements of all points and area for the Zisser and the Le Fort groups. Wilcoxon signed ranks test was used for the comparison.

Surgical movements (T2-T1)	Mean	SD	P
PNS-PPW			
Zisser ($N = 7$)	−0.2	0.7	0.45
Le Fort ($N = 7$)	6.5	3.6	0.03*
PNS-PPW90			
Zisser ($N = 7$)	−0.1	0.9	0.52
Le Fort ($N = 7$)	6.1	2.7	0.03*
U-PPW			
Zisser ($N = 7$)	0.6	1.5	0.27
Le Fort ($N = 7$)	1.9	2.4	0.14
U-PPW90			
Zisser ($N = 7$)	1.0	1.2	0.08
Le Fort ($N = 7$)	1.2	1.7	0.14
PNS-ANS			
Zisser ($N = 7$)	5.8	2.9	0.02*
Le Fort ($N = 7$)	1.5	2.0	0.07
PNS-U			
Zisser ($N = 7$)	1.0	1.6	0.14
Le Fort ($N = 7$)	2.1	3.0	0.12
SN-ANS90			
Zisser ($N = 7$)	2.3	5.9	0.35
Le Fort ($N = 7$)	1.9	2.3	0.12
SN-PNS90			
Zisser ($N = 7$)	0.5	2.7	0.50
Le Fort ($N = 7$)	3.0	4.8	0.12
SN-PP angle			
Zisser ($N = 7$)	−0.9	4.1	0.72
Le Fort ($N = 7$)	1.0	2.2	0.29
Area			
Zisser ($N = 7$)	10.4	21.9	0.18
Le Fort ($N = 7$)	66.4	62.2	0.03*

*Significant difference.

Table 3: Postsurgical movements of all points and area for the Zisser and the Le Fort groups. Wilcoxon signed ranks test was used for the comparison.

Postsurgical movements (T3-T2)	Mean	SD	P
PNS-PPW			
Zisser ($N = 7$)	2.0	5.4	1.0
Le Fort ($N = 7$)	−1.6	3.9	0.59
PNS-PPW90			
Zisser ($N = 7$)	2.7	3.7	0.69
Le Fort ($N = 7$)	−1.7	3.0	0.29
U-PPW			
Zisser ($N = 7$)	−1.0	2.1	0.30
Le Fort ($N = 7$)	−0.3	2.1	0.59
U-PPW90			
Zisser ($N = 7$)	−0.9	22	0.60
Le Fort ($N = 7$)	0.3	1.5	1.0
PNS-ANS			
Zisser ($N = 7$)	−0.2	0.8	0.41
Le Fort ($N = 7$)	−0.3	7.5	0.66
PNS-U			
Zisser ($N = 7$)	−2.7	1.8	0.03*
Le Fort ($N = 7$)	−1.6	2.1	0.29
SN-ANS90			
Zisser ($N = 7$)	0.3	3.1	0.89
Le Fort ($N = 7$)	2.8	1.4	0.11
SN-PNS90			
Zisser ($N = 7$)	0.9	2.2	0.35
Le Fort ($N = 7$)	2.4	2.0	0.11
SN-PP angle			
Zisser ($N = 7$)	−0.3	1.4	0.58
Le Fort ($N = 7$)	−3.0	3.6	0.18
T3.area			
Zisser ($N = 7$)	3.0	32.7	0.92
Le Fort ($N = 7$)	1.0	52.4	1.0

*Significant difference.

(Figure 5). On the other hand Zisser group's measurements showed no significant change. This supports that conventional Le Fort I osteotomy increases velopharyngeal space and may cause velopharyngeal insufficiency but Zisser's osteotomy does not.

The Le Fort I group versus Zisser group relationship regarding the T2-T1 (surgical changes) values with the Mann-Whitney tests revealed no significant differences between the differences at all time points except PNS-PPW, PNS-PPW90, and PNS-ANS distances and the measured area ($P = 0.003$, $P = 0.003$, $P = 0.02$, and $P = 0.02$, resp.) (Figure 6). This also supports that there is a significant difference between Le Fort osteotomy and Zisser osteotomy's sagittal pharyngeal tracings.

The comparison of all measured parameters on T1 time points between the Zisser and Le Fort groups showed a significant difference in the evaluation of the U-PPW distance ($P = 0.03$) (Figure 7). Additionally, the results of the PNS-PPW, PNS-PPW90, and PNS-U distances on the T2 time points between the Zisser and Le Fort groups were significantly different ($P = 0.02$, 0.04, and 0.04, resp.) (Figure 8).

Distraction versus nondistraction comparison with Mann-Whitney tests at the T1 time point revealed no significant difference for all parameters measured at the three time points.

Cleft versus noncleft comparison with Mann-Whitney tests at the T1 time point revealed no significant difference, except the velopharyngeal area of T1 ($P = 0.04$).

There is a negative correlation between the amount of maxillary advancement and area of velopharyngeal space measured at T1 ($P = 0.004$) and cleft palate and area of the velopharyngeal space measured at T1 ($P = 0.03$) for all patients. A positive correlation was found between maxillary

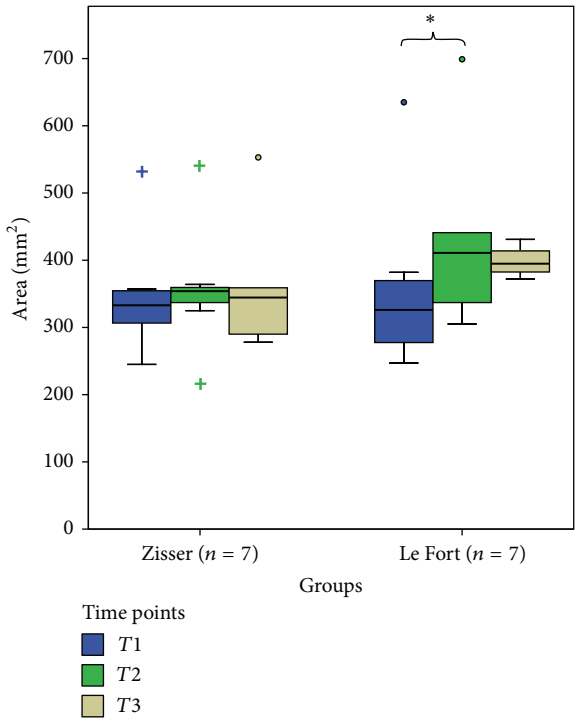

Figure 5: A statistically significant difference was found between T1 and T2 measurements for the area of velopharyngeal space in the Le Fort group. (Box plots show the median, interquartile range, 95% percentile, and outliers as circles and extreme values as plus signs. ∗ indicates significant difference.)

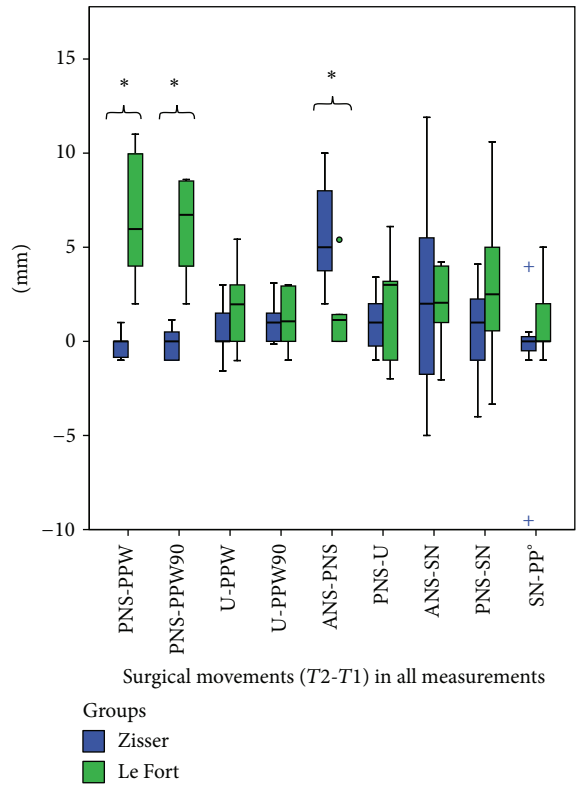

Figure 6: Statistically significant differences were found between Zisser and Le Fort groups' surgical changes (T2-T1) regarding the PNS-PPW, PNS-PPW90, and ANS-PNS distances. (Box plots show the median, interquartile range, 95% percentile, and outliers as circles and extreme values as plus signs. ∗ indicates significant difference.)

advancement and SN-PP angle measured on T2 ($P = 0.049$). Other correlations revealed no significant relationship.

Intraobserver reliability was ≥0.95 for all representative measurements.

4. Discussion

Velopharyngeal insufficiency and hypernasality are serious problems commonly observed in cleft lip palate patients. These patients have increased risk of speech deterioration, especially after maxillary advancement procedures [17–19]. Velopharyngeal closure is a complex mechanism affected by multiple factors, such as the soft palate's length, function, and posture, the dimensions of the nasopharynx, and the activity of the posterior and lateral pharyngeal walls, according to Mazaheri et al. [20]. There is no single method to assess all of these factors affecting velopharyngeal function. Static measurement on lateral cephalograms gives information for the morphological changes in the velopharyngeal anatomy [21]. Based on the previous literature related to velopharyngeal evaluation, the cephalometric landmarks used in this study were chosen [21, 22].

Different authors provided clear evidence showing the deleterious effect of maxillary advancement and clearly documented that the forward shift of the maxilla produced velopharyngeal inadequacy and hypernasal resonance [10–12, 23]. There was a significant increase in the measurements of PNS-PPW, U-PPW, and the area of the velopharyngeal space, which may have a potential role in velopharyngeal insufficiency with one-segment maxillary advancement in the current study as well.

Zisser's approach was described especially for retrusive hypoplastic maxilla cases, such as patients with cleft lip palate [14]. Osteotomy between the second premolar and first molar, as well as advancement of the anterior segment, provides maxillary advancement without a deleterious effect on the velopharyngeal space, in theory. The main advantage of the technique is that the position of the soft palate is not changed substantially, and it is expected that speech impediments such as those possibly arising following Le Fort I osteotomy are possibly obviated. Another positive effect of Zisser maxillary advancement is the effective closure of the anterior open bite. However, no study in the current literature revealed any quantitative measurement for the evaluation of Zisser maxillary advancement regarding the velopharyngeal structure and functionality. It is shown that Le Fort group patients show significant increase regarding PNS-PPW and velopharyngeal area on the lateral cephalogram (Table 2, Figure 6). On the other hand, the Zisser group showed no significant change in the mentioned measurements. Therefore, we suggest that

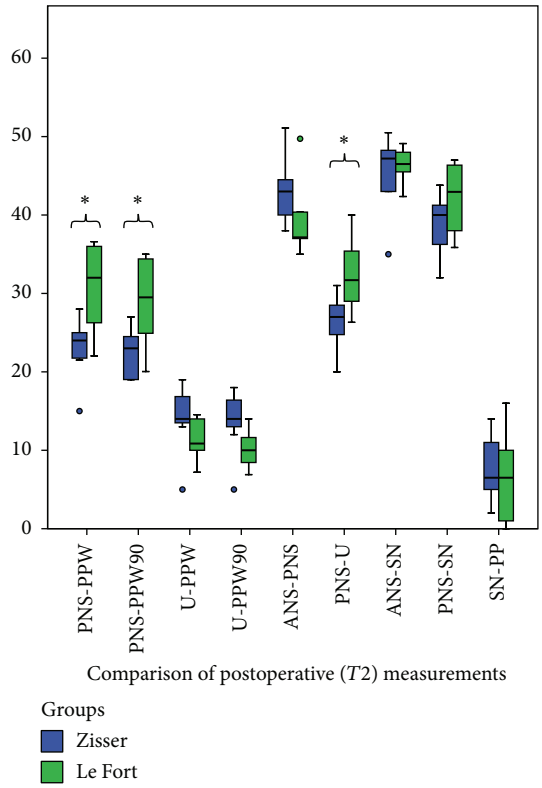

Figure 7: A statistically significant difference was found between the Zisser and Le Fort groups' measurements of T1 regarding the U-PPW distance. (Box plots show the median, interquartile range, 95% percentile, and outliers as circles and extreme values as plus signs. ∗ indicates significant difference.)

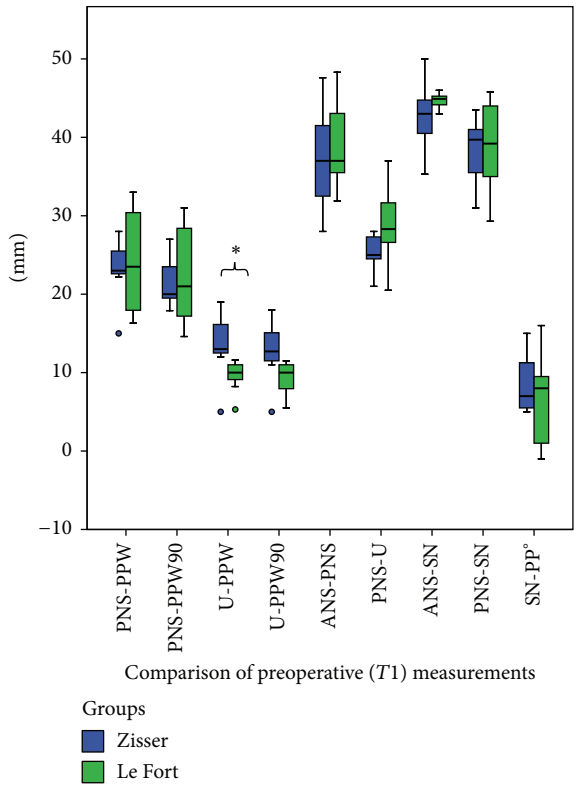

Figure 8: Statistically significant differences were found between the Zisser and Le Fort groups' measurements of T2 regarding the PNS-PPW, PNS-PPW90, and PNS-U distances. (Box plots show the median, interquartile range, 95% percentile, and outliers as circles and extreme values as plus signs. ∗ indicates significant difference.)

maxillary segmental advancement with Zisser osteotomy will not compromise velopharyngeal function.

