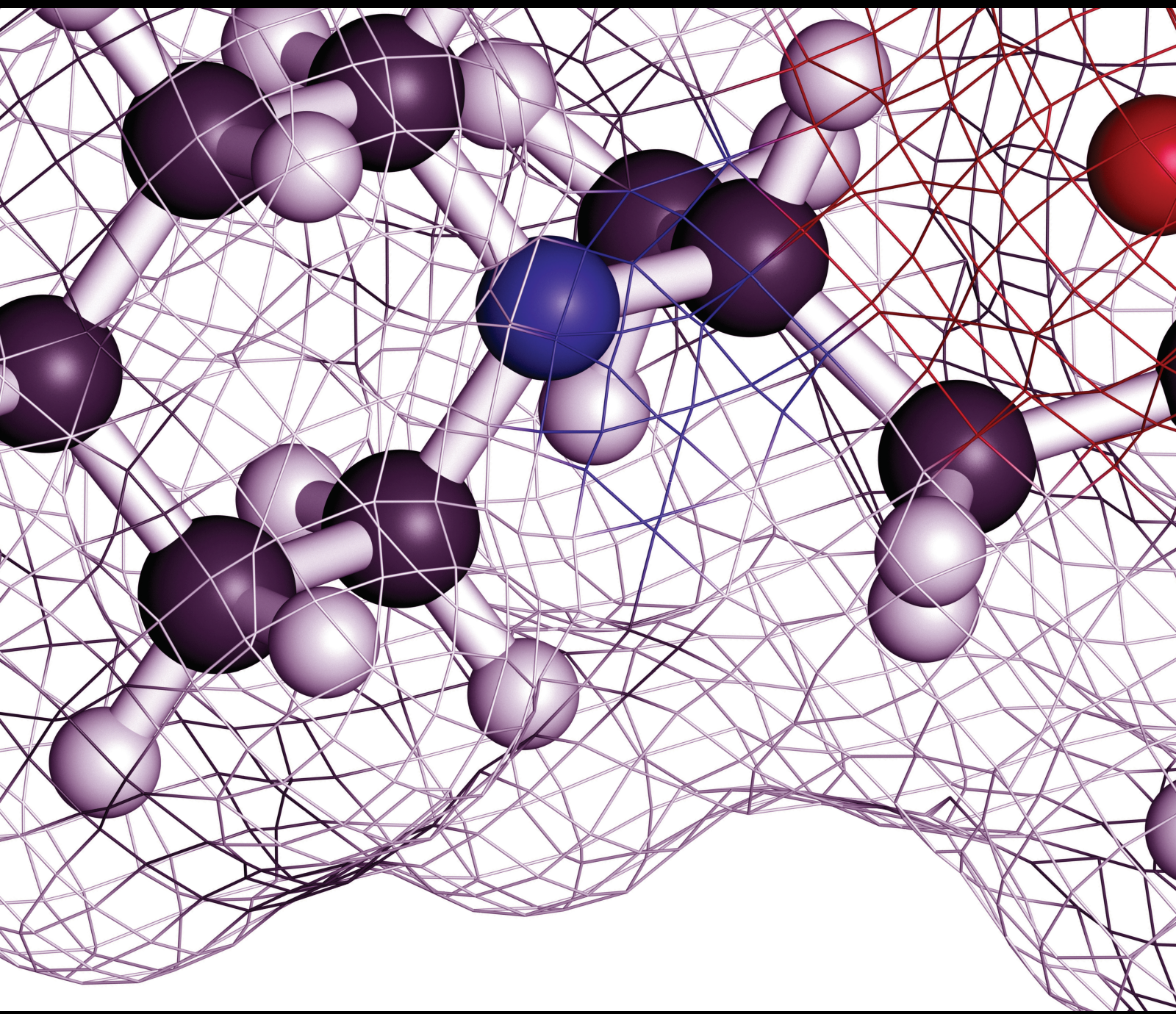
Pain Research and Management

Pain Research and Management with Digital Dentistry

Lead Guest Editor: Mohammad Khursheed Alam
Guest Editors: James Dudley and Nafij Jamayet



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Research Article

Photobiostimulatory Effect of a Single Dose of Low-Level Laser on Orthodontic Tooth Movement and Pain

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Objective. To assess the effect of low-level laser applied at 3 weeks intervals on orthodontic tooth movement (OTM) and pain using conventional brackets (CB). *Materials and Methods*. Twenty patients with Angle's class II div 1 (10 males and 10 females; aged 20.25 ± 3.88 years) needing bilateral extractions of maxillary first bicuspids were recruited. Conventional brackets MBT of 0.022 in slot (McLaughlin Bennett Trevisi) prescription braces (Ortho Organizers, Carlsbad, Calif) were bonded. After alignment and levelling phase, cuspid retraction began with nitinol closed coil spring on 19 × 25 stainless steel archwire, wielding 150 gram force. 7.5 J/cm^2 energy was applied on 10 points (5 buccal and 5 palatal) on the canine roots on the investigational side using gallium-aluminum-arsenic diode laser (940 nm wavelength, iLase™ Biolase, Irvine, USA) in a continuous mode. Target tissues were irradiated once in three weeks for 9 weeks at a stretch (T0, T1, and T2). Patients were given a feedback form based on the numeric rating scale (NRS) to record the pain intensity for a week. Silicon impressions preceded the coil activation at each visit (T0, T1, T2, and T3), and the casts obtained were scanned with the Planmeca CAD/CAM™ (Helsinki, Finland) scanner. *Results*. The regimen effectively accelerated (1.55 ± 0.25 mm) tooth movement with a significant reduction in distress on the investigational side as compared to the placebo side (94 ± 0.25 mm) ($p < 0.05$). *Conclusions*. This study reveals that the thrice-weekly LLLT application can accelerate OTM and reduce the associated pain.

1. Introduction

Fixed orthodontic treatment is a lengthy and time-consuming process and on average takes 12–36 months [1] and is associated with adverse outcomes, particularly pain and difficulty to carry out oral hygiene practices. Prolong treatment and difficulty is to maintain proper oral hygiene on mobile, and tender dentition is not only detrimental to the teeth and surrounding periodontal tissues but also influence patient compliance and productivity of the healthcare professionals [2]; therefore, orthodontic contemporaries are toiling on efficient and fast force delivery mechanics and approaches [3].

Interventions such as a local injection of pharmacological agents, use of magnets or direct current, and invasive surgical approaches (corticotomy) trim the total treatment time by stimulating bone remodelling but at the expense of either increased patient's suffering or systemic side effects [4].

Low-level laser therapy (LLLT) is being used to alleviate musculoskeletal pain for decades. However, its use in dentistry is gaining popularity as a noninvasive and safe modality. Moreover, its anti-inflammatory effects and potential to induce peripheral neural blockage makes it a suitable candidate for postactivation pain and healing of tissues [5].

LLLT, when applied at correct intensity and duration, has been proven to amp up tissue healing by increasing cell proliferation (fibroblasts, osteoclasts, and osteoblasts), angiogenesis, and collagen synthesis [6]. At the molecular level, red or infrared light donates free electrons to the electron transport chain in mitochondria to curb the oxidative stress and generate more ATP [7]. This cascade of reactions, in turn, triggers growth signalling pathways and upregulates various transcription factors [8], with an overall increase production of growth factors [5].

A handful of researchers document the effect of LLLT on OTM, but the diversity of results pertains to different laser specifications, dosages, points of application, and intervals of application results [9–12], therefore requiring further insight into precise and specific emissions of radiation to get optimal results.

This research was aimed at providing a single dose of LLLT application to expedite tooth movement and lessen the discomfort associated with it.

2. Materials and Methods

This was the placebo-controlled clinical study, and the research was conducted in the Department of Orthodontics at Baqai Medical University, Pakistan. Twenty-two patients, age ranging from 12 to 30 years (10 males and 10 females), with healthy medical and dental status (no missing or impacted teeth except third molars) and no history of orthodontic treatment were recruited in the trial.

The inclusion criteria were patients with 1/4 or half cusp, molar class II division 1 warranting extraction of upper bicuspids on both sides. Patients who require lower premolar extraction were excluded from the study because simultaneous lower canine retraction interferes with the retraction of upper canines. Patients with TMJ problems or taking medicines that modify bone turnover or interferes with tooth retraction, e.g., NSAIDs, bisphosphonates, and corticosteroids, were disqualified.

Regular diagnostic orthodontic records were collected and thoroughly examined after the approval from the ethical board of Baqai Medical University. The whole procedure was verbally explained, and assent form was signed from the patients and legal guardians of minors.

Split-mouth design was chosen by flipping a coin to circumvent individual bias, randomly assigning one side as an experimental and the other placebo group.

After all the necessary procedures, banding and bonding were carried out. MBT (McLaughlin Bennett Trevisi) of 0.22 inch slot prescription braces (Ortho Organizers, Carlsbad, Calif) were bonded. The first stage of levelling and alignment was commenced with 0.014 inch heat-activated nitinol (NiTi) wire and after that by 0.016 inch NiTi, 0.017×0.025 in NiTi, 0.019×0.025 inch NiTi, and 0.019×0.025 SS as the final working wire. The first bicuspid was then extracted at day 21, and individual canine retraction began with 6 mm close coil NiTi spring, stretched to 150 gm force, measured with the orthodontic dynamometer (Forestadent, Germany) and secured with a ligature tie between the power arm of canine and first molar band.

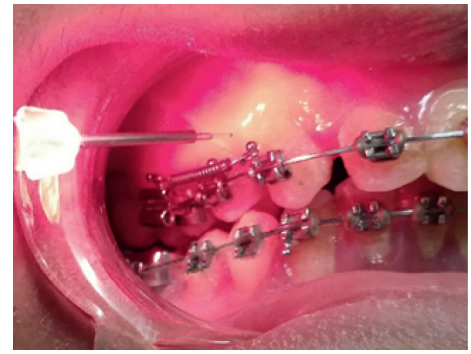

Figure 1: Laser application.

LLLT irradiation was applied soon after the placement of spring on the experimental side and was held at the placebo side without turning it on (Figure 1). The springs were activated at a three-week interval. Silicon impressions were taken before the first activation (T0) and repeated at every appointment before activation for nine consecutive weeks, i.e., T1, T2, and T3. Dental casts were scanned with the Planmeca CAD/CAM lab scanner for further analysis.

2.1. Laser Specification. Ga-Al-As diode laser (Ilase, USA) operated at 940 nm wavelength in a continuous, uninterrupted beam of light was used. Irradiations were delivered through the 0.04 cm^2 diameter optical fibre tip in light contact with the oral mucosa.

The target area was irradiated on ten sites, five points buccally and five palatally, for 3 secs each. The areas were as follows:

(i) Mesial and distal to the cervical area of the canine

(ii) Mesial and distal to the apical area of the canine

(iii) One point in the middle of the root

The power output set at 100 mW for 3 sec at each point made the cumulative of 7.5 J/cm^2 energy density. A separate room with loud music was reserved for the procedure. All the personnel wore protective shades near irradiated laser (patient, assistant, and dentist). To avoid the carryover effect, a plastic shield of the same wavelength as that of the laser was used.

2.2. Measurements

2.2.1. Rate of Canine Movement. To assess the effectiveness of regimen, the comparison of right and left sides was made, i.e., experimental and placebo at T0, T1, T2, and T3. A system suggested by Gebauer was used, and x and y marks were drawn on 3D imageries of study cast [13]. Y-axis was

Table 1: Median values and standard deviation of canine movements in experimental and placebo groups with confidence interval and p values.

	Experimental side (mean (SD))	95% CI		Placebo side (mean (SD))	95% CI		P value
		Lower bound	Upper bound		Lower bound	Upper bound	
T0-T1	1.79 (0.25)	1.63	1.95	1.12 (0.21)	0.98	1.25	<0.001*
T1-T2	1.59 (0.29)	1.40	1.78	0.91 (0.19)	0.79	1.03	<0.001*
T2-T3	1.29 (0.25)	1.12	1.45	0.80 (0.24)	0.64	0.95	<0.001*

*Significant at $p < 0.05$ (Mann–Whitney U test).

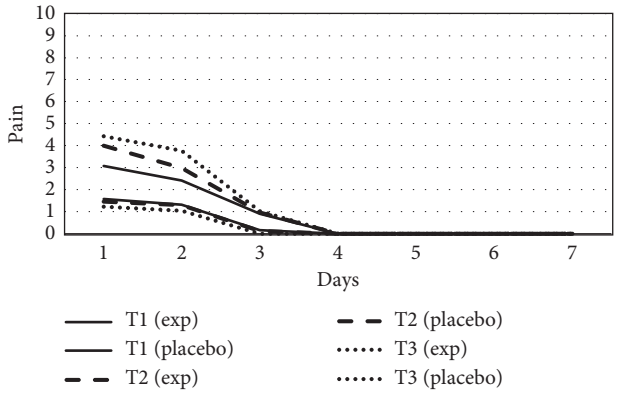

Figure 2: Comparison of pain among experimental side and placebo side in group A at T1, T2, and T3.

drawn a parallel to raphe line, and medial end of the prominent rugae marked the plane for the x-axis. The distance covered by canine was given by measuring the distance from x coordinate to the most distal point on canine on both the sides, and the two reading were later compared for the effectiveness.

2.3. Postactivation Pain. The analgesic effect of the LLLT evaluated by a feedback form was designed based on 11 points (from 0 to 10) numeric rating scale (NRS) where zero indicates no discomfort and 10 excruciating, terrible pain.

The form was given to the patient at each appointment and collected at the subsequent show-up. They were instructed to record the pain four hours after the activation and thereupon every 24-hour interval for the next 7 days. Patients were told not to take any analgesics if needed and advised to jot it down.

2.4. Statistical Analysis. Data were put in and interpreted on the SPSS 20.0 version. The Mann–Whitney U test was performed to compare the canine movement and Kruskal–Wallis test for pain comparison.

3. Results

3.1. Rate of Canine Retraction. 22 patients were recruited in the study, and two of them later were disqualified due to spring dislodgement and use of analgesics.

The Mann–Whitney U test shows a statistically significant acceleration in canine movement on the experimental side in comparison to the placebo group (Table 1). In 9 weeks, canine achieved 4.67 mm movement on the experimental side and 2.87 mm on the placebo side. Moreover, the average cuspid displacement in the experimental and placebo groups was 1.55 ± 0.25 mm and 0.94 ± 0.25 mm, respectively. The overall rate of displacement in the experimental group exceeded 1.66 times than the placebo group.

Pain. Most patients experienced the highest level of discomfort on the day the spring got activated. Females reported heightened pain sensitivity as compared to males. A significant reduction in pain in the lased group for initial 2 days was found. No difference was noted in the remaining days of the week.

Highest pain scores were recorded in the placebo side at T3 (Figure 2). There was a significant reduction in pain on the experimental side at all stages of treatment (T1, T2, and T3) as the level of pain was significantly higher on placebo sides.

4. Discussion

This research was undertaken to appraise the effectiveness of a single dose of laser on OTM and twinge using conventional brackets, applied at 3 weeks' interval.

Pain and rate of movement are subjective quantities and are greatly influenced by age, gender, hormones, pain threshold, and anatomic variations [14]. Therefore, the split-mouth design was considered to circumvent chances of error. However, it holds an inherent disadvantage of the carryover effect. For that, a plastic shield of the same wavelength as that of the laser was placed in the midline.

To maximize the effectiveness of placebo design, the whole protocol was carried out in a separate room, and loud music was played on to mingle it with the beeping sound of the laser. None of the patients complained about the heating, burning sensation, or any form of discomfort.

A bunch of researchers has employed single-blind trials with split-mouth design, but none of them brought the carryover effect and blinding into consideration [9, 10, 15–18].

Ga-Al-As semiconductor diode with 940 nm wavelength was used due to its deeper depth of penetration, about its low absorption coefficient in haemoglobin and water and its subsequent ability to stimulate osteoblastic activity on the target tissue [19]. Several previous authors also used Ga-Al-As with the wavelength ranging from 650 nm to 860 nm. Energy output, however, varied in all the studies and led to speckled results [2, 9–11, 15–18, 20].

In this study, energy dose was kept 7.5 J/cm^2 at each point as low doses impart biostimulatory effects [4, 21].