Some authors claimed that maxillary advancement might improve or worsen certain aspects of speech in patients [18, 24]. Different authors suggest that maxillary advancement may improve articulation due to correction of the occlusion but cause hypernasal speech. It is shown that assessment of palatal length and pharyngeal depth on cephalometric radiographs is helpful in predicting postoperative velopharyngeal insufficiency development [19, 25]. Therefore, we used cephalometric parameters showing pharyngeal depth as a predictor of velopharyngeal insufficiency and compared two maxillary advancement techniques with these parameters.

Zisser osteotomy not only has the advantage of preventing risk of increased velopharyngeal space but also helps to increase the sagittal length of the maxilla, which is important for gaining extra space for prosthodontical treatment in patients with short maxilla. Significant increase in the distance of ANS-PNS with Zisser osteotomy in the current study also showed Zisser osteotomy's effect on maxillary lengthening (Table 2, Figure 6).

One limitation of the present study is the small sample size. Since the indication for Zisser osteotomy is rare, setback and three-piece osteotomies are excluded, and only patients with advancement of more than 4 mm were included in the study. Thus, we had relatively few cases. Another limitation of the study is the lack of functional evaluation, such as video fluoroscopy. However, the main aim of our study was to file the changes of the static cephalometric parameters regarding the morphology of the velopharyngeal structures. It is already shown in the literature that increased velopharyngeal space is associated with increased risk of velopharyngeal insufficiency after the maxillary advancement procedures [12, 19, 23, 26, 27]. The Zisser osteotomy group revealed no significant changes in PNS-PPW and U-PPW distances, whereas the Le Fort I osteotomy group evidenced significant changes in the same distances, including an extension of the upper airways and an increase in the velopharyngeal space.

5. Conclusion

Zisser's anterior segmental osteotomy is a reliable procedure for advancement of maxilla with respect to morphological changes in the velopharyngeal structures, especially sagittal measurements and measurements of area of velopharyngeal space on lateral cephalograms. Zisser's osteotomy may become the best solution in selected cases, such as cleft patients who have anterior open bites and increased risk of postoperative velopharyngeal insufficiency.

Ethical Approval

This study was approved (accepted as exempt) by local ethics committee (Ethics Committee of the Medical Association of West Falen-Lippe and Medical Faculty of the University of Munster).

Disclosure

Names of the authors in the front matter are ordered according to the order of the authorship. The study was accomplished in the University Hospital Münster, Oral and Maxillofacial Surgery Clinics.

Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contribution

Furkan Erol Karabekmez, Johannes Kleinheinz, and Susanne Jung have made substantial contributions to conception and design of the study. Furkan Erol Karabekmez, Johannes Kleinheinz, and Susanne Jung have been involved in drafting the paper. All authors have given final approval of the last version.

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Review Article

Current Controversies in Diagnosis and Management of Cleft Palate and Velopharyngeal Insufficiency

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Background. One of the most controversial topics concerning cleft palate is the diagnosis and treatment of velopharyngeal insufficiency (VPI). *Objective*. This paper reviews current genetic aspects of cleft palate, imaging diagnosis of VPI, the planning of operations for restoring velopharyngeal function during speech, and strategies for speech pathology treatment of articulation disorders in patients with cleft palate. *Materials and Methods*. An updated review of the scientific literature concerning genetic aspects of cleft palate was carried out. Current strategies for assessing and treating articulation disorders associated with cleft palate were analyzed. Imaging procedures for assessing velopharyngeal closure during speech were reviewed, including a recent method for performing intraoperative videonasopharyngoscopy. *Results*. Conclusions from the analysis of genetic aspects of syndromic and nonsyndromic cleft palate and their use in its diagnosis and management are presented. Strategies for classifying and treating articulation disorders in patients with cleft palate are presented. Preliminary results of the use of multiplanar videofluoroscopy as an outpatient procedure and intraoperative endoscopy for the planning of operations which aimed to correct VPI are presented. *Conclusion*. This paper presents current aspects of the diagnosis and management of patients with cleft palate and VPI including 3 main aspects: genetics and genomics, speech pathology and imaging diagnosis, and surgical management.

1. Imaging Procedures for the Assessment of Velopharyngeal Function during Speech: Multiplanar Videofluoroscopy and Intraoperative Videonasopharyngoscopy

At the present time, the combination of videonasopharyngoscopy (VNP) and multiplanar videofluoroscopy (MPVF) is the procedure of choice for assessing velopharyngeal function during speech. VNP can provide images of the entire vocal tract in motion during speech production also known as articulation. MPVF provides X-ray images of the vocal tract during this same function [1–4].

The earliest recorded examination of the velopharyngeal sphincter in motion during speech was reported by Hilton in 1836. The earliest radiographic assessment of the velopharyngeal valve appeared in 1909 [5]. Since those earlier reports, after extensive research and technological advancement, VNP and MPVF are today the state of the art for the examination of the upper vocal tract during speech including the velopharyngeal sphincter. Although some centers use

only the lateral or sagittal view of the soft palate and posterior pharyngeal wall during speech, in combination with VNP [6], several reports have emphasized the importance of a three-dimensional conceptualization of velopharyngeal seal during speech, that is, to study the velopharyngeal valve from the coronal, sagittal, and axial planes [1–3].

One of the most important elements of velopharyngeal closure is lateral pharyngeal wall motion. The use of only a sagittal view precludes the observation of this element. Furthermore, due to velar overlapping it is relatively frequent that lateral pharyngeal wall motion cannot be appropriately examined by VNP.

The advantage of VNP is that the soft tissue structures of the vocal tract, especially the velopharyngeal sphincter, can be examined at different levels and from different angles. However, it is not possible to make real-size measurements of the spaces and structures because the image becomes enlarged as the scope approaches the target and it becomes smaller when the scope is being pulled away. In contrast, MPVF provide visualization of the velopharyngeal sphincter in motion during speech by creating an X-ray image through tissues. Using digital imaging, MPVF can also provide real-size measurements by a ratio of selected distance markings and pixels.

The vocal tract can be conceived as the enclosed space between the vocal cords at the glottis and the lips. The space includes the hypopharynx or laryngopharynx, the oropharynx, the rhinopharynx, the nasal cavities, and the oral cavity. Several structures limit the space at different levels including the epiglottis, the walls of the pharynx at different levels, the base of the tongue, the dorsal aspect of the tongue, the soft palate or velum, the hard palate, the alveolar arches, and the lips. Furthermore, movements of the jaw can significantly modify the shape and dimensions of the vocal tract during speech production [5].

The sound sources of speech production are pulses of air expelled into the vocal tract by adduction and vibration of the vocal folds. These pulses are denominated vocal sources. The pulses resonate on different structures along the vocal tract, also called articulators. The complex and subtle modifications of the fundamental sound wave, also called harmonics, provide the acoustic characteristics to the sounds in order to make them intelligible, that is, to become phonemes or speech sounds. Vocal tract motion for speech production is regulated by the central nervous system [5–7].

One of the acoustic characteristics of speech is nasal resonance. Resonance refers to the quality of the speech sounds by the participation of the nasal cavities into the articulation process. The velopharyngeal sphincter regulates the communication between the nasal cavities and the rest of the vocal tract. Thus, by creating a complete seal, the velopharyngeal sphincter can enhance intraoral pressure for the production of specific phonemes (plosives, fricatives, and affricates). Also, by increasing or decreasing coupling between cavities, the velopharyngeal sphincter balances resonance during speech. An increased nasal resonance is called hypernasality, whereas a decreased nasal resonance is called hyponasality [7, 8].

There have been several attempts to standardize the results of VNP and MPVF. Since VNP does not provide real-size measurements, the use of movement ratios of each one of the structures of the velopharyngeal sphincter seems to be the best approach for describing velopharyngeal function. Although interobserver reliability of the movement ratios has been shown to be statistically nonsignificant, they have become a useful clinical estimate. Movement ratios have also been used for describing velopharyngeal function as observed by MPVF. However, at the present time digital imaging can provide real-size measurements with significant interobserver reliability [1–5, 9].

The velopharyngeal sphincter is comprised by the velum in the anterior aspect, the lateral pharyngeal walls and the posterior pharyngeal wall. Velum motion during speech is accomplished by the synergic movement of the musculus uvulae and the levator veli palatini muscle. Movements of lateral and posterior walls are the result of the action of the superior pharyngeal constrictor. All velopharyngeal muscles are innervated by the IX and X cranial nerves [5].

The adenoid or pharyngeal tonsil is a pad of lymphoid tissue on the posterior wall at the rhinopharynx. The size of the adenoid pad significantly modifies velopharyngeal space.

VNP and MPVF during speech should be video-recorded with sound. In order to perform an adequate assessment of velopharyngeal function it is essential to have a solid Speech and Language Pathology background. The selection of an appropriate speech sample is extremely important. Moreover, before attempting to visualize the velopharyngeal valve it is necessary to rule out the presence of compensatory articulatory errors. When compensatory errors occur, velopharyngeal motion globally decreases providing a "false" picture of the velopharyngeal sphincter in action [5, 7].

The examiner must assure that the patient is capable of repeating at least isolated words including fricative and plosive phonemes with adequate articulation placement [7].

Velopharyngeal inability for creating an efficient seal during speech is defined as velopharyngeal insufficiency (VPI). The etiology of this dysfunction may be anatomical as in cases of cleft palate or functional as in cases of myasthenia gravis among other neuromuscular disorders [5, 12].

VPI is an eminently clinical diagnosis. Although Nasometry can provide objective data for evaluating nasal resonance (measured as mean nasalance), the diagnosis of VPI is made by an accurate Speech and Language Pathology evaluation including assessment of articulation placement and manner, oral, and pharynx examination through direct vision and palpation of the hard and soft palate. The main use of the imaging procedures is to individually study velopharyngeal motion of each of the structures, velopharyngeal closure pattern, and size and shape of the gap during speech. Also, it is extremely important to determine if there is a significant risk of airway obstruction considering the surgical procedure which will be performed in order to correct VPI. If such risk is detected, tonsils and adenoid should be surgically removed in preparation for velopharyngeal surgery. A few months after this initial procedure, after adequate tissue healing, surgical correction of VPI can be performed with the best probability of success [1, 3, 13, 14].

VPI can occur as a consequence of a cleft palate as an isolated malformation. However, cleft palate can be associated with a congenital syndrome and in some of these cases surgical management has to be modified. The most common syndrome associated with cleft palate is 22q11.2 microdeletion syndrome. In these cases, it is common to find internal carotid arteries with an abnormally midline displacement at the level of the pharynx. VNP has been reported as useful for detecting pulsations on the lateral and posterior pharyngeal walls and this information can lead to the diagnosis of a syndromic cleft palate [15–18].

The most important element for performing successful imaging procedures of the velopharyngeal sphincter is to achieve adequate compliance from the patient in order to perform a complete and accurate evaluation. A recent study assessed whether postponing VNP until the patient is in the operating room under light preoperative sedation could result in similar or even better outcomes than performing both procedures during the presurgical evaluation. The goal of this project was to reduce the inefficiencies of the presurgical evaluation and expedite care for patients who require velopharyngeal surgery and may be intolerant of VNP. As mentioned herein, velopharyngeal surgery aims to correct residual velopharyngeal insufficiency in patients with cleft palate. Preoperative MPVF and VNP provide data for customizing the surgical technique for correcting VPI. Although the combination of these procedures during the presurgery appointment is considered the gold standard for the presurgical evaluation of VPI, it has been demonstrated that, without sedation, MPVF is significantly better tolerated than VNP [9, 19].

The study protocol included performing a detailed clinical speech and vocal tract assessment, a Nasometry during the repetition of standardized and phonetically balanced reading passage ("The Rainbow Passage"), and a sustained/e/sound and a sustained/a/sound. Also, a MPVF for assessing the velopharyngeal sphincter function during speech as well as the possible risk of obstruction after velopharyngeal surgery is performed. According to the results of these initial evaluations, velopharyngeal surgery was indicated. If a risk of obstruction was detected, an adenoidectomy and tonsillectomy were scheduled in preparation of the velopharyngeal surgery.

VNP was performed when the patient was already in the operating room under the effect of preoperative light sedation. Patients were still capable of cooperating during the procedure by repeating the speech samples presented by the examiner. The surgical procedure was customized individually in each case, according to the findings of the previous MPVF and the "intraoperative" VNP. That is, the height at which the pharyngeal flap or flaps should be located and the symmetry or skewedness and the width of the flap or flaps were tailor-made depending on the specific structural and anatomical characteristics of each case. It should be pointed out that it has been demonstrated that the anatomical and motion patterns of the velopharyngeal sphincter during speech significantly vary from individual to individual [1, 2, 14].