Research studies catering laser photobiostimulation on OTM reveals that patients had to make some additional visits along with the regular ones for the regimen, making it difficult for them to stick to it [9–12, 22]. In our research, LLLT was applied once in three weeks, and a profound acceleration was observed because LLLT works best to stimulate bone remodelling if applied within 48 hours after force application [23]. This is in agreement with few previous research studies which found a single dose of LLLT to be efficient in accelerating OTM and reducing associated pain [24–26].

Since bone remodelling is directly related to cytokine production, LLLT stimulates bone remodelling by accelerating the production of IL-β, and receptor activator which is crucial for osteoclastic activity on day 2 or 3 after laser application [27].

The overall rate of canine movement was 1.65 times greater in the present study. However, Youssef and Sousa concurred with twice the rate and Doshi-Mehta, and Bhad Patil found it to be 1.3 times faster than the control group [10–12]. Others found no significant acceleration [20, 28]. Qamruddin et al. reported 2.02 times acceleration in canine movement; however, more acceleration attributes to the use of frictionless self-ligating brackets in the study [24].

In previous research studies, the measurements were made from canine cusp tip or distal surface of canine to mesiobuccal cusp of the first molar with a digital calliper, held directly on the dental cast [11, 12, 15]. Curved palatal anatomy, rotated molars, and difficulty in holding the calliper directly over the cast pose difficulty in recording the precise measurements, therefore, in this research, we took medial part of most prominent rugae as a stable reference landmark [29] and scanned the respective models through the CAD/CAM scanner [20] to assure the accuracy in measurements.

To assess the pain levels in patients undergoing LLLT therapy, a questionnaire (feedback form) was formulated using NRS in contrast to others who employed a visual analogue scale (VAS). NRS is more accurate and easily understood by patients of any age and educational background [30].

In the present study, the pain rating was very low in the lased as well as the placebo group. Highest pain scores were reported on day 1 of coil activation, which agrees with the previous studies [31–33]. Experimental and placebo groups showed a significant difference in the level of pain. This is well supported by some studies which documented the pain-alleviating effect of LLLT [34–37] experienced during canine retraction [11, 12]. Almallah et al. also revealed a 12% decrease in discomfort after a single dose of low-level helium-neon laser in the experimental group [34]. Few more studies evinced the analgesic effects laser. However, the effects were on pain linked with the insertion of initial archwire [31–33]. Some authors find a nonsignificant difference in pain associated with canine retraction between the control and lased groups [9, 20].

5. Conclusion

Application of LLLT at regular orthodontic visits (3 weeks intervals) accelerates OTM and decreases the pain significantly. Hence, the above regimen can be implemented in fixed orthodontic treatment to avoid the risk of patient and operator burnout.

Data Availability

The data used to support the findings of this study are presented within the results section as tables and are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Irfan Qamruddin and Mohammad Khursheed Alam are the first authors. Verda Mahroof carried out clinical application. Mubassar Fida supervised the study. Mohd Fadhli Khamis and Adam Husein were involved in statistical input and final formatting.

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Research Article

Biostimulatory Effects of Low-Intensity Pulsed Ultrasound on Rate of Orthodontic Tooth Movement and Associated Pain, Applied at 3-Week Intervals: A Split-Mouth Study

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Objective. Low-intensity pulsed ultrasound (LIPUS) is a noninvasive modality to stimulate bone remodeling (BR) and the healing of hard and soft tissues. This research evaluates the biostimulatory effect of LIPUS on the rate of orthodontic tooth movement (OTM) and associated pain, when applied at 3-week intervals. *Methods*. Twenty-two patients (11 males and 11 females; mean age 19.18 ± 2.00 years) having Angle's Class II division 1 malocclusion needing bilateral extractions of maxillary first bicuspids were recruited for this split-mouth randomized clinical trial. After the initial stage of alignment and leveling with contemporary edgewise MBT (McLaughlin–Bennett–Trevisi) prescription brackets (Ortho Organizers, Carlsbad, Calif) of 22 mil, followed by extractions of premolars bilaterally, 6 mm nickel-titanium spring was used to retract the canines separately by applying 150 g force on 0.019 × 0.025-in stainless steel working archwires. LIPUS (1.1 MHz frequency and 30 mW/cm^2 intensity output) was applied for 20 minutes extraorally and reapplied after 3 weeks for 2 more successive visits over the root of maxillary canine on the experimental side whereas the other side was placebo. A numerical rating scale- (NRS-) based questionnaire was given to the patients on each visit to record their weekly pain experience. Impressions were also made at each visit before the application of LIPUS (T1, T2, and T3). Models were scanned with a CAD/CAM scanner (Planmeca, Helsinki, Finland). Mann–Whitney *U* test was applied for comparison of canine movement and pain intensity between both the groups. *Results*. No significant difference in the rate of canine movement was found among the experimental (0.90 mm ± 0.33 mm) and placebo groups (0.81 mm ± 0.32 mm). There was no difference in pain reduction between experimental and placebo groups ($p > 0.05$). *Conclusion*. Single-dose application of LIPUS at 3-week intervals is ineffective in stimulating the OTM and reducing associated treatment pain.

1. Introduction

As face and smile is the core of communication, people from different walks of life have become more aware of their dentofacial proportions and facial esthetics. More and more people are seeking fixed orthodontic treatment, but their prime concern is the lengthy course of treatment and discomfort associated with tooth movement [1]. Orthodontic tooth movement is a complex process of bone resorption and deposition in response to mechanical force [2], which involves sequential mechanical cyclical stretches of periodontal ligaments, fluid shear stress and compression,

inflammatory cytokine production, and cellular differentiation and multiplication, followed by remodeling of the surrounding [3, 4].

Acceleration of bone remodeling under physiological conditions is highly desirable in orthodontic patients to reduce the treatment duration. Several surgical procedures (corticotomies), pulsed electromagnetic fields, direct electrical current, and biomolecule injections may accelerate bone remodeling, but the challenge here is to accelerate bone remodeling in a noninvasive manner [5–7]. Among the least invasive procedures, low-level laser therapy and mechanical vibration have recently gained some popularity in expediting the orthodontic tooth movement and also minimizing the associated pain; however, the results are not predictable [8–11].

In this regard, low-intensity pulsed ultrasound (LIPUS) has been shown to enhance cell metabolism. Its efficacy for bone regeneration and healing of fractures has long been proven for which it is approved by the US Food and Drug Administration and the UK National Institute for Health and Care Excellence [12, 13]. Mechanical loading of bone is pertinent to maintain its mass and strength. When a bone is physiologically loaded, the fluid in the spaces surrounding bone cells produces fluid shear stress that stimulates different cell lines of bone. LIPUS works on the principle of mechanotransduction where external acoustic waves convert fluid shear stress into biochemical changes at a cellular level [14]. In vitro studies have revealed that LIPUS promotes differentiation of bone-forming cells and extracellular matrix formation through modulation of growth factors and other signaling factors [15]. Although very limited research studies have been conducted to assess the effects of LIPUS on orthodontic tooth movement, few animal-based studies have revealed the acceleratory effect of LIPUS on the rate of tooth movement [16, 17]. Low level of toxicity, low immunogenicity, noninvasiveness, and highly targeted approach make it a suitable adjunct to conventional treatment. However, varied techniques, different application strategies, and ultrasound specifications might pose difficulty to clinicians to get the desired results [18].

Pain wearing orthodontic appliances experience varying degrees of pain. Nearly 99% of patients experience some form of discomfort. Patients experience it as soreness and a feeling of compression and stretch in the affected teeth. It results in a decline in oral health (often manifests as weight loss), compromising the masticatory performance and speech. More often they become indifferent to treatment outcomes and stop cooperating [19]. Therefore, it is a matter of concern to find an approach that reduces pain without jeopardizing bone remodeling.

The aim of our research was to evaluate the effectiveness of a single dose of LIPUS on the tooth retraction phase of OTM and the pain associated with it.

2. Materials and Methods

This is a randomized clinical trial conducted in the Orthodontic department of Baqai Medical University, Karachi, Pakistan. The study duration was nine months from October 2015 to July 2016. Ethical approval was obtained by the Ethics Committee of Baqai Medical University. Written consent was taken from the patients and the guardians of minors prior to all diagnostic records. The sample size was calculated using power analysis, based on the tooth movement objective. The sample size was determined using power analysis, having 80% power; alpha which indicates significance level was set at 0.05. According to the sample size calculation, twenty-two Pakistani patients, ages ranging from 15 to 30 years (19.18 ± 2.00 years), were selected for the study. Subjects who fell under the following criteria were selected:

(1) Male and female subjects with age between 15 and 30 years with a full set of permanent dentition and no missing or impacted teeth except for the third molars
(2) No systemic disease or pregnancy
(3) Patients having half cusp class II molar relationship, necessitating exclusively bilateral bicuspid extraction
(4) Good oral hygiene and compliance

The exclusion criteria include the following:

(1) Chronic use of nonsteroidal anti-inflammatory drugs, corticosteroids, and bisphosphonates
(2) Patients with any metabolic bone disease
(3) Patients with a previous history of fixed orthodontic treatment

2.1. Randomization and Study Design. To ensure maximum efficacy, a split-mouth design best suited the study. The right and left sides of the patients who fulfilled the criteria were randomly divided into experimental and placebo groups by a simple randomization technique. Tossing a coin for each patient that enters the trial such that head for the experimental group and tail for the placebo group. Patients did not know which side was experimental or placebo; however, the clinician knew it. The experimental group received the LIPUS irradiation extraorally on the canine root; the transducer was kept at the placebo side for the same duration without turning it on. Blinding was satisfactory as US waves are inaudible and imperceivable.

2.2. Methodology. Treatment was initiated with banding and bonding procedures. Preadjusted edgewise MBT prescription brackets (Ortho Organizers, Carlsbad, Calif) of 0.22-in slot were glued following conventional steps of etching and bonding.

For leveling and alignment, a series of NiTi wires were placed, starting from 0.014-in heat-activated nickel-titanium (NiTi) wire followed by 0.016-in NiTi, 0.017×0.025-in NiTi, and 0.019×0.025-in NiTi upgraded after every 21 days. The final working wire was 0.019×0.025 SS. First premolars were extracted on both sides on the 21st day of the final working wire placement. A week after extractions, the canine retraction was commenced. Prior to the beginning of canine retraction, proper leveling and alignment of incisors,

Figure 1: LIPUS application.

bilateral symmetry, and correct angulation of both canines were ensured. The incisors were secured together with 0.010-in steel ligature to prevent inadvertent tooth movement during the retraction phase. A horizontal force was applied by stretching a 6 mm close coil NiTi spring up to 150 g through Orthodontic Dynamometer (Forestadent, Germany) and held with a ligature wire between the power arm of the canine and first molar. Patients were told to meticulously maintain oral hygiene and to inform immediately if spring is severed or displaced. They were also discouraged to take analgesics and also advised to note it down if taken for the severity of pain.

Immediately after force application, LIPUS was applied extraorally on the experimental side (Figure 1). Ultrasound gel was applied on the transducer of LIPUS for homogenous penetration, followed by placement over the whole length of the root of the maxillary canine [20]. The transducer of the LIPUS device was also held on the placebo side without turning the device on, so that the placebo design is not disturbed. The procedure was repeated after every 3 weeks after measuring the level of force with the same force measuring gauge, which should be 150 g. Silicone impressions were made before the beginning of retraction (T0) and then were repeated at 3-week intervals for approximately 4 months, i.e., T1, T2, and T3. Dental casts were scanned with Planmeca CAD/CAMTM Lab scanner for the analyses explained in the section later.

2.3. LIPUS Specification. LIPUS (Metron accusonic model GS 170 Australia) was used which generates a frequency of 1.1 MHz as it has been used successfully to accelerate BR [21]. The LIPUS wave was delivered in burst for 10 milliseconds followed by a pause of 800 μs. The recommended intensity output for clinical use is 30 mW/cm^2, which was applied for 20 minutes with a 2.5 cm lead zirconate titanate transducer.

2.4. Rate of Canine Retraction. To evaluate the effectiveness of the regimen, the experimental side was compared with the placebo side. A subtle method presented by Gebauer was selected, where x and y coordinates were drawn on 3D images of the dental cast. Raphe line was taken for the y-axis and the medial end of the most prominent rugae was taken for the x-axis [22]. The distance between the most distal points on the canine was measured in millimeters from the x coordinate in both the groups and measurements on both sides were compared.

2.5. Pain Intensity Evaluation. For pain measurement, numerical rating scale was used [8, 9]. The 11-point scale rates the pain intensities with the understanding that 0 stands for no discomfort and 10 for the worst possible pain. Pain recording was commenced four hours after the instigation of spring and patients were asked to record the score that best describes their pain intensity throughout the day after every 24 hours for consecutive 7 days.

2.6. Statistical Analysis. The data were recorded, and the results were evaluated on SPSS 20.0 version. Since the data were not normally distributed, nonparametric Mann–Whitney U test was used for canine movement and pain comparison.

3. Results

Twenty-two patients were selected for the study and the whole process of data collection took seven months. Two patients were dropped out due to spring dislodgement during the retraction, reducing the sample size to twenty patients.

There was no significant difference in canine movement among the two genders. Mann–Whitney U test reveals no statistically significant difference in canine movement among experimental and placebo groups. Over a period of 9 weeks, the canine achieved 2.72 mm ± 0.11 movement on the experimental side and 2.45 mm ± 0.98 mm on the placebo side. Moreover, the mean canine movement in experimental groups and placebo groups was 0.90 mm ± 0.33 mm and 0.81 mm ± 0.32 mm, respectively (Table 1).

Our study concludes pain intensity peaked within 24 hours after force activation and subsided at the end of 4th day at most stages of treatment. Females reported a slightly higher score of pain intensity, but the statistical test showed an insignificant difference in pain intensity among the two genders.

No significant difference was found in the pain intensity between experimental and placebo sides at any stage of treatment (Figure 2).

4. Discussion

LIPUS has showed its potent clinical efficacy in soft and hard tissue healing in the field of medicine [23, 24]. Moreover, its effect on the repair and regeneration of orthodontically induced root resorption cannot be overemphasized [20]. It stimulates not only osteogenic cells but also cementoblasts that aid in root regeneration [25, 26]. The effect of LIPUS on OTM and pain in humans has gained little attention.

Table 1: Mean values and standard deviation of canine movements in experimental and placebo groups with confidence interval and p values.

	Experimental side mm (SD)	95% confidence interval		Placebo side mm (SD)	95% confidence interval		Mean difference	p value
		Lower bound	Upper bound		Lower bound	Upper bound		
T0-T1	0.97 (0.28)	0.78	1.16	0.79 (0.37)	0.54	1.04	0.18	0.251
T1-T2	0.86 (0.59)	0.46	1.25	0.64 (0.47)	0.32	0.96	0.22	0.253
T2-T3	0.89 (0.31)	0.68	1.11	1.02 (0.14)	0.93	1.12	−0.13	0.433

*Significant at $p < 0.05$ (Mann–Whitney U test).

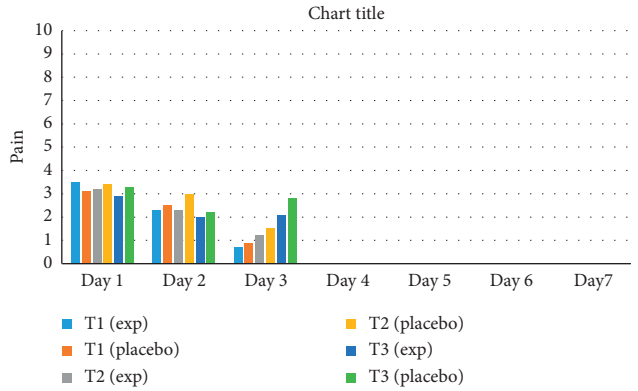

Figure 2: Comparison of pain among the experimental side and placebo side in group A at T1, T2, and T3.