VPI is present in every case with an ouvert cleft palate and some cases with submucous cleft palate. After palatal repair, 20–40% of the cases persist with residual VPI which requires a second surgical procedure. At present time, pharyngeal flaps and sphincter pharyngoplasties are the two surgical procedures of choice for correcting residual velopharyngeal insufficiency [1, 14, 20].

It has been described that VNP and MPVF can provide anatomical and dynamic data which can be used to select and design the most efficient procedure for correcting velopharyngeal insufficiency. Moreover, several reports support the statement that when surgery is customized individually according to the findings of videonasopharyngoscopy and videofluoroscopy, the speech outcome is significantly improved [1, 3, 9, 14].

Although the combination of VNP and MPVF is considered as the current standard of care protocol for performing preoperative planning in preparation for velopharyngeal surgery, there are important differences between these two procedures. VNP provides *in vivo* view of the velopharyngeal sphincter motion during speech. It does not involve radiation and there are practically no possible complications. However, VNP is poorly tolerated by most young children aged four to ten or by persons with disabilities.

More specifically, due to discomfort during this procedure, without sedation it is sometimes difficult to obtain appropriate compliance from these patients. Thus, the preoperative VNP evaluation must often be rescheduled within this population due to procedural noncompliance and patient discomfort. Furthermore, in several of these cases, the total time necessary to appropriately complete the procedure is frequently prolonged. Before starting the procedure, it usually takes longer time to explain the procedure to younger children and to try to convince them to comply with the instructions. During the procedure, if the patient is not being cooperative, it takes longer to obtain all the necessary data for an adequate selection, planning, and design of the surgical treatment. As a result of these situations, resources can be potentially wasted and quality of care may be potentially reduced.

In contrast, MPVF also provides visualization of the motion of the velopharyngeal valve during speech. This procedure involves a small amount of radiation for the patient. Nonetheless, it has been demonstrated that MPVF is significantly better tolerated than VNP [9, 19].

A prospective, cross-sectional, open clinical trial was carried out in order to study whether a VNP performed in the operating room under light preoperative sedation could provide an adequate assessment of velopharyngeal motion during speech for planning operations aimed to correct VPI. Also, the study would assess comfort of this intraoperative procedure as compared with a VNP performed as an outpatient procedure. The study protocol was reviewed and approved by the Internal Review Board of Beaumont Health, Royal Oak, MI. It was anticipated that patients who received the VNP under light preoperative sedation in the operating room would have similar surgical outcomes concerning correction of VPI and including postoperative mean nasalance scores and clinical nasal emission assessment

as compared to patients who received both preoperative evaluation procedures prior to the operation. Additionally, it was anticipated that procedure compliance and patient comfort would be improved in patients who received delayed VNP.

The goal was to reduce the inefficiencies of the preoperative evaluation and expedite care for patients who require velopharyngeal surgery and may be intolerant of VNP. In other words, the study tested whether postponing VNP until the patient would be in the operating room under light preoperative sedation could result in similar or even better outcomes than performing both procedures during the preoperative evaluation.

In 1979, Shprintzen et al. reported that varying the type of insertion of the flap into the palate, postoperative flap width could be tailored to the size of the gap in the velopharyngeal sphincter [21].

Gart and Gosain [1] used pharyngeal flaps and sphincter pharyngoplasties which were performed according to findings of VNP and MPVF. They found that these imaging procedures can provide anatomical and physiological data for planning the surgical procedures for correcting hypernasality. Ysunza et al. [19] reported that MPVF is a safe and reliable procedure for assessing adenoid hypertrophy and velar movement in children.

In 2009, Marsh reported that while the diagnosis of velopharyngeal dysfunction is made by auditory perceptual evaluation, identification of the mechanism of dysfunction requires instrumental visualization of the velopharyngeal port during specific speech tasks. Matching the specific intervention for correcting velopharyngeal dysfunction with the abnormal anatomy can maximize the result while minimizing the morbidity of the intervention [22].

Ysunza et al. found that MPVF seems a reliable method without serious complications for evaluating adenoid hypertrophy and velopharyngeal closure in children, besides being a procedure that is better tolerated, as compared with VNP [19].

The main barrier which may impede widespread implementation of "intraoperative" VNP is that VNP equipment may not be available inside the operating room in all centers.

For the project addressing the use of intraoperative VNP for planning velopharyngeal surgery, twenty patients aged 4–10 years of age or otherwise impaired were studied. All patients presented with residual VPI after surgical repair of a cleft palate. The following questions were presented to the patient and family:

(1) How would you/or your child rate the discomfort your child experienced during the MPVF done on (date of the procedure)? (a) No discomfort; (b) mild discomfort; (c) moderate discomfort; (d) extremely uncomfortable.

(2) How would you/or your child rate the discomfort your child experienced during the VNP performed in the operating room on (date of the procedure)? (a) No discomfort; (b) mild discomfort; (c) moderate discomfort; (d) extremely uncomfortable.

The results of the survey were analyzed. The VNP which were performed in the operating room were considered as "no discomfort" by 16 (80%) of the patients. It seems reasonable to assume that none of these patients even remembered the procedure. The remaining 4 (20%) patients considered the procedure as "minor discomfort." It should be pointed out that it was difficult to interpret this finding.

It was questionable if the patients actually vaguely remembered the procedure or they just replied randomly. However, it is evident that none of the patients (whether remembering the procedure or not) considered the procedure as "moderately" or "extremely" uncomfortable. Moreover, if the "intraoperative" VNP is compared with the MPVF which is performed as an outpatient without any sedation, a Mann-Whitney U test demonstrated a nonsignificant difference between procedures (VF = 15 (75%), "no discomfort," and 5 (25%), "minor discomfort" ($P > 0.9$)). Data from the previous report [19] mentioned herein about MPVF were similar: VF = 71%, "no discomfort"; 29%, "minor discomfort."

In contrast, data from the previous report concerning VNP in outpatients without sedation demonstrated that the procedure is significantly less well tolerated: "no discomfort" = 0; "minor discomfort" = 20%; "moderate discomfort" = 70%; "extremely uncomfortable" = 10%.

The questionnaire was also applied to 20 additional patients who underwent the VNP as outpatients during the last year here in our center. It should be pointed out that these patients were not included in the protocol. They were referred from another center and their surgical procedures were not performed here. The age range was not the same as in the protocol but the difference between median ages was nonsignificant. (a Mann-Whitney U test $P > 0.05$). Results were also similar as described herein: "no discomfort" = 0; "minor discomfort" = 17%; "moderate discomfort" = 71%; "extremely uncomfortable" = 12%.

As far as the effectiveness of the "intraoperative" VNP for assessing velopharyngeal closure and how useful the data was for tailoring the pharyngeal flap, the surgical procedure completely corrected hypernasality (as measured by Nasometry-Nasalance) in 18 out of 20 patients (90% success rate).

The height of implantation of a pharyngeal flap on the posterior pharyngeal wall is one of the key elements for a successful outcome. A relatively high pharyngeal flap decreases the risk of postoperative airway obstruction, specifically sleep disordered breathing. Also, the lateral borders of a high pharyngeal flap can more efficiently help to seal the velopharyngeal sphincter by contacting the lateral walls at motion during speech.

The height of the implantation of the flap was measured by postoperative MPVF using the level of the hard palate as reference. In the 20 patients who underwent a pharyngeal flap operation which was tailored according to findings of a preoperative MPVF and an "intraoperative" VNP, the mean distance between the hard palate and the flap was 2.5 mm. This distance was compared with the findings of a postoperative MPVF of 20 patients who had undergone a pharyngeal flap operation which was performed elsewhere without preoperative imaging procedures. The mean distance of the flaps in this group of patients was 10 mm. It should be

Table 1: Types of compensatory articulations.

CA type	Where?	How?	Main substitutes
Glottal stop	Larynx	Glottal closure	Plosives
Pharyngeal stop	Pharynx	Base of the tongue contacts the posterior wall	Velars
Pharyngeal fricative	Pharynx	A fricative made in the pharynx	Sibilant fricatives
Pharyngeal affricate	Larynx Pharynx	Combines fricative and glottal stops	Oral affricates
Posterior nasal fricative	Pharynx	Constriction between the velum and posterior pharyngeal wall	Sibilant fricatives and affricates
Middorsum palatal stop	Midpalatal area	Tongue contact central area of palate	Plosives /t/, /k/, /d/, /g/
Nasal fricative	Nose	Nonturbulent nasal emission	Fricative

Adapted from Peterson-Falzone et al., 2006 [10], and Golding-Kushner, 2001 [11].

pointed out that 2 of these patients presented with clinical data suggestive of sleep disordered breathing.

Conclusion. Surgical treatment of residual VPI after initial cleft palate repair should not be performed without individual careful planning. VNP and MPVF provide the necessary information for the appropriate planning of operations aimed to correct residual VPI. MPVF is better tolerated than VNP, especially by young children. Performing MPVF as an outpatient procedure and delaying VNP till the patient is in the operating room under the effect of preoperative sedation seems a safe and reliable sequence for planning operations for restoring efficient velopharyngeal closure during speech.

2. Speech and Language Pathology Treatment of Articulation Disorders Associated with Velopharyngeal Insufficiency in Patients with Cleft Palate

Patients with cleft palate (CP) may be at risk for speech disorders. Certain articulation disorders are generally regarded as compensatory behaviors secondary to velopharyngeal insufficiency (VPI). These errors include dysfunction not only of the velopharyngeal sphincter, but also of the entire vocal tract and higher levels of articulation control in the central nervous system [23].

Cleft palate speech is associated with VPI and includes deviations in the resonance such as hypernasality or hyponasality, errors that are obligatory with VPI like nasal emission and weak pressure consonants, and compensatory articulation [11].

Hypernasality is excessive nasal resonance during production of vowels, usually caused by VPI, and is relatively frequent in these patients. Some patients especially with repaired cleft palate can also show other resonance alterations like a reduction in normal nasal resonance resulting from nasal blockage called hyponasality (i.e., turbinate hypertrophy, nasal septum deviation, and obstructing pharyngeal flap). Also, in cleft palate speech mixed resonance can be heard and it is when hypernasality and hyponasality occur simultaneously. Finally, Cul-de-sac resonance is a variation of hyponasality associated with tight anterior nasal constriction producing a muffled quality to sounds [10].

Nasal emission is the escape that accompanies the production of consonants requiring high oral pressure (plosives, fricatives, and affricates). It is considered an obligatory error if it is consequence of VPI or the presence of fistulae and requires physical management.

Compensatory Articulations (CA) are abnormal patterns of articulation and occur when the articulating structures are placed inappropriately resulting in one sound substituting another. CA affects intelligibility and requires speech therapy for correction. This disorder can be considered as a phonologic disorder since it may initially occur as a consequence of the cleft, but the errors become incorporated into the child's developing rule system producing a phonologic disorder [24]. Different authors have described different types of CA in cleft palate speech including glottal stop, pharyngeal stop, pharyngeal fricative, pharyngeal affricate, posterior nasal fricative, middorsum palatal stop, and nasal fricative (see Table 1).

The results from the speech evaluation will help to establish the goals for intervention. However, correcting CA should be the main focus in speech intervention in patients with cleft palate.

Speech intervention with a phonetic approach considers articulation learning as a specific time of motor learning that occurs at a peripheral level. Consequently, intervention procedures are based on the notion that articulation errors are due to faulty control of the articulators [25]. In contrast, in a phonologic approach children must learn more than articulatory patterns associated with words. They must learn a complete phonology—rule system—that occurs at a central level and requires cognitive-phonological processing [26].

When two different approaches for speech intervention in children with cleft palate and CA were compared—phonetic versus phonologic—the total time of speech intervention necessary for correcting CA was critically reduced when a phonological approach was used [27].

Because the phonological system is integrated with the language system it is also suggested that the language of children with CA should also be assessed. Hoffman in 1992 [26] stated that children's speech sound production and perception errors are related not only to phonological knowledge but also to higher organizational levels of language processing. Other researchers have also identified language problems in children with cleft palate, including syntax

(i.e., grammar), morphology, and vocabulary [28, 29]. Moreover, Pamplona and Ysunza, 2000, studied the relationship between CA and the child's language system. They found that children with CA showed linguistic performance below the expected level according to chronological age. Hence, if we assume that children presenting with CA show linguistic organization disorders, an intervention aimed to correct CA should include a simultaneous approach for enhancing cognitive linguistic organization.

Whole language principles state that phonologic information should not be separated from the other areas of language, such as pragmatics or syntax. Thus, the same activity provides several pieces of information about all areas of language, including phonology. Phonologic information, such as articulation, is provided in an integrated way within a significant event such as storybook reading or symbolic play with the use of abstract and complex levels of language that leads to a coherent and structured discourse [30].

Storybooks are a perfect context for stimulating cognitive and language development in children [24]. Stories have all the elements of the narrative and discourse structure including the relationships that provide order and structure such as temporality, causality, or perspective. Also, they provide stability for seeing those relationships and for working on specific language needs such as articulation patterns of words and/or sounds. Other activities that promote working with speech and language in an integrated way are art, cooking, music, or symbolic play [31].

Conclusion. Intervention for cleft palate speech should emphasize working with articulation within a whole event. For articulation, focusing on the target sounds during a naturalistic situation such as storybook reading by analyzing words or patterns could help the child to match events with words and sounds for improving articulation and developing phonemic awareness. This would facilitate generalization of articulation into connected speech.