Our research showed no significant difference in the rate of canine movement among genders as well as among experimental and placebo sides. Since LIPUS has never been tested on humans for its rate accelerating and analgesic effects in orthodontic patients, therefore, direct comparison with similar researches was not possible. However, a marked acceleration in the rate of OTM has been reported in animals [27, 28]. Dahhas applied LIPUS on ovariectomized rats for 28 days at alternate days and found normal orthodontic tooth movement postulating that LIPUS induces normal bone turnover and could be beneficial in orthodontic treatment in postmenopausal women with osteoporosis [27]. Our research investigated a single 20 min application in three weeks suggesting the reason for the ineffectiveness of this treatment regime. On the other hand, Aldagheer applied LIPUS for 20 min for four consecutive weeks on beagle dogs and found no significant acceleration on OTM. Instead, he found that LIPUS diminished resorptive areas on the root by 68% and also reduced the resorption initiation areas by 71% [29]. Few more studies found LIPUS effective in accelerating tooth movement, but the exact biological mechanism has not been completely understood. It has been stipulated from mandibular organ culture study that LIPUS alters tooth movement by promoting alveolar remodeling [30]. Xue in his in vitro rat model study postulated enhanced alveolar bone remodeling through gene expression of HGF/Runx2/BMP-2 signaling pathway. He also applied LIPUS to human PDL cells and observed the expression of BMP-2mRNA and protein due to Runx2 expression which was in agreement with previous research studies [16, 31, 32]. This increased expression of BMP has previously been reported in response to mechanical compression of bone which induces differentiation and proliferation of osteogenic cells inducing bone remodeling [33, 34]. On the contrary, ultrasound also downregulates receptor-activated nuclear factor kappa-B ligand/osteoprotegerin (RANKL/OPG) ratio, tumor necrosis factor-alpha, and interleukin-1b3 which are critical for the differentiation of bone cells and osteoclastic activity [25, 35]. These two contradictory effects of LIPUS may nullify the acceleration and retardation effect of LIPUS on bone remodeling.

LIPUS delivers micromechanical stresses to the tissues. Most of the researchers have applied these micromechanical stresses either on daily basis or on alternate days for at least 28 days to assess the rate accelerating effect of LIPUS on OTM and healing effect on orthodontically induced root resorption [20, 28]. However, we applied a single dose of LIPUS to make it more convenient for the patient, suggesting that this dose is not effective in expediting the rate of orthodontic tooth movement.

Our study did not find any analgesic effect of LIPUS in the reduction of orthodontic pain. The analgesic effect of LIPUS on pain related to OTM has never been investigated previously; however, it has been found efficient in reducing lower back pain and improving the functional ability of patients [36]. Ebadi et al., on the other hand, did not find LIPUS as a modality for analgesia for the management of nonspecific lower back pain [37].

Our clinical trial did not reveal any favorable effect of LIPUS on the rate of OTM and pain. Due to scarce data available in this domain, more studies are required to understand its effectiveness and mechanism of action.

5. Conclusion

Single dose of LIPUS applied at 3 weeks neither accelerates the orthodontic tooth movement nor reduces the pain associated with orthodontic tooth movement.

Data Availability

The data used to support the findings of this study are included within the article as Table 1 and Figure 2. Raw data are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Irfan Qamruddin and Mohammad Khursheed Alam contributed equally to this study. Both are first author and corresponding author. Verda Mahroof contributed to clinical application. Meenaz Karim, Mohd Fadhli Khamis, and Adam Husein were responsible for statistical input and final formatting. Mubassar Fida supervised the study.

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Review Article

Machine Learning and Intelligent Diagnostics in Dental and Orofacial Pain Management: A Systematic Review

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Purpose. The study explored the clinical influence, effectiveness, limitations, and human comparison outcomes of machine learning in diagnosing (1) dental diseases, (2) periodontal diseases, (3) trauma and neuralgias, (4) cysts and tumors, (5) glandular disorders, and (6) bone and temporomandibular joint as possible causes of dental and orofacial pain. *Method*. Scopus, PubMed, and Web of Science (all databases) were searched by 2 reviewers until 29th October 2020. Articles were screened and narratively synthesized according to PRISMA-DTA guidelines based on predefined eligibility criteria. Articles that made direct reference test comparisons to human clinicians were evaluated using the MI-CLAIM checklist. The risk of bias was assessed by JBI-DTA critical appraisal, and certainty of the evidence was evaluated using the GRADE approach. Information regarding the quantification method of dental pain and disease, the conditional characteristics of both training and test data cohort in the machine learning, diagnostic outcomes, and diagnostic test comparisons with clinicians, where applicable, were extracted. *Results*. 34 eligible articles were found for data synthesis, of which 8 articles made direct reference comparisons to human clinicians. 7 papers scored over 13 (out of the evaluated 15 points) in the MI-CLAIM approach with all papers scoring 5+ (out of 7) in JBI-DTA appraisals. GRADE approach revealed serious risks of bias and inconsistencies with most studies containing more positive cases than their true prevalence in order to facilitate machine learning. Patient-perceived symptoms and clinical history were generally found to be less reliable than radiographs or histology for training accurate machine learning models. A low agreement level between clinicians training the models was suggested to have a negative impact on the prediction accuracy. Reference comparisons found non-specialized clinicians with less than 3 years of experience to be disadvantaged against trained models. *Conclusion*. Machine learning in dental and orofacial healthcare has shown respectable results in diagnosing diseases with symptomatic pain and with improved future iterations and can be used as a diagnostic aid in the clinics. The current review did not internally analyze the machine learning models and their respective algorithms, nor consider the confounding variables and factors responsible for shaping the orofacial disorders responsible for eliciting pain.

1. Introduction

Pain is a subjective sensation and has varying tolerance thresholds [1]. Orofacial pain has multiple origins and varying intensities. The pain may arise from exposed dentin (hypersensitivity pain) [2] or from carious infection of the dental pulp (pulpitis) [3]. Untreated dental pulp encourages the infection to spread through the root canals into the periodontal tissue (apical periodontitis) [4, 5] and may cause swelling, infection, and bone loss

(periapical abscess) [6]. Periodontal tissue can also be painfully infected without carious activity (gingivitis and periodontitis) [7]. Maxillofacial fractures [8], as well as iatrogenic trauma/infection during dental restorative/endodontic treatment [2], may elicit varying levels of pain. Bone diseases [9], temporomandibular joint disorders [10], space infections [11], salivary gland disorders [12, 13], and sinusitis [14] elicit pain. Furthermore, neuralgia and secondary sensory nerve compression due to growing cysts and tumors can elicit severe pain [15, 16]. These conditions are categorized as common diseases and disorders that elicit dental and orofacial pain in the dental clinic [17].

The clinician's ability to diagnose such events swiftly and accurately is pivotal in successful patient management. However, various studies have shown that incorrect diagnoses are fairly common among clinicians in such situations [5, 6, 18]. While pain itself might not be reliably quantified, machine learning/artificial intelligence (AI) has been recently deployed to detect and quantify various diseases which elicit pain within the orofacial region to aid in accurate diagnostics and management.

AI and computerized support, although not new to healthcare, have lately received a lot of attention within the sphere of dentistry. These reviews covered their potential dental applications [19], success in detecting precancerous lesions and metastases [20], effectiveness in improving the quality of maxillofacial radiology [21], success in orthodontic treatment [22], and orthopedic rehabilitation [23], as well as concurrent application with virtual reality to decrease anxiety in young patients [24]. However, the aforementioned reviews did not systematically explore the current diagnostic capabilities of AI in identifying common orofacial diseases and disorders and/or the subsequently elicited pain [17].

Therefore, the current review was conducted and narratively synthesized to explore the influence of machine learning in the following diagnostic roles: (1) pain associated with dental diseases, (2) pain associated with periodontal diseases, (3) pain associated with trauma and neuralgias, (4) pain associated with cysts and tumors, (5) pain associated with glandular disorders, and (6) pain arising from bone and temporomandibular joint. The clinical effectiveness of machine learning, potential variations and probable causes, and human versus machine comparisons were also explored. The effectiveness of AI's influence was quantified using accuracy (ability to correctly differentiate disease from control), sensitivity (correctly identifying diseased subjects), specificity (correctly identifying disease-free subjects), and precision (repeated correct diagnoses) as appropriate.

2. Materials and Methods

2.1. Research Design. The study adhered closely to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Diagnostic Test Accuracy (PRISMA-DTA) guidelines but followed a narration-based, qualitative approach to represent the included literature [25].

2.2. Eligibility Criteria. The following inclusion and exclusion criteria were developed for the current systematic review.