3. Genetics and Genomics of Cleft Palate

3.1. Palatogenesis and Cleft Palate

3.1.1. Development of the Primary and Secondary Palate. Craniofacial development in mammals is a highly regulated, complex process that occurs as a result of the interaction of many different gene products with environmental factors during early embryonic development.

The palate is a structure formed by bony or osseous and muscular tissues. The *primary palate* (also named *premaxilla*) is the most anterior aspect of the hard or osseous palate, beyond the anterior incisive foramen. The *secondary palate* is formed by the dental arches, excepting the incisive portion, the palatine osseous vaults, and the muscular soft palate or velum. These structures serve as a structural separation between the oral and the nasal cavity [32].

Development of the human face begins around week four of embryogenesis [33]. It starts with the formation of five facial prominences that surround the mouth: a rostral frontonasal prominence, a lateral pair of maxillary prominences, and a caudal pair of mandibular prominences. These structures are populated by cranial neural crest cells, which are particularly sensitive to perturbations of certain pathways that have been implicated in the occurrence of clefting syndromes [32].

Development of the palate begins around week 6 of gestation in humans (embryonic day E12 in mice) and is identifiable by the appearance of palatal primordia at the lateral edges of the maxillary prominences. These processes fuse coordinately to form the nostrils, upper lip, and palatal shelves that will, in turn, give origin to both primary and secondary palate [32].

Later (week 9 in humans, E14-15 in mice), the bilateral palatal shelves that had been allowed to elevate above the dorsum of the tongue as a consequence of the lengthening of the mandible towards the front of the face grow toward each other and will form the midline edge seam that consists of epithelial cells that produce a glycoprotein coat and desmosomal junctions that allow cell-cell interactions [34].

The mechanism that promotes sealing of the midline seam is unclear. Three hypotheses have been proposed: programmed cell death or apoptosis of cells in this region, migration to other regions of the palatal region (oral or nasal), and finally epithelial-mesenchymal transition (EMT). The process of palatal fusion is completed by week 12 in humans (E16 in mice) and is marked by the complete disappearance of the midline edge seam. Successive ossification that will form the hard (primary) palate will only occur upon successful completion of the fusion process.

Palatal fusion and ossification will ultimately give rise to a normal palate. This process is regulated by a myriad of factors, including growth factors, proteins from the extracellular matrix (ECM), and adhesion molecules. Because of this, palatal fusion has been under intense scrutiny in regard to its implications in the etiology of cleft palate (CP). We next summarize the role of selected genes and pathways implicated in palatal fusion and in the development of CP.

3.1.2. Molecular Pathways Involved in Palatogenesis

The TGFβ Pathway. This family of secreted proteins is perhaps the most widely studied in palatal development. TGFβ is a member of a family of growth factors that includes bone morphogenic proteins (BMPs) and activins. Almost every cell in the human body, including epithelial, endothelial, and mesenchymal cells, produces TGFβ in any of its isoforms (1, 2, or 3) and has receptors for it [35]. TGFβ activity can have different consequences depending on context. For example, TGFβ can induce differentiation of stem cells but cell cycle arrest in epithelial cells. The number of genes under control of the TGFβ pathway varies from a few in pluripotent stem cells to hundreds in differentiated cells [36].

Classical (or canonical) TGFβ-dependent signaling regulates gene expression by receptor-mediated activation of SMAD transcription factors, including SMAD2 and SMAD3 (receptor-activated SMADS or R-SMADS), which are phosphorylated by the Ser/Thr kinase domain in the type II receptors. Phosphorylation of SMAD2 and SMAD3 leads to association with SMAD4 (co-SMAD) and the subsequent

translocation of this complex into the nucleus, where it regulates expression of many target genes in association with other DNA-binding transcription factors.

Extensive cross-talk exists between this pathway and other signaling pathways. For example, activation of the mitogen-activated kinase (MAPK) pathways by other growth factors can lead to inhibitory phosphorylation of SMAD2 and SMAD3 in the regulatory "linker region" and thus inhibition of signaling propagation [36]. Ligand-activated TGFβ receptors can also activate the MAPKs ERK, JNK, and p38 (examples of so-called noncanonical TGFβ signaling).

Increases or decreases in the production of TGFβ are associated to several diseases, such as cancer, fibrotic disease of kidney or skin [37], and those of the connective tissue and cardiovascular system [38–40].

The importance of TGFβ signaling in palatogenesis has been robustly demonstrated through animal models that lack TGF-β3 production (KO mice), which consistently develop cleft palate among other developmental abnormalities [41, 42].

Sonic Hedgehog (SHH) Pathway. Sonic hedgehog is one of three members of the family of the Hedgehog proteins (the others are Indian and Desert hedgehog). This pathway is involved in the regulation of cell proliferation, fate specification, and many other developmental processes. *SHH* signaling occurs through binding of the morphogen with its receptor (patched1, *PTCH1*) and subsequent activation of several transcription factors from the Gli family [43]. There is great consensus that *SHH* plays a key role in angiogenesis and vascularization processes in general, and more recently it has also been involved in osteogenesis [44].

SHH is expressed in the epithelium on the oral surface, which corresponds to the region where the *rugae palatini* will form. During palatogenesis, *SHH* is involved in cell signaling in both epithelium and mesenchyme highlighting the role this pathway plays in the process of sealing of the secondary palate during embryonic development [45, 46].

Mutations in the *SHH* gene in humans cause holoprosencephaly, which is characterized by abnormal forebrain and facial development, including cleft palate [34]. This is confirmed by generation of mice that are null for *SHH* and that fully recapitulate the phenotype [47].

WNT Signaling Pathway. This family of proteins regularly binds to cell-surface receptors of the Frizzled family activating specific patterns of gene expression. It regulates cell-fate determination and tissue patterning during embryonic development [48]. Several proteins from this family are expressed during palatogenesis and genetic variation within these elements is associated with nonsyndromic cleft palate [49–51]. Moreover, there are several mouse models of impairing mutations in several members of the Wnt family that present cleft palate as one of the phenotypes [34].

3.2. Syndromic and Nonsyndromic Causes of Cleft Palate. Orofacial clefts are among the most common major congenital anomalies in humans, with average incidences of 1 in 700 live births, and exhibit marked ethnic and geographic differences ranging from 1 in 500 in northern Europe to 1 in 2,500 in Africa [52]. This observation suggests that the contribution of susceptibility genes and/or the frequency of their variants may vary across populations. Based on clinical manifestations, patterns of recurrence, and biological knowledge, orofacial clefts are broadly classified as cleft lip (CL), cleft lip and palate (CLP), and cleft palate (CP), with the first two considered part of a spectrum, distinct from CP. Several studies have documented that, with few exceptions, familial recurrence tends to be specific: for example, in a 35-year population cohort study in Norway, Sivertsen et al. [53] found relative risks of recurrence of 32 (95% CI 24.6–40.3) for any CL (with or without CP), 56 (37.2–84.4) for CP alone, and only 3 (1.3 to 6.7) for "crossover" between both conditions. This emphasizes that there are different causes for these conditions.

Nonsyndromic forms are defined as those in which there are no other evident anomalies or features and account for approximately 50% of cases of CP and 70% of CL and CLP [54]. In contrast, syndromic forms have additional manifestations, and their causative genes, although not completely known, have been better characterized than the nonsyndromic forms, which are more likely of multifactorial etiology with interaction between genetic susceptibility and environmental causes.

3.2.1. Syndromic Causes of Cleft Palate. The designation of orofacial clefts as syndromic is usually based on the presence of additional physical or cognitive abnormalities and, as stated above, it is estimated that approximately 50% of cases of CP are present in the context of a syndrome [54]. A search in commonly used clinical genetic databases shows close to 300 entries for syndromes with CP (excluding CL) in Orphanet (http://www.orpha.net/consor/cgi-bin/index.php) and almost 500 in POSSUM (http://www.possumcore.com/nuxeo/login.jsp). A few of the most common syndromes that include CP include the following.

Velocardiofacial syndrome (OMIM # 192439 and 188400) most commonly includes abnormalities of the palate, heart, and recognizable facial features. Initially delineated in 1978, it is caused by a 1.5–3 Mb microdeletion of chromosome region 22q11. With an overall incidence of one in 4000–6000 live births, it is the most common microdeletion syndrome [55]. Palate involvement has a frequency of 60–80% [56] and is usually manifested as cleft of the soft palate, submucous CP, or bifid uvula. Most of the manifestations are thought to arise as a consequence of haploinsufficiency of the TBX1 transcription factor [57].

Other clefting syndromes for which the genetic basis has been identified include *Loeys-Dietz syndrome* (OMIM # 609191), a condition caused by imbalanced TGFβ signaling and caused by mutations in either subunit of the TGFβ receptor, *TGFBR1/2* [38]. *Shprintzen-Goldberg syndrome* (OMIM # 182212) is caused by mutations in *SKI*, a suppressor of TGFβ signaling [58].

CP is also a frequent feature of several craniosynostosis syndromes, such as *Apert* (OMIM # 101200), *Crouzon* (OMIM # 123500), and *Saethre-Chotzen* (OMIM # 101400)

syndromes, and also in disorders affecting collagen synthesis, like *Stickler* syndrome (OMIM # 108300), that also includes ocular, auditory, and skeletal manifestations.

3.2.2. Nonsyndromic Cleft Palate. A variety of genetic approaches have been used to identify genes and pathways underlying nonsyndromic CP (nsCP), including mouse models, cytogenetic linkage analysis, candidate gene, and genome-wide association (GWAS) studies. Nevertheless, because, among "typical clefts," nsCP is less common, fewer molecular and epidemiological studies have been performed for this condition compared with CL and CLP [59, 60].

Candidate Gene Approaches. As described above, the TGFβ pathway has been implicated in palatal closure. Consistent with this knowledge, several studies have found evidence of association between nsCP and variants in genes in this pathway as well as in TFGα [61–63], but others have not replicated this finding [64]. Similarly, these same studies also explored and identified variants in MSX1 associated with the presence of CP [63, 64]. Msh homeobox 1 (*MSX1*) encodes a member of the muscle segment homeobox gene family. The encoded protein functions as a transcriptional repressor during embryogenesis and may also have roles in limb-pattern formation, craniofacial development, particularly odontogenesis, and tumor growth inhibition. MSX1 is considered a "crossover" gene, since alterations in it have been found in cases of both CP and CLP [65]. Similarly, variants in *FOXE1,* encoding for a transcription factor of the forkhead family, have been associated both with CL and CP in a large study of individuals of European and of Mesoamerican origin [66].

Genomic Approaches. As with many other complex disorders, GWAS have been useful in identifying regions in the genome that could potentially harbor causative variants. A search on the NHGRI Catalogue of published genome-wide studies displays 17 loci in regions encoding for 20 genes and 4 loci in intergenic regions associated with clefts, although most of them (if not all) are focused on cleft lip with and without cleft palate [67–69].

Within these regions, some genes previously found to be causative of syndromic forms of CL/P have been confirmed, with *IRF6* (causing van der Woude Syndrome that usually presents with CL) being the most prominent example, but also some other genes in the TGFβ pathway have also been replicated, such as BMP6 [70].

While GWAS and linkage studies have shed light into genes that play major roles in palatogenesis and defects in this process, they fail (by nature) to point towards mechanisms underlying the phenotype studied. In this regard, the advent of the "-omics" era has allowed researchers to study this complex phenotype from a global perspective, mainly in the form of gene expression profiling.

Jakobsen et al. performed a global profile of gene expression in palatal tissue from patients with nonsyndromic forms of cleft palate and cleft lip and palate, identifying genes such as *OPN* (encoding for osteopontin) and *CCR4* (encoding for chemokine receptor 4) that were differentially expressed between these groups suggesting a role in palatal development [71].

Functional studies in animal models are performed by introducing genetic perturbations of previously identified genes. One of the most widely used animal models for nonsyndromic CP has been the deletion of TGFβ3 alleles both in haploinsufficient and complete null animals [41]. This has allowed the performing of global analyses that point to the role of new, previously unsuspected genes that could regulate palate development in conjunction with *TGFβ3* [72, 73].

In summary, the availability of genome-wide approaches has helped us understand better the interaction between key players (those genes with major effect in syndromic or nonsyndromic CL/P) and others that, even though could not be identified in case-control or family-based genetic studies, have been functionally validated as previously described. These complementary approaches will greatly advance our understanding of this complex disease.

3.3. Teratogens. Several environmental agents and extrinsic agents have been implicated in the pathogenesis of CP, such as maternal smoking and maternal alcohol consumption, as well as lack of use of folic acid supplementation [74]. As with several environmental agents, not all of those exposed manifest the consequences that suggest the existence of a susceptible population. From the epidemiological perspective, this is being explored by means of gene-environment interaction studies (GxE). Several of these have pointed to known genes involved in nsCP, such as TGF-α, in which maternal and fetal variants were found to be associated with CP susceptibility in the presence of tobacco exposure during pregnancy in a meta-analysis [75], and variants in TGFβ associated with submucous clefts and maternal smoking [76]. In addition, other recent candidate and genome-wide GxE studies have revealed other novel candidates that may modulate the effect of tobacco, such as *TBK1, ZNF 236* [77], *SLC2A9,* and *WDR1* [78]. These studies have also pointed to variants in *MLLT3* and *SMC2* related to CP in the context of prenatal alcohol exposure [77]. The findings are relevant, since they may help identify individuals at particularly high risk of developing preventable forms of CP, as well as point to novel pathways involved in orofacial development and palatal closure.

3.4. Therapeutic Implications of Molecular Findings. Although surgery is and will continue to be the mainstay for treatment of CP, it is expected that molecular understanding of the processes involved in palate formation will hopefully lead to novel strategies for prevention and treatment of clefts and to diminishing or avoiding its many complications.

Interesting studies in animal models have been published recently in this regard: as mentioned above, there are mice models of Loeys-Dietz syndrome due to deletion of Tgfbr2. These mice develop cleft palate as a result of abnormal TGFβ activation via TGF-β receptor types I and III- (TβRI/TβRIII-) mediated TRAF6/TAK1/p38 signaling pathway. Two recently published experimental approaches illustrate the feasibility and consequences of modulating the defects caused by the alteration of this pathway.

Iwata et al. [79] described that a loss of Tgfbr2 in mouse cranial neural crest cells results in an elevated expression of TGF-β2 and TβRIII and defective cell proliferation in the palatal mesenchyme. They found that Tgfb2, Tgfbr1, or Tak1 haploinsufficiency disrupted TβRI/TβRIII-mediated signaling and rescued the craniofacial anomalies in Tgfbr2 mutant mice, suggesting that modulation of TGF-β signaling may be beneficial for the prevention of congenital craniofacial birth defects.

Subsequent work by this group in the same mouse model showed that Tgfbr2 mutant palatal mesenchymal cells accumulate lipid droplets from reduced lipolysis activity and fail to respond to the cell proliferation stimulator sonic hedgehog, derived from the palatal epithelium. Treatment with p38 mitogen-activated protein kinase (MAPK) inhibitor or telmisartan, a modulator of p38 MAPK activation and lipid metabolism, blocked abnormal TGFβ-mediated p38 MAPK activation, restoring lipid metabolism and cell proliferation activity both *in vitro* and *in vivo*. These results show the influence of TGFβ signaling on lipid metabolism and the role of metabolic defects in cell proliferation and palate formation. This discovery has broader implications for the understanding of metabolic defects and potential prevention of congenital birth defects [80].

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Differences in Velopharyngeal Structure during Speech among Asians Revealed by 3-Tesla Magnetic Resonance Imaging Movie Mode

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Objective. Different bony structures can affect the function of the velopharyngeal muscles. Asian populations differ morphologically, including the morphologies of their bony structures. The purpose of this study was to compare the velopharyngeal structures during speech in two Asian populations: Japanese and Thai. *Methods.* Ten healthy Japanese and Thai females (five each) were evaluated with a 3-Tesla (3 T) magnetic resonance imaging (MRI) scanner while they produced vowel-consonant-vowel syllable (/asa/). A gradient-echo sequence, fast low-angle shot with segmented cine and parallel imaging technique was used to obtain sagittal images of the velopharyngeal structures. *Results.* MRI was carried out in real time during speech production, allowing investigations of the time-to-time changes in the velopharyngeal structures. Thai subjects had a significantly longer hard palate and produced shorter consonant than Japanese subjects. The velum of the Thai participants showed significant thickening during consonant production and their retroglossal space was significantly wider at rest, whereas the dimensional change during task performance was similar in the two populations. *Conclusions.* The 3 T MRI movie method can be used to investigate velopharyngeal function and diagnose velopharyngeal insufficiency. The racial differences may include differences in skeletal patterns and soft-tissue morphology that result in functional differences for the affected structures.

1. Introduction

Two potential complications after primary surgery for cleft palate repair are oronasal fistula and persistent velopharyngeal insufficiency (VPI) [1–4]. In VPI, inadequate soft palate function results in its inability to lift and thus produce a complete seal with the posterior pharyngeal wall. This condition affects normal speech production and typically manifests as hypernasality and the nasalization of oral sounds [5]. The levator veli palatini (LVP) muscle is the primary muscle for velar elevation [6]. Its origins are the cartilaginous portion of the auditory tube and the petrous portion of the temporal bone. The LVP runs parallel to the Eustachian tube and inserts at the palatine aponeurosis and the midsection of the velum [7–9]. Cadaver and histological studies have shown that 40% of muscle length in the velum is contributed by the LVP [9, 10]. In addition to being part of the velum, the LVP acts as its muscle sling [10]. Contraction of the LVP influences the superior and posterior movements of the velum from the latter's midpoint, which provides the seal between the nasopharynx

Table 1: Demographic data of the two groups.

	Japanese subjects ($N = 5$)	Thai subjects ($N = 5$)	Significance
Age (years)	28.2 ± 1.3	29.2 ± 1.3	NS
Weight (kg)	49.5 ± 5.9	53.2 ± 5.1	NS
Height (cm)	158.3 ± 6.4	161.4 ± 2.3	NS
Body mass index (kg/m^2)	19.7 ± 0.8	20.4 ± 1.6	NS

NS: not significant.

and oropharynx during speech production [11–15]. Other muscles, such as the palatoglossus and palatopharyngeus muscles, also assist in normal velopharyngeal closure [16].

VPI also occurs in submucous cleft palate and as a postsurgical complication of adenoidectomy [17]. Nasal endoscopy and fluoroscopy are commonly used in the diagnosis of VPI. However, nasal endoscopy requires a high degree of tolerance by the patient, whereas fluoroscopy exposes the patient to radiation [17–19]. The role of magnetic resonance imaging (MRI) in evaluating VPI has been the focus of several studies [20–23]. Among the advantages of MRI are its noninvasiveness, its ability to clearly show the anatomy, and its reproducibility [20–23]. Thus, MRI has been used to investigate velopharyngeal structure and function [6, 14, 22–24], with several researchers using dynamic MRI to evaluate velopharyngeal function in real time [14, 25–27].

All of the muscles of the soft palate have bony origins. For example, the LVP originates from the temporal bone, the musculus uvulae from the palatine bone, and the tensor palatine from the sphenoid bone [7]. Bony structures are known to vary depending on age, race, and sex [28–34]. Racial differences have been demonstrated using lateral cephalometric analysis. For example, using lateral cephalometric radiography, Beugre et al. [28] found differences in the dental, skeletal, and soft-tissue facial morphologies of three African populations. de Freitas et al. [33, 34] demonstrated variations in the bony structures of Brazilian populations: white Brazilians have a larger upper anterior facial height whereas black Brazilians have a larger lower facial height. Moreover, black, but not white, Brazilians have a bimaxillary skeletal, dentoalveolar, and soft-tissue protrusion, although both groups have normal occlusion. Furthermore, there is greater protrusion of the upper and lower lips in black than in white Brazilians, but their lip thicknesses are similar. Asian populations have characteristic skeletal and soft-tissue morphologies that are different from those of Caucasian populations [35–42]. Somboonsap et al. (2011) used lateral cephalometric radiographs to characterize the morphology of the hard tissues of patients with obstructive sleep apnea syndrome and compared the cephalometric data of the study's Caucasian, Hispanic, African American, Singaporean, Japanese, and Thai participants. The authors reported that East Asians have more prominent upper and lower jaws than Westerners.

Differences in the bony structures that serve as the origins of the muscles of the soft palate together with differences in soft-tissue morphology might account for the observed differences in velopharyngeal function. For example, MRI studies have shown that males have a larger LVP than females [15, 24, 43]. However, there are few MRI studies on racial differences. Thus, it may be that the morphological differences among Asian populations include different velopharyngeal structures. The aim of this study was to use dynamic MRI to investigate the moment-to-moment changes in velopharyngeal structures during speech production in Asian populations, specifically, between Japanese and Thai subjects.

2. Methods

2.1. Subjects. Since gender is known to have effects on velopharyngeal structures [15, 43], only female subjects were included in this study. Ten healthy adult females (five Japanese and five Thai) participated in this study. All subjects had a normal body mass index (BMI), thus avoiding variations in the pharyngeal airways because of obesity. The mean age of the Japanese group was 28.2 ± 1.3 (mean ± standard deviation (SD)) years and that of the Thai group 29.2 ± 1.3 years. The two groups did not significantly differ with respect to age, height, weight, and BMI (Table 1). None of the participants had a history of neurological, craniofacial, musculoskeletal, speech, or hearing disorders, nor did they have any sign of cold, allergic rhinitis, or respiratory infectious disease at the time of the experiment. Written informed consent was obtained from all ten subjects prior to their participation in the study. The research protocol was approved by the Institutional Ethical Review Board of the Tokyo Medical and Dental University (number 886).

2.2. Magnetic Resonance Imaging. Custom-made circuitry was connected to a 3-Tesla (3 T) MRI apparatus (Magnetom Spectra, Siemens, Germany), which included a head and neck coil. At the start of the experiment, the subject was placed in the supine position, with her head stabilized inside the head coil, and fitted with headphones, which provided an auditory cue to synchronize pronunciation with the scanning time. A programmed external trigger pulse was used to control the timing scan sequence and to provide the acoustic cue, allowing the scan to be synchronized with pronunciation. A fiber-optic microphone (FOMRI, Phone-or, Or-Yehuda, Israel) was placed in front of the subject's lips to capture her pronunciation. A connected digital recorder (PMD670, 2-channel solid state recorder, Marantz Professional, Kingsbridge House, Middlesex, UK) was used to record the pronunciation and the external trigger pulse. Image acquisition consisted of a gradient-echo sequence, fast low-angle shot (FLASH) with segmented cine and parallel imaging technique (GRAPPA). The mid-sagittal plane was

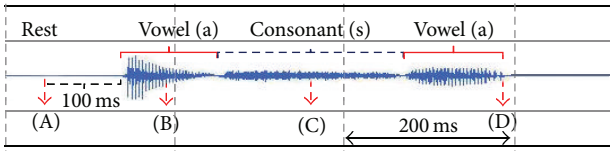

Figure 1: A representative sound wave and determination of the timing used in the analysis. Images acquired during the rest stage, 100 ms before production of the first vowel (A stage), in the middle of production of the first vowel (B stage) and the consonant (C stage), and immediately after production of the second vowel (D stage) were analyzed.

imaged using the following settings: repetition time (TR) = 22.5 ms, echo time (TE) = 2.07 ms, flip angle (FA) = 12°, field of view = 256 × 256 mm, matrix size = 256 × 128, pixel size = 1 × 2 mm, slice thickness = 4 mm, and acceleration factor = 2.

2.3. Speech Task. An external trigger pulse was fed to the MRI scanner 16 times and the subjects were required to repeat (echo) the vowel-consonant-vowel (VCV) syllable (/asa/) 16 times at 1500 ms intervals and in a synchronized manner in response to the auditory cue. The consonant /s/ was chosen because a previous study showed that during /s/ production the velopharyngeal structures are not affected by the supine position [44]. The subjects were asked to breathe between repetitions of the VCV articulation and to return the tongue and mandible to the resting position at the beginning and end of every pronunciation.

2.4. Sound Data Manipulation. The recorded sound data were manipulated using the free software SoundEngine (Code Helium, Japan), which allows the time of articulation and the sound wave to be recorded. The manipulated sound data also assisted in stage determination. Images acquired during the rest phase (before pronunciation, 100 ms), the first vowel (the middle of the first vowel /a/), the consonant (the middle of consonant /s/), and after speech (the end of the second vowel /a/) were chosen for analysis (Figure 1). The speech duration of each subject was measured and compared between the Japanese and Thai subjects. The start and finish points of each pronunciation were determined when the sound signal exceeded 3 SD of the baseline value.

2.5. Area of Interest and Measurements. Four images, from the four above-described stages, were obtained at five distances from each subject (Figure 2). The measurement parameters were adapted from the study of Perry [44]. All parameters and their definitions are shown in Table 2.

2.6. Statistical Analysis. Each image was measured five times over 5 days. A single examiner (KN) conducted the measurements to avoid interobserver error. Intraobserver reliability was assessed by intraclass correlation coefficients (ICC). The measurement errors determined by the ICC were very small (range: 0.95–0.99), showing that the measurements were reproducible. Levene's test (F) was used to assess the equality of variances; ANOVA and Tukey's test were used to compare

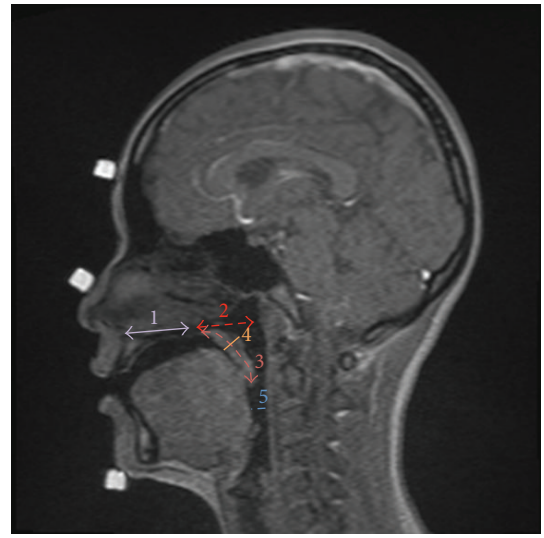

Figure 2: The measurement parameters: 1, hard-palate length; 2, velopharyngeal depth; 3, velar length; 4, velar thickness; 5, retroglossal space. See the text for definitions.