2.2.1. Inclusion Criteria

(1) Original articles describing the use of intelligent computer-guided decision-making to diagnose orofacial diseases that produce symptomatic pain in humans

(2) Studies that incorporated diagnostic management of pain and inflammation using deep learning and intelligent decision-making systems within all specialties of dentistry

(3) Studies of intelligent technologies for emotion and facial expression recognition applied in facial pain diagnostics and healthcare

2.2.2. Exclusion Criteria

(1) Literature demonstrating the application of expert systems, deep learning, and intelligent tools for anatomical and physiological morphology and radiomics quality analyses

(2) Studies on intelligent systems used to detect precancerous or metastatic cancerous lesions, monitor surgically intervened malignancies, or assess the quality of life changes following tumor metastasis and chemo/radiation therapy

(3) Editorials, reviews, book chapters, opinion letters, magazine issues, product advertisements, conference proceedings, social media and blog posts, and articles written in a foreign language without accompanying English translation

2.3. Specific Study Characteristics for Diagnostic Comparisons. Eligible and included studies that made human versus machine diagnostic comparisons were further screened according to the following criteria:

(i) Index test and evaluating parameters: the sensitivity and/or specificity of clinically trained machine learning models

(ii) Reference standards: diagnostic accuracy of clinicians in identifying target conditions

(iii) Target conditions: isolation of dental diseases that lead to symptomatic pain in the following conditions: dentinal, pulpal, periodontal, and alveolar inflammatory diseases; traumatic and cranial neuralgic disorders; odontogenic and nonodontogenic orofacial growths; orofacial glandular inflammation, obstruction, and impaired function; and facial bone and joint disorders

2.4. Information Source. All data were extracted from Scopus, PubMed, and Web of Science (all databases) by one clinician specializing in digital rehabilitation and one

computing and imaging specialist. The Web of Science databases included the WoS Core collection, Current Contents Connect, Derwent Innovations Index, KCI Korean Journal Database, Medline, Russian Science Citation Index, and SciELO Citation Index. The data was extracted from 2020 backward with no lower limits. The final search was made in early November 2020.

2.5. Electronic Search Strategy. The strategy was specifically formulated using Boolean Logic (AND) and wildcards (*) to allow for the same search terms to be applicable for all databases without requiring any modifications thereby maximizing data output [26]. The following combinations were used in the search:

[Big AND data AND dent* AND pain]; [Deep AND learning AND smart AND dent*]; [Expert AND system* AND dent]; [Expert AND system* AND maxill* AND pain]; [Machine AND learning AND dent* AND pain]; [Neural AND network AND dent* AND pain]; [Neural AND network AND maxill* AND pain]; [Generative AND adversarial AND dent*]; [Fuzzy AND network AND dent*]; [Artificial AND intelligen* AND dent* AND pain]; [Artificial AND intelligen* AND caries AND pain]; [Intelligen* AND ulcer AND pain]; [Smart AND dent* AND pain]; [Comput* AND Intelligen* AND pain AND diagnos* AND dent*]; [Smart AND diagnos* AND dent* AND pain]; [Smart AND diagnos* AND facial AND pain]; [Intelligen* AND pain AND face]; [Intelligen* AND pain AND dent*]; [Intelligen* AND device* AND dent* AND pain]; [Intelligen* AND Sensor* AND diagnos* AND dent* AND pain]; [Electr* AND Sensor* AND diagnos* AND maxill* AND pain]; [Intelligen* AND biosens* AND oral]; [Artificial AND Somatosensor* AND facial]; [Intelligen* AND Somatosensor* AND dent*]; [intelligen* AND inflam* AND facial]; [Tensor AND pain AND dent*]; [Comput* AND language AND inflam* AND face]; [Intelligen* AND oral AND carcinoma]; [Augment* AND reality AND dent* AND pain]; [Virtual AND dent* AND diagnos* AND pain]; [Artificial AND Intelligen* AND implant* AND pain]; [Deep AND learning AND maxil* AND surg*]; [Intelligen* AND ortho* AND pain AND dent*]; [Deep AND learning AND radio* AND oral]; [Deep AND learning AND radiol* AND pulp*]; [Deep AND learning AND radiol* AND periodon*].

2.6. Study Selection and Data Collection Process. Titles were screened for duplicates using Endnote v8.2, and the remaining manuscripts were then screened by abstract based on predefined eligibility criteria. The articles excluded during abstract screening were documented along with the theme of the study and the reasons for exclusion. The level of agreement between the two reviewers was measured using the kappa coefficient, and all disagreements were resolved by a face-to-face meeting. Finally, full papers were read, and ineligible articles were removed with the reason for removal being noted.

2.7. Data Extraction. The following data were extracted from the methodology and result sections of the selected papers: quantifications related to dental pain and the machine learning classification models used to develop the intelligent system; the number and conditional characteristics of the training dataset that was used to train the intelligent system; the number of test data used to evaluate the newly trained system with possible human comparisons along with their subsequent learning outcomes; and finally, the clinician's specific role in training or validating the machine learning model which was also documented.

2.8. Diagnostic Accuracy Measures. Specificity (Sp) and sensitivity (Sn) were measured along with accuracy (Ac) and precision (Pr) data which were collected. All obtained values were standardized to 0.00–1.00, and normalized data were given a 1-point standard deviation [27]. The number of learning data (n^L) and test data (n^T) was also collected. No eligible papers were excluded for not presenting one or more of the aforementioned summary measures.

2.9. Risk of Bias and Applicability. Studies that made a direct comparison to clinicians as reference standards were assessed for bias and applicability. The appropriateness of the machine learning model was evaluated using the Minimum Information about Clinical Artificial Intelligence Modeling (MI-CLAIM) checklist [28]. The risk of bias among studies and possible inconsistencies in the comparison were assessed using Joanna Brigg's Institute Critical Appraisal for Diagnostic Test Accuracy (JBI-DTA) checklist [29]. The findings from the MI-CLAIM and JBI-DTA were then used to evaluate the quality of the diagnostic evidence produced in the studies by using the Cochrane GradePro (GRADE approach) [30].

2.10. Additional Syntheses. A meta-analysis was deemed inappropriate due to the substantial functional differences and clinical heterogeneity present across the various disease classifications and machine learning models.

3. Results

3.1. Study Selection. During the screening process, the reviewers had a fair agreement ($k = 0.68$) in the screening process. 34 articles were eventually selected for full paper reading based on eligibility criteria (Figure 1).

3.2. Study Characteristics and Individual Results. The study characteristics and their individual findings have been tabulated and presented as supplementary documents with this manuscript. The papers and tables are categorized into the following subsections: (1) pain associated with dental diseases [1–3, 31–37] (Supplementary Table S1), (2) pain associated with periodontal diseases [4–7, 18, 38–41]

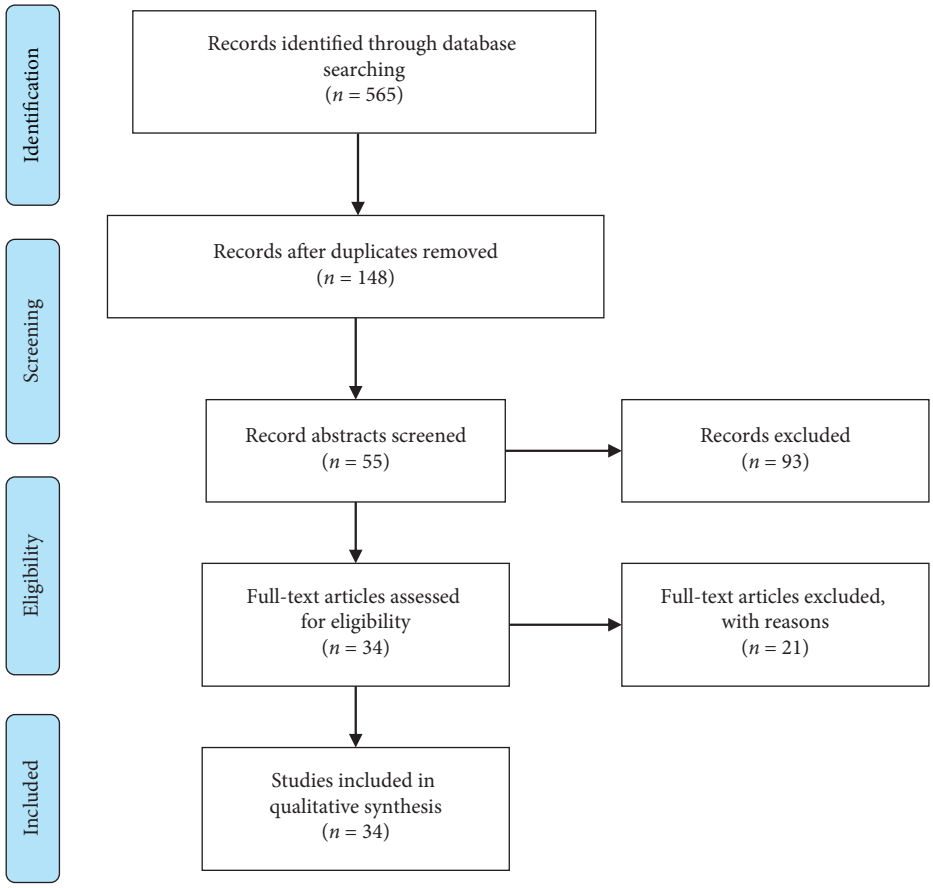

Figure 1: PRISMA flowchart of summary findings.