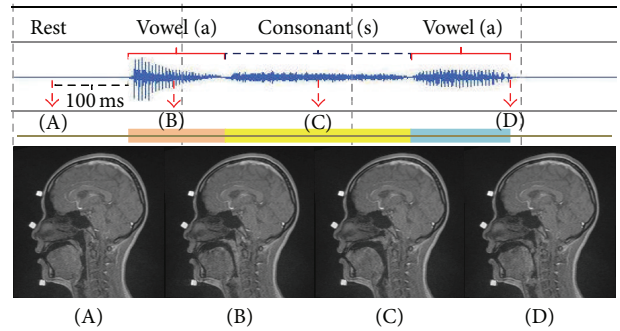

Figure 3: Representative sound data combined with movie MRI of a Japanese subject. A–D are the corresponding sound signals and MR images.

the parameters of the Japanese versus Thai subjects with respect to the different stages of pronunciation. The duration of speech in the two groups was compared by first using the Kolmogorov-Smirnov Z test to verify the suitability of a paired sample t-test. Significance was defined as $p < 0.05$.

3. Results

3.1. Japanese Subjects. Four stages were analyzed in this study: rest stage, 100 ms before production of the first vowel (A stage), in the middle of production of the first vowel (B stage) and the consonant (C stage), and immediately after production of the second vowel (D stage). Representative sound data combined with the movie MRI of a Japanese subject are shown in Figure 3. At the A stage, the articulators were in the rest position, with the velum placed on the posterior aspect of the tongue. At the B stage, the velum was elevated in a superoposterior direction and made contact with the posterior pharyngeal wall. In only one Japanese subject was there no contact between the velum and the

Table 2: The study parameters and their definitions.

Parameter	Definition
Hard-palate length	Distance between the anterior nasal spine (ANS) and the posterior nasal spine (PNS)
Velopharyngeal depth	Distance between the PNS and the posterior pharyngeal wall on the plane parallel to the hard palate
Velar length	Distance between the PNS and the tip of velum on the curvature along the velum
Velar thickness	Distance between the velar knee and velar dimple
Retroglossal space	Distance between the tongue and posterior pharyngeal wall on the plane parallel to the hard palate and through the anteroinferior border of the second vertebra (C2)

Table 3: The duration of speech in the Japanese and Thai groups.

Sounds	Japanese ($N = 5$) (ms)	Thai ($N = 5$) (ms)	Significance
First vowel	160.4 ± 47.7	140.4 ± 29.3	NS
Consonant	183.8 ± 42.5	87.0 ± 22.6	*
Second vowel	164.8 ± 67.5	160.6 ± 46.3	NS

* $p < 0.05$; NS: not significant.

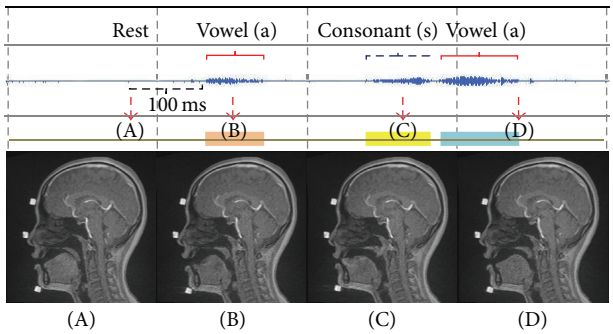

Figure 4: Representative sound data combined with movie MRI of a Thai subject. A–D are the corresponding sound signals and MR images.

posterior pharyngeal wall during this stage; instead, the tongue moved in an anterior direction. The retroglossal space was diminished during the B stage compared with the rest stage. At the C stage, the tongue actively moved in the anterior direction towards the premaxillary area. The velum achieved a higher position than during vowel pronunciation and the retroglossal space was enlarged. At the D stage, the tongue moved backward and the velum downward such that the retroglossal space again became smaller.

3.2. Thai Subjects. Figure 4 shows representative data from the Thai group. Although two groups pronounced the same VCV syllable (/asa/), Thai subjects trended to produce a significantly shorter ($p < 0.05$) consonant than Japanese subjects (Table 3). In the Thai group, there was a short break between the first vowel and the consonant. During the A stage, the velum of Thai subjects was placed on the posterior tongue, as observed in the Japanese group. During the B stage, however, the Thai group differed from the Japanese group in that an obvious groove formed near the tip of the tongue. The velum was elevated but there was no contact between it and the posterior pharyngeal wall. In only one subject was there contact between the two structures during this stage. During the C stage, the tongue moved anteriorly and the velum was further elevated, similar to the Japanese group. Contact between the velum and the posterior pharyngeal wall was observed. Finally, in the D stage, the tongue moved posteriorly and the velum moved downward.

3.3. Differences in the Velopharyngeal Structures between the Two Groups. A time-to-time quantitative comparison of the data of the Japanese and Thai groups is shown in Figure 5. Thai subjects had a significantly longer hard palate than Japanese subjects (36.36 ± 2.22 and 33.66 ± 1.82, resp.) but the velopharyngeal depth did not differ significantly between the two groups at any stage (Figure 5(a)). The temporal changes were the same: the velopharyngeal depth was deepest during the rest stage and decreased during pronunciation. A combined assessment of the length of the hard palate and the velopharyngeal depth showed a longer dimension in the Thai group than in the Japanese group at every stage: rest stage (67.79 ± 2.66 versus 66.32 ± 3.85), first vowel stage (66.25 ± 2.43 versus 64.41 ± 3.37), consonant stage (65.58 ± 1.70 versus 64.15 ± 3.17), and the last vowel stage (65.89 ± 2.05 versus 66.04 ± 3.42). Velar length did not differ significantly between the two groups and was stable at every stage of measurement (Figure 5(b)). The velar thickness was similar at the rest, first vowel, and post-second-vowel stages; however, during the consonant stage the velum became significantly thicker in the Thai than in the Japanese subjects. In the latter, velar thickness was nearly stable at every measurement stage whereas in the Thai group the velum became markedly thicker during production of the consonant than during production of the first vowel but it significantly decreased in thickness after production of the second vowel (Figure 5(c)). The retroglossal space of the Thai group was significantly wider than that of the Japanese group during the rest, first vowel, and consonant stages. There was no significant difference between the two groups in the post-second-vowel stage, and similar patterns in the dimensional change of the retroglossal space were observed; that is, the space was broad in the rest stage, significantly narrower during the first vowel,

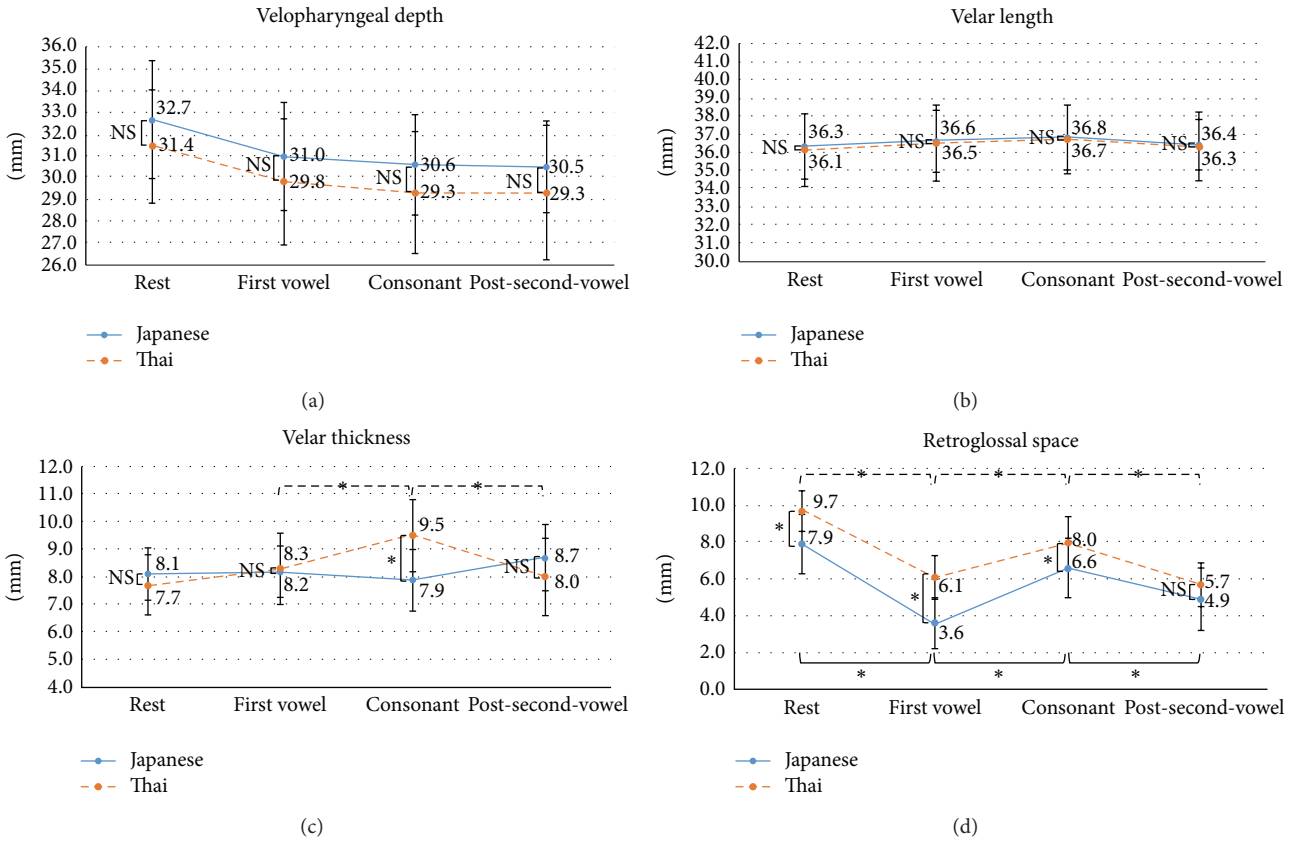

FIGURE 5: Time-to-time changes in the velopharyngeal structures of Japanese and Thai subjects. The graphs show the dimensional changes in each area of interest: velopharyngeal depth (a), velar length (b), velar thickness (c), and retroglossal space (d). The x-axis shows the measurement stages and the y-axis shows the distance in millimeters. $^{*}p < 0.05$; NS: not significant.

markedly wider during consonant production, and narrower again during the post-second-vowel stage (Figure 5(d)).

3.4. Speech Duration in the Japanese and Thai Groups. The speech duration of all subjects is shown in Figure 6 and the mean speech duration of the two groups in Table 3. Japanese subjects had a tendency to produce sounds continuously whereas Thai subjects paused at the end of every sound; the pause between the first vowel and the consonant was longer than that between the consonant and the second vowel. Thai subjects produced significantly shorter consonants than Japanese subjects, while there was no difference in the vowel sounds of the two groups.

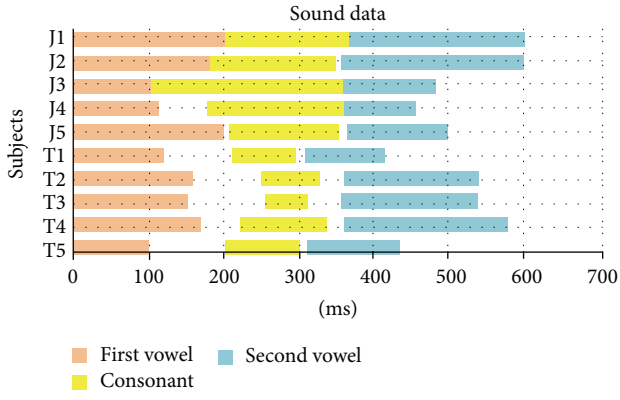

FIGURE 6: Speech duration in the 10 Japanese (J) and Thai (T) subjects. The x-axis shows the duration of speech in ms.

4. Discussion

MRI movie mode is an effective and noninvasive method of studying velopharyngeal function and articulation in real time [25, 27]. Although subjects are in the supine position during the experiments, gravity has been shown to only minimally affect velar and pharyngeal dimensions [44]. In fact, for the complete production of normal sound, adequate function of the soft palate is needed for the formation of an adequate seal with the posterior pharyngeal wall and for separating the nasopharynx from the oropharynx, to prevent both nasal escape during pressure consonants and hypernasality [5]. MRI movie mode can also be used to visualize the events that form the basis of the diagnosis, treatment, and prognosis of VPI.

Japanese and Thai groups did not differ significantly with respect to velopharyngeal depth whereas Thai subjects had a significantly longer hard palate. These findings are in agreement with previous studies in which lateral cephalometric

analysis showed a normal skeletal pattern in Japanese and Thai populations [41, 42]. Our comparison of cephalometric norms between Japanese and Thai females [41, 42] showed some differences: the Thai subjects had larger sella–nasion–A and sella–nasion–B point angles (SNA and SNB) and facial angles than their Japanese counterparts, while the A point–nasion–B point angles (ANB) were similar (Thai: SNA = 85.22 ± 3.94, SNB = 81.26 ± 3.68, and ANB = 3.96 ± 1.70; Japanese: SNA = 82.32 ± 3.45, SNB = 78.90 ± 3.45, and ANB = 3.39 ± 1.77) [41, 42]. Thai females had a more protruding profile than Japanese females, as indicated by the facial angle (Thai = 90.36 ± 2.59, Japanese = 84.83 ± 3.05) and the angle of convexity (Thai = 9.42 ± 4.76, Japanese = 7.58 ± 4.95) [41, 42]. This suggests that the size difference in the upper airway, especially at the site of the velopharyngeal constriction during pronunciation, is negligible despite the significant differences between the Thai and the Japanese regarding the hard tissues of the oropharyngeal region.

The velar lengths of the two groups were similar at every stage of measurement, consistent with the results of a previous study [44] that used MRI to evaluate the velopharyngeal structures in white females placed in the upright and supine positions. In our study, the mean velar lengths during rest (Japanese: 36.3 mm, Thai: 36.1 mm) and consonant production (Japanese: 36.8 mm, Thai: 36.7 mm) were shorter than the values reported by Perry [44] (40.3 mm during rest and 43.9 mm during consonant /s/ production). The difference may be attributable to the racial differences in the morphology of the craniofacial region: brachycephalic in the Mongoloid population and dolichocephalic in the Caucasian population.

The mean velar thickness in the Asian females in this study was smaller than that reported for the white females in the Perry's study [44]: during the resting stage, 8.1 mm in Japanese, 7.7 mm in Thai, and 9.7 mm in whites; during the consonant stage: 7.9 mm in Japanese, 9.5 mm in Thai, and 11.1 mm in whites. While both studies showed velar thickening during consonant production, our Japanese and Thai subjects differed in that in the latter group thickening of the velum during consonant production was significantly greater. This difference may affect the quality of consonant sound because although the participants were instructed to produce the same consonant, the consonant sounds of the two groups of subjects were unique, with the Thai group producing a shorter consonant sound than the Japanese group (Figure 6). This difference may be related to the amount of velar thickening needed to clearly produce a consonant sound and thus to compensate for the large retroglossal space within a short time frame.

The mean retroglossal space of Asians seems to be smaller than that of white females, based on a comparison between our findings and those of Perry [44] (rest stage: 7.9 mm in Japanese, 9.7 mm in Thai, and 10.8 mm in whites; consonant stage: 6.6 mm in Japanese, 8.0 mm in Thai, and 15.3 mm in whites). The reason why the retroglossal space of Asians decreases in size from the rest stage to consonant production while in whites it increases is unclear.

According to our findings, in Japanese and Thai populations velopharyngeal function is nearly the same, except for the difference in velar thickening during consonant production and in the retroglossal space during rest and speech production (Figure 5). Based on our measurements of hard-palate length and on the cephalometric norms reported in previous studies [41, 42], our results suggest that the differences in the soft-tissue morphology among Asian populations reflect differences in their skeletal patterns. Further studies of the interaction between the hard and soft tissues in different races and of the effects of race on velopharyngeal structure and function would certainly be of broad interest but will require much larger sample sizes than used in this study.

5. Conclusions

To produce a normal consonant sound, a complete seal in the posterior pharyngeal space is necessary, which requires the participation of the soft palate and related muscles. Our study demonstrated significant differences in hard-palate width, velopharyngeal depth, retroglossal space, and velar thickness during the production of the test consonant by Japanese and Thai subjects. The racial features of the two groups included structural and functional differences in skeletal patterns and soft-tissue morphology.

Using 3 T MRI in movie mode, velopharyngeal structures and their variations in different populations can be precisely observed in real time, thereby improving our understanding of velopharyngeal function. This imaging approach is also useful for the diagnosis and treatment of patients with VPI and in the evaluation of outcome. Studies such as ours will allow patient-tailored treatment of VPI based on gender, race, skeletal patterns, and velopharyngeal structures.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

In Situ and Home Care Nasopharyngeal Intubation Improves Respiratory Condition and Prevents Surgical Procedures in Early Infancy of Severe Cases of Robin Sequence

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Aim. To evaluate the clinical outcome of infants with Robin Sequence (RS) and severe respiratory obstruction managed with nasopharyngeal intubation (NPI). *Methods*. This prospective study was conducted with 107 infants with RS admitted to the Hospital for Craniofacial Anomalies of the University of São Paulo (HRAC-USP), from July 2003 to June 2010, diagnosed with severe RS and treated with NPI. The infants were followed up for the first year of life. Clinical findings, morbidity, and mortality were recorded. *Results*. Of the 223 infants with RS admitted to the hospital in the period studied, 149 were diagnosed with severe respiratory distress and 107 (71.81%) matched all the inclusion criteria. Of those, 78 (73%) presented Isolated Robin Sequence and 29 (27%) presented other syndromes or anomalies associated with RS. NPI treatment lasted an average of 57 days and the mean hospitalization time was 18 days. Although all infants presented feeding difficulties, 85% were fed orally and only 15% underwent gastrostomy. Morbidity was 14% and no deaths occurred. *Conclusions*. The children treated with the RS treatment protocol adopted at the HRAC-USP had improved respiratory and feeding difficulties, required a shorter hospitalization time, and presented low morbidity and mortality during the first year of life. The general outcome prevented surgical procedures in early infancy.

1. Introduction

Previously known as the Pierre Robin syndrome, Robin Sequence (RS) affects one in 8,500 live human births [1]. It is characterized by shortened mandible (micrognathia) and posteriorly placed tongue (glossoptosis). Cleft palate may also be present, but it is not observed in all cases [2]. Micrognathia seems to be the trigger for a cascade of events leading to tongue displacement, cleft palate, and respiratory distress, feeding difficulties, and consequent poor growth (hence the term "sequence") [3]. RS can occur as an isolated anomaly (IRS) or in association with other syndromes or anomalies (SRS) [4, 5].

Infants with RS present a challenge to pediatricians and other specialists because of their increased risk of airway obstruction and resultant hypoxia, cor pulmonale, failure to thrive, and cerebral impairment. As the infants grow, airway obstruction improves as the mandible grows and the coordination of the parapharyngeal muscles improves in conjunction with voluntary tongue control [6]. The goal of the initial treatment is to minimize any airway obstruction to prevent hypoxia and to promote normal neurologic development and include prone positioning [3], nasopharyngeal intubation (NPI) [7–10], glossopexy [11, 12], mandibular distraction osteogenesis [13, 14], and tracheostomy [15]. However, because of the lack of studies based on a large number of children with RS in a single center, much controversy remains about the use of both nonsurgical and surgical intervention strategies to manage respiratory obstruction in RS patients.

One of the current treatment strategies, the NPI procedure, helps the tongue to move forward, freeing the airway and allowing the child to breathe through the nasopharyngeal tube. Previous studies report having used NPI to relieve airway obstruction successfully in RS infants [16, 17] and to

prevent the use of surgical procedures during early infancy of RS patients [6]. These reports suggest that natural growth may lead to resolution of airway obstruction without the use of unnecessary surgical interventions.

In 2003, the Hospital for Craniofacial Anomalies of the University of São Paulo (HRAC-USP) established a new RS treatment protocol replacing glossopexy with NPI for the treatment of severe cases of children with RS. Over the years, the HRAC-USP has gained a large experience with NPI management of RS [8–10]. Here, we present the current RS treatment protocol employed at the HRAC-USP and analyze the evolution of a large series of severe cases of children with RS treated exclusively with NPI. We recorded the duration of NPI use, the frequency of gastrostomy, the age at the time of referral, associated syndromes, clinical symptoms, type of respiratory obstruction, and clinical complications during the first year of life and mortality. The data collected was used for the longitudinal and prospective analysis reported here. The results revealed herein may help clinicians make decisions regarding the need for surgical intervention strategies to manage airway obstruction in infants with severe RS.

2. Methods

2.1. Patients. Two hundred and twenty-three infants with RS were admitted to the HRAC-USP from July 2003 to June 2010. The infants were diagnosed as mild, moderate, or severe cases through objective airway assessment carried out using continuous oxygen saturation and through clinical observation by experienced staff. Severe cases presented recurrent crises of pallor and/or cyanosis and/or apnea, intercostal and supraclavicular retractions, oxygen saturation < 90% measured by continuous pulse oximetry with an oxygen requirement to improve this condition, and severe feeding difficulties for which feeding tubes were necessary. Mild cases had little respiratory difficulty without intercostal retraction or retraction of the furcula, O_2 saturation measured by continuous pulse oximetry equal to or higher than 90.0%, and few feeding difficulties (feeding exclusively by the oral route); moderate cases had intercostal retraction or retraction of the furcula without cyanosis, apnea, or pallor, satO_2 greater than 90.0%, and important feeding difficulties (feeding by a nasogastric tube) [18]. Of 223 infants, 74 presented mild or moderate symptoms and were managed with prone positioning and 149 infants presented severe symptoms. Of 149 severe cases, 107 were treated exclusively with NPI and 42 underwent tracheostomy. Only children diagnosed as severe RS, submitted to the RS management protocol adopted at the HRAC-USP and treated exclusively with NPI, were included in the study. Thus, of the infants hospitalized during this period, 107 children met the inclusion criteria.

2.2. RS Treatment Protocol at the HRAC-USP. Nasopharyngoscopy was performed in all children during the first days of hospitalization and the type of respiratory obstruction was classified according to Sher et al. [19]: type 1: the tongue is retro positioned and touches the posterior pharynx wall; type 2: the tongue presses the palate against the pharynx wall; type 3: there is a medial contraction of the pharynx and the pharynx is the cause of obstruction, while the tongue does not touch the pharynx wall; and type 4: the contraction of the pharynx is sphincteric.

All exams were performed by the same professional, a plastic surgeon with extensive experience in nasopharyngoscopy, and nasopharyngoscopy took place in the operating theater, in a room appropriate for this purpose. The infants were examined in horizontal dorsal decubitus without head flexion, awake, and without any type of sedation. An Olympus nasopharyngoscope (Tokyo, Japan) for infants with an INF P3 fiber (OTV-SC video camera system with a DSR 20 MD digital videocassette) was introduced through the right nostril with topical lidocaine chlorohydrate 2% (gel). All evaluations were performed by the same professional.

NPI was performed in infants with type 1 and 2 respiratory obstructions who displayed severe respiratory symptoms. NPI consists of a whitish Portex silicone tube of 3.0–3.5 cm that is introduced 7 to 8 cm into the nostril, cut 1 cm out of the nostril, and fixed with micropore tape. The tube is placed just above the epiglottis to allow the air to flow through it (Figure 1).

Improvement of respiratory discomfort with NPI was considered to have occurred when O_2 saturation, measured by continuous pulse oximetry, was maintained above 90% in ambient air (with no oxygen requirement) during 24 hours; when the respiratory effort was reduced (reduction of pallor and cyanosis crises, of intercostal and furcula retraction, and of inspiratory noise characteristic of glossoptosis observed by pulmonary auscultation); when it was possible to stimulate oral feeding and the child became comfortable with NPI, without accumulation of secretions and saliva in the oral and/or nasal cavity and/or in the tube for NPI. After the infant's respiratory discomfort had improved the parents were trained to manage NPI. Patients are only discharged after a period of monitoring with the NPI in situ and when clinical staff was sure of caretakers competence.

After discharge from the hospital, return visits to the hospital were scheduled every 15 days during its continuous use. At each return the infant was hospitalized for 24 hours for observation, and the definitive removal of NPI was performed only when, in the absence of the NPI, O_2 saturation remained above 90% in ambient air for 24 hours with no onset or worsening of respiratory discomfort. Otherwise, NPI was maintained until reevaluation on subsequent return visits.

Clinical observations and assessment were performed by multidisciplinary staff (nurses, pediatricians).

After decannulation, children are followed up at three-month intervals until the end of the first year of life.

Children with types 1 or 2 who did not improve with NPI were submitted to tracheostomy. Because types 3 and 4 are not considered RS but Robin complex (as the tongue is not the cause of respiratory obstruction), all children diagnosed as these types and with severe symptoms were submitted to tracheostomy to release the airways due to the severity of the respiratory obstruction [6].