(Supplementary Table S2), (3) pain associated with trauma and neuralgias [8, 11, 16, 42] (Supplementary Table S3), (4) pain associated with cysts and tumors [15, 43, 44] (Supplementary Table S4), (5) pain associated with glandular disorders [12–14, 45] (Supplementary Table S5), and (6) pain arising from bone and temporomandibular joint [9, 10, 46–48] (Supplementary Table S6). The details of the articles excluded (and the entire study selection process) during systematic screening have been documented in Supplementary Material S7; Section 1.

3.3. Risk of Bias and Applicability. The current study of 34 published documents identified 8 articles [5, 6, 12–15, 31, 39] that made direct comparisons between the diagnostic accuracy of machine learning models and human clinicians. Of the 15 points evaluated from the MI-CLAIM checklist, all but one paper [39] scored over 13. JBI-DTA was assessed over 7 points where all papers scored 5 or more. Five of the 8 articles [5, 12–15, 39] could not avoid a case-control design as it was an integral part of the machine training process as found during MI-CLAIM. A "Range from studies" GRADE approach was undertaken to evaluate the collective diagnostic certainty of machine learning applicability. The GRADE approach suggested that a high certainty of diagnostic evidence for both positive and negative cases was present in machine learning. However, there were serious risks of collective bias and design inconsistencies among the cross-sectional cohorts that should be considered alongside the overall GRADE score. The conditions and explanations for all findings have been provided in Supplementary Material S7; Sections 2, 3, and 4.

3.4. Diagnostic Measure Comparisons. All 34 studies have been individually documented within Supplementary Tables S1 to S6. Only the articles that made direct comparisons to clinicians have been documented in Table 1. All the studies mentioned in Table 1 have also been discussed in detail within the supplementary tables.

4. Discussion

4.1. Summary of Findings. The current review explored the clinical influence, effectiveness, limitations, and human comparison outcomes of machine learning. The findings of all 34 papers included within the systematic review have been discussed in the following subsections: (1) pain associated with dental diseases, (2) pain associated with periodontal diseases, (3) pain associated with trauma and neuralgias, (4) pain associated with cysts and tumors, (5) pain associated with glandular disorders, and (6) pain arising from bone and temporomandibular joint.

Table 1: Summary outcomes of studies comparing diagnostic measures.

Author	Target condition definition	Testing sample size[a]	Index test outcomes[b]	Reference test outcomes[c]
Cantu et al. [31]	Extent and infiltration of proximal caries into dentinal tissue	141	Sn = 0.75, Sp = 0.83	Sn = 0.36, Sp = 0.91
Endres et al. [5]	Detect and classify periapical inflammation	102	Sn = 0.51	Sn = 0.51
Kise et al. [13]	Diagnose Sjogren syndrome in parotid and submandibular glands	40	*Parotid Gland* Sn = 0.90, Sp = 0.89 *Submandibular Gland* Sn = 0.81, Sp = 0.87	*Parotid Gland* Sn = 0.67, Sp = 0.86 *Submandibular Gland* Sn = 0.78, Sp = 0.66
Yang et al. [15]	Detect the presence of pathologic growth	181	Sn = 0.68	*Oral surgeons* Sn = 0.67 *General dentists* Sn = 0.64
Kim et al. [39]	Localize periodontal bone loss and classify apical lesions	800	Sn = 0.77, Sp = 0.95	Sn = 0.78, Sp = 0.92
Kise et al. [12]	Identify fatty degeneration within the salivary glands	100	Sn = 1.00, Sp = 0.92	*>3 years' experience* Sn = 0.99, Sp = 0.97 *<3 years' experience* Sn = 0.78, Sp = 0.89
Krois et al. [6]	To detect the extent of periodontal bone loss	353	Sn = 0.81, Sp = 0.81	Sn = 0.92, Sp = 0.63
Murata et al. [14]	Identify features of sinusitis	120	Sn = 0.86, Sp = 0.88	*>3 years' experience* Sn = 0.90, Sp = 0.89 *<3 years' experience* Sn = 0.78, Sp = 0.75

Sn: sensitivity; Sp: specificity; [a]Testing samples: medical imaging data (radiographs/ultrasound/computed tomography); [b]Index test: machine learning model; [c]Reference test: human clinicians.

4.1.1. Pain Associated with Dental Diseases. Real-time quantification of subjective dental pain demonstrated varying degrees of accuracy across multiple machine learning models when Hu et al. [1] attempted to detect (Ac = 0.80, Sn = 0.41, Sp = 0.89) and localize (Ac = 0.74, Sn = 0.54, Sp = 0.86) the source and intensity of dentin hypersensitivity pain arising from prefrontal and primary sensory cortices. The findings, in combination with Chattopadhyay's results [33], may contraindicate the implementation of an intelligent pain prediction system for perceived dental pain. Machine learning models based on clinically perceived pain produced less accurate outcomes for pulpal (Ac = 0.74–0.78, Sn = 0.48–0.71, Sp = 0.73–0.93) and periodontal diseases (Ac = 0.81, Sn = 0.78, Sp = 0.88), with the least accuracy (Ac = 0.64, Sn = 0.64, Sp = 0.96) for alveolar abscess [33]. Therefore, it can be argued that identifying the elusive source of dental pain is a more reliable estimate than quantifying pain as a symptom.

However, both proximal and periapical radiographs (Ac = 0.80, Sn = 0.75, Sp = 0.83) [31, 34] as well as histologically (Ac = 0.98, Pr = 0.98) trained models [2, 34] were able to reliably detect caries as a source for pain. While the aforementioned is considerably more efficient than clinicians (Ac = 0.71, Sn = 0.36, Sp = 0.91), dental specialists play an important role in training the machine from radiographs [3] or histological data [2]. Therefore, the prediction of the system may be directly dependent on the experience and agreement of the trainers.

Even periapical radiographs were capable of effectively (Ac = 0.82) detecting caries progression in posterior teeth [3]. Training dataset based on photographs ($n^L = 425$, Sn = 0.77–0.98, Sp = 0.84–0.96) [32] and photodetection ($n^L = 24$, Ac = 1.0) [37] produced varying outcomes when they were used to localize the progression of carious infiltration within the dentin layer [32]. This can be due to the funneling nature of caries progression as well as the small training datasets used. Many carious lesions, which visually appear negligible on the enamel surface, can funnel out within the dentin layer and cause sensitivity pain. Such factors were not considered in Rahman's study [37]. Researchers also attempted to provide camera-based intelligent solutions for end-users (patients). In such designs, video-learned systems ($n^L = 10{,}080$) produced reasonably reliable diagnoses of caries (Sn = 0.98, Sp = 0.93) and periodontitis (Sn = 0.97, Sp = 0.95) but were not very sensitive to painful microdefects like cracked teeth (Sn = 0.75, Sp = 0.99) [36].