All children were submitted to feeding facilitating techniques (FFTs) to improve oral feeding [20] and were given a hypercaloric diet. FFTs include sucking on a pacifier,

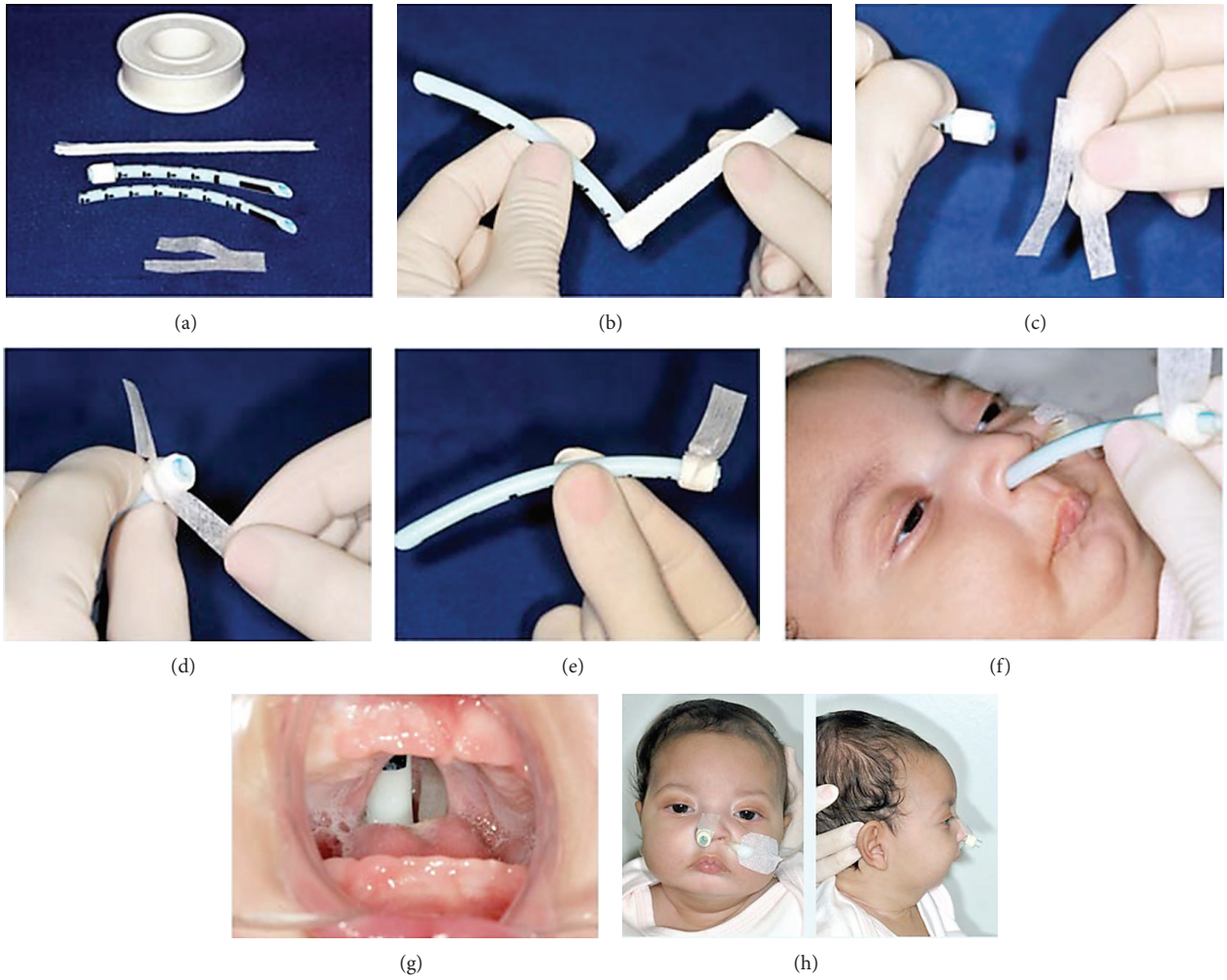

Figure 1: Nasopharyngeal intubation. (a) The Portex silicone tube and tape for marking the tube; (b) tube marked with a tape at the 7.5 cm level for positioning of the tube 7.5 cm inside and 1 cm outside the nostril; (c) the 5 cm micropore, partially divided in half; (d) the micropore tape fixed on the tube through divided parts; (e) the tube ready for introduction into the nostril; (f) the tube being introduced into the nostril; (g) a view of a tube through the cleft palate; (h) infant with PRS and nasopharyngeal intubation.

receiving a massage to interiorize and relax the tongue, improving lip closure and preventing oral escape of the food, using a long and soft nipple with a hole enlarged to 1 mm, and using thickened milk. To thicken the milk, corn-based industrially modified flour is added to the concentration of approximately 3%, until a thickened liquid consistency is achieved. The hypercaloric diet consists of a milk formula supplemented with 5 to 7% glucose polymers and 3 to 5% medium-chain triglycerides with essential fatty acids.

Children were considered ready for exclusively oral feeding when they were able to ingest 70% of the milk volume recommended for their age, in less than 30 minutes, without choking and/or a reduction in oxygen saturation.

3. Ethics

This study was approved by the Research Ethics Committee of HRAC-USP (SVAPEPE-CEP number 265/2011). All patients' parents or legal guardians signed a written informed consent.

4. Results

One hundred seven infants, 52 boys (48.6%) and 55 girls (51.4%), were followed up during the first year of life. Mean age at the time of referral was 31.7 +/− 29 days (ranging from one day to five months). Most patients (62/107) were younger than one month of age at referral. Seventy-eight children (73%) presented IRS and 29 (27%) presented SRS (Table 1).

All infants presented severe symptoms at the time of admission, and 56 infants (52%) were admitted to the intensive care unit. Ninety-five (89%) infants presented upper airway obstruction type 1 and two infants (11%) presented type 2 obstruction (Table 2).

The mean time of NPI use was 57.4 +/− 37.6 days (ranging from 1 to 173, median 54) and the mean hospitalization time for children treated with NPI was 18 days (ranging from 2 to 57, median 16). All patients were followed up until the NPI was no longer required and there were no nasal injuries, no untoward incidences at home, and no problems related to the use of NPI.

Table 1: Frequency of syndromes.

Syndrome	*N*	%
IRS	**78**	**73.00**
SRS		
Undefined syndrome	12	11.21
Stickler syndrome	9	8.41
Treacher Collins syndrome	4	3.70
Oculoauriculovertebral spectrum	1	0.92
Facial femoral syndrome	1	0.92
Otospondylomegaepiphyseal dysplasia (OSMED)	1	0.92
Otopalatodigital syndrome	1	0.92
Total	107	100.00

IRS: Isolated Robin Sequence.
SRS: Syndromic Robin Sequence.

Most patients had cleft palate (104/107). All infants presented feeding difficulties; 91 infants (85%) were fed orally and gastrostomy was performed in 16 infants (15%). Gastrostomy was more frequent in infants with SRS (31%) than with IRS (9%) (Table 3).

The most frequent complication was pneumonia. Morbidity was 14% and no deaths occurred (Table 4).

5. Discussion

RS is a combination of micrognathia and glossoptosis that occurs with or without cleft palate [2]. It can occur as a single syndrome (IRS) or associated to other syndromes or anomalies (SRS) [4, 5]. Associated anomalies are common; the reported incidence varies from 26 to 82%, with 25 to 38% being syndromic cases [3, 21]. In the present study, 27% of RS infants presented associated anomalies or syndromes. The lower frequency of syndromes or other anomalies associated with RS observed herein may be due to the fact that we excluded infants who presented type 3 or 4 airway obstructions. Indeed, infants with type 3 or 4 airway obstruction usually have associated syndromes or other anomalies and tracheostomy is always required for respiratory release [4, 6].

The HRAC-USP is one of the few reference centers for cleft lip and palate in Brazil. Patients, mainly severe cases, come from distant hospitals from all over the country that lack specialized knowledge or adequate infrastructure to treat RS, which explains the high rate of severe cases and a wide age range of the patients treated at the HRAC-USP. Ideally, patients should be admitted to the HRAC-USP soon after birth, but, unfortunately, this does not usually happen in Brazil. However, in this study, most patients (62/107) were less than one month old at the time of their admission to the HRAC-USP.

The main clinical problems in RS infants are upper airway obstruction and feeding difficulties. Symptoms are highly heterogeneous, ranging from mild respiratory distress to severe asphyxia crises which become more frequent and more severe during the first months of life [4, 6]. In this series, all infants had upper airway obstruction with severe symptoms and feeding difficulties and only patients presenting type 1 and 2 airway obstruction were included. Type 1 was the most frequent, occurring in 89% of patients.

There have been many reports on different strategies to manage airway obstruction in patients with RS, but no consensus has been reached so far. Since the obstruction occurs at the base of the tongue, the treatments aim to move the tongue base forward, away from the airway. Interventions include prone positioning, NPI, glossopexy, tracheostomy, and osteogenesis mandibular distraction osteogenesis [6, 7, 9, 12, 13]. However, the lack of studies involving a large number of children with RS in a single center has hampered decision-making regarding the choice of treatment, especially whether or not surgical approaches should be used.

NPI has been used to relieve airway obstruction in patients with RS for over 25 years [7]. Because NPI improves breathing, this procedure also improves infants' ability to feed orally and, being an extremely simple procedure, can be performed at home by parents after being duly trained by the nursing staff during the infants' hospitalization [22]. Wagener et al. [23] reported successful outcomes in 20 children with RS. In their study, the children required NPI for 16–104 days but their entire time was spent in the hospital. Anderson et al. [24] reviewed the outcomes of home management of upper airway obstruction in RS using NPI and showed that treatment reduced in-patient stays and remained effective in home care. In addition, employing home management of RS patients, Abel et al. [17] successfully treated 63 of 77 patients with moderate and severe upper airway obstruction. In the present study, the total average time that the nasopharyngeal airway remained in situ was 57 days and the average hospital stay was 18 days, which is shorter than the average stay in similar studies [16, 22, 24]. The duration of NPI use in a hospital setting reported herein was similar to the results shown in previous studies [6, 8]. We also show that NPI was effectively and safely managed at home by trained parents, making early hospital discharge possible. All 107 patients were followed until NPI was no longer required and none of them needed tracheostomy, and they were decannulated with success.

Most infants (104/107) had cleft palate and all infants presented feeding difficulties. Generally, respiratory obstruction in infants with RS leads to difficulties in the coordination of suction and of swallowing and glossoptosis impairs anteriorization of the tongue which is necessary in order to obtain adequate suction. In addition, cleft palate creates a deficit in the negative intraoral pressure necessary to efficient suction, as well as inducing nasal reflux of food [20]. In this group of patients the improvement of respiratory difficulties with NPI led to improvement of feeding difficulties, and 85% of patients were fed orally. Fifteen percent underwent gastrostomy and the rate of gastrostomy was high in infants with SRS.

The natural history of patients with RS is an improvement with growth, for both the airway obstruction and feeding difficulties. Along with growth, airway obstruction improves as the mandibular growth and the coordination of the parapharyngeal muscles improves in conjunction with voluntary tongue control. The NPI improves breathing, allowing

Table 2: Type of respiratory obstruction in Isolated Robin Sequence and Syndromic Robin Sequence.

Syndrome	Type of respiratory obstruction					
	1		2		Total	
	N	%	*N*	%	*N*	%
IRS	71	91	7	9	78	100
SRS	24	83	5	7	29	100
Total	95	89	12	11	107	100

IRS: Isolated Robin Sequence.
SRS: Syndromic Robin Sequence.

Table 3: Gastrostomy in Isolated Robin Sequence and Syndromic Robin Sequence.

Syndrome	Gastrostomy					
	Yes		No		Total	
	N	%	*N*	%	*N*	%
IRS	7	9	71	91	78	100
SRS	9	31	20	69	29	100
Total	16	15	91	85	107	100

IRS: Isolated Robin Sequence.
SRS: Syndromic Robin Sequence.

Table 4: Morbidity rate in severe Robin Sequence managed with nasopharyngeal intubation during the first year of life.

Morbidity	IRS ($N = 78$)	SRS ($N = 29$)
Pneumonia	4	4
Bronchoaspiration	1	2
Apnea		1
Bronchospasm	1	
Gastrostomy other complications		1
Digestive hemorrhage	1	
Total	7 (8.97%)	8 (27.58%)

IRS: Isolated Robin Sequence.
SRS: Syndromic Robin Sequence.

natural growth and resolution of airway obstruction without unnecessary surgical intervention.

The most relevant contribution of the present study is to present the NPI management protocol for children with RS adopted by the HRCA-USP, which was developed after extensive experience with these patients, and the fact that our results were obtained from a large number of patients from a single center. Indeed, NPI was the definitive treatment performed in all of the 107 infants studied here, corresponding to 48% of all patients with RS admitted to the HRAC-USP during the period studied. The children studied presented low morbidity and only 14% of them presented clinical complications in the first year of life. The main complication detected was pneumonia. Pulmonary complications and aspiration are the most severe and frequent complications of RS, generally due to deglutition disorders. The reported mortality varies from 2.6 to 30% [25, 26]. Indeed, Caouette-Laberge et al. [27] reported a 22.8% mortality rate in children with SRS and 5.9% for those with IRS. Importantly, no deaths occurred among the severe cases of RS treated exclusively with NPI using the HRAC-USP protocol.

We did not perform polysomnography (PSG), a sophisticated method to assess respiratory patterns and detect differences among infants not identified by oxygen saturation monitoring. The use of PSG could have improved the diagnostic accuracy in assessing the severity of upper airway obstruction (UAO). However, objective airway assessments using continuous oxygen saturation monitoring and clinical evaluation make the pediatric practice at the HRAC-USP and have been shown to be sufficient to diagnose the severity of airway obstruction and to detect clinical improvement [8, 9].

The HRAC-USP does not perform mandibular distraction osteogenesis during the neonatal period for the treatment of RS respiratory obstruction. Various studies have reported that mandibular distraction may avoid tracheostomy [28]. Mandibular distraction can help correct micrognathia by pulling the jaw forward, allowing the tongue to be pulled anteriorly via its anterior attachment to the mandible and thereby relieving airway obstruction. However, potential complications include inferior alveolar nerve damage, infections, dislodgment of distractor pins (causing injury to tooth buds), and anesthetic and surgical risks for newborns and young infants [27]. Thus, no consensus has been reached regarding the risks and benefits of this procedure for individuals with RS. Over the last few years, glossopexy surgery has been used less and less because the postsurgical results have been unsatisfactory in terms of airway release, especially in severe cases [29].

By studying a large series of infants with RS managed in a single center, we showed that NPI can be used to successfully treat these patients. The management of RS patients with NPI at the HRAC-USP involved a multidisciplinary and experienced team that was able to achieve a safe airway relief, low morbidity, and zero mortality rates for the infants treated.

6. Conclusions

NPI is an effective method for improving breathing and feeding in infants with RS and preventing surgical procedures in early infancy. The children treated with the NPI treatment protocol adopted at the HRAC-USP required a short hospitalization time and presented low morbidity and zero mortality during the first year of life.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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