4.1.2. Pain Associated with Periodontal Diseases. The majority of the periodontal pain was associated with periodontal bone loss and root attachment loss which were, therefore, the primary quantification parameters [5]. Clinicians' experience was assumed to play a critical role in dictating the overall accuracy of radiographic differential diagnosis in machine learning. This assumption was confirmed by Chang et al. [38], Kim et al. [39], and Krois et al. [6] who found clinicians to make poorer diagnoses (Ac = 0.76, Sn = 0.78–0.92, Sp = 0.63–0.92) than their intelligent prodigies (Ac = 0.81, Sn = 0.77–0.81, Sp = 0.81–0.95). This was eventually reflected on the deep learning model as less accurate results with more variations were obtained contradicting Endres et al. [5], who found no significant

correlation in their study. This could be due to the relatively low agreement ($k = 0.48$–0.52) between dental specialists [6, 18] in diagnosing a radiograph. Furthermore, Setzer's study [40] showed that the sensitivity of the machine in detecting periodontal diseases (Sn = 0.93, Sp = 0.88) was the same as the agreement between highly experienced specialists ($k = 0.93$). The clinicians themselves were inaccurate in diagnosing 31% of the time [5], and therefore, machine learning was deemed more specific. Periodontal conditions involved with larger bone defects [6] and indeciduous or crowded dentitions could affect predictive outcomes on panoramic radiographs (Sn = 0.84, Sp = 0.88, Pr = 0.81) [41]. Real-time/clinical machine learning, however, was less influenced by the operator's prowess [7] and heavily dependent on the accuracy of patient feedback (Ac = 0.82, Sn = 0.87, Sp = 0.76) during pain sensation [4].

4.1.3. Pain Associated with Trauma and Neuralgias. Pain associated with root fractures is difficult to diagnose without a clear radiograph. With machine learning applied to clear panoramic radiographs, the intelligent system was less sensitive to localizing fractures on anterior teeth (Sn = 0.53, Pr = 0.88) as opposed to the posterior teeth (Sn = 0.70, Pr = 0.95) [8]. This was probably due to the vertebral shadow superimposing on the dental root anatomy [8, 18]. Trauma is often accompanied by painful swelling. Zhang et al. [11] demonstrated that a trained machine with a detailed patient history was able to accurately predict (Ac = 0.94–0.98) which patients were likely to experience painful swelling after tooth extractions.

McCartney et al. [16] and Limonadi et al. [42] designed and compared questionnaire-based intelligent systems to diagnose the source of facial pain. While the systems were accurate in diagnosing typical trigeminal neuralgia (Sn = 0.84–0.92, Sp = 0.83–0.84), it was observed that deep learning was not very sensitive to atypical neuralgias (Sn = 0.50–0.63, Sp = 0.94–0.95) [16, 42]. This is partly due to the idiopathic nature of certain diseases, which cause varying clinical symptoms including pain. Such variations can cause further disagreement in differential diagnoses among specialists, whose opinions are in turn used to train and validate the intelligent systems [6, 18]. The questionnaire-based method of deep learning hinges on the patients' ability to accurately report their conditions and pain intensity and was therefore may not be preferable for evaluating dental pain [1, 33].

4.1.4. Pain Associated with Cysts and Tumors. Although most cysts, tumors, and other pathologic growths in the oral cavity are initially asymptomatic, growing lesions tend to elicit painful responses [15]. All the intelligent systems designed for tumor detection [15, 43, 44] were trained from panoramic radiographs by 2 expert radiologists. Watanabe et al. [44] carried out deep learning on larger (>10 mm) lesions, specifically radicular cyst lesions from panoramic radiographs ($n^L = 330$) where the authors found that the cortical thickness around the canine fossae and the maxillary sinus cavities drastically reduced prediction sensitivity (Sn = 0.46, Pr = 0.88 from Sn = 1.00, Pr = 0.92). Kwon's findings [43] agreed with Watanabe in that maxillary lesions were harder to predict. However, Kwon's results, which were based on a larger dataset ($n^L = 946$) and a pretrained neural network, saw comparatively better outcomes for radicular cysts (Ac = 0.96, Sn = 0.99, Sp = 0.83). This may indicate that the parameters used for machine learning in predicting oral tumors are more important than the experts who train the system. Deep learning produced better results for odontogenic keratocyst (Ac = 0.94, Sn = 0.70, Sp = 0.92, Pr = 0.63) when compared to diagnoses made by both surgeons (Sn = 0.67, Pr = 0.67) and general dentists (Sn = 0.64, Pr = 0.65) [15, 43]. This human-based discrepancy is probably due to the irregular shape and radiolucency of the tumor in respect to the rest of the mandibular anatomy. However, clinicians in Yang's study [15] were more sensitive (Sn = 0.36–0.45) to detecting well-defined ameloblastomas from radiographs than the trained machine (Sn = 0.33) [15].

4.1.5. Pain Associated with Glandular Disorders. Maxillary sinusitis is an important differential diagnosis when evaluating the source of maxillary anterior pain. This can be done clinically by observing mucus discharge or through radiographs exhibiting glandular thickening within the sinus lining [14]. Kim et al. [45] and Murata et al. [14] showed machine learning to accurately detect sinusitis from both Water's view paranasal sinus (PNS) (Ac = 0.94, Sn = 0.89, SP = 0.99) and panoramic radiographs (Ac = 0.88, Sn = 0.86, Sp = 0.88). Deep learning outcomes from panoramic radiographs were comparable to diagnoses made by radiologists who had >20 years of experience (Ac = 0.90, Sn = 0.90, Sp = 0.89) and better agreement ($k = 0.85$) in diagnoses. [14, 45] Kim also demonstrated that when multiple trained virtual machines unanimously ($k > 0.90$) diagnose an image (majority decision analysis system), they produce accurate results (Ac = 0.94) [45] comparable to radiologists with over 30 years of diagnostic experience (Ac = 0.98) [12].

When assessing glandular disorders, radiologists demonstrated better agreement ($k = 0.65$) for disorders of visibly larger glands (parotid) as opposed to smaller glands ($k = 0.51$) obstructed by bony anatomy (submandibular gland) [13]. This deemed machine learning more sensitive to glandular anomalies but was also equally prone to making mistakes. Kise developed deep-learned systems to diagnose Sjogren's syndrome from both ultrasound imaging (*parotid gland*: Ac = 0.89, Sn = 0.90, SP = 0.89; *submandibular gland*: Ac = 0.84, Sn = 0.81, Sp = 0.87) [13] and computed tomography (Ac = 0.96, Sn = 1.00, SP = 0.92) [12]. The authors found that only clinicians with >30 years of experience were able to compete (Ac = 0.98, Sn = 0.99, Sp = 0.97) with the deep learning algorithm (Ac = 0.96, Sn = 1.00, Sp = 0.92) in diagnosing salivary gland disorders from 3D CT images [12]. The outcomes for clinicians were, however, substantially poorer when made to diagnose 2D radiographs (*parotid gland*: Ac = 0.77, Sn = 0.67, Sp = 0.86; *submandibular gland*: Ac = 0.72, Sn = 0.78, Sp = 0.66) [13]. Regardless, deep learning was shown to be a valuable diagnostic support for inexperienced clinicians (Ac = 0.77–0.84, Sn = 0.78,

Sp = 0.75–0.89) [12, 14] to accurately diagnose gland-related orofacial pain.

4.1.6. Pain Arising from Bone and Temporomandibular Joint. Temporomandibular joint (TMJ) disorders can cause severe pain for the patients [10]. Some of the painful disorders addressed by machine learning include joint osteoarthritis (Ac = 0.82, Sn = 0.83, Pr = 0.81) [47, 48], osteoporosis (Ac = 0.93, Sn = 0.97, Sp = 0.86) [10], reducible disk displacements (*unilateral*: Sn = 0.80, SP = 0.95; *bilateral*: Sn = 1.00, Sp = 0.89), and nonreducible disk displacements (*unilateral*: Sn = 0.69, SP = 0.91; *bilateral*: Sn = 0.37, Sp = 1.00) [46]. However, machine learning is still in its infancy primarily due to the complex diagnostic criteria required to confirm diseases like osteoarthritis [47]. The disease requires diagnostic confirmations from clinical, radiological, and serological findings and thereby complicate the machine learning procedure. Furthermore, Nam et al. [9] found pericoronitis and alveolar abscess to commonly (44%) mimic TMJ disorders which could be accurately differentiated (Ac = 0.96, SP = 0.99, Sn = 0.69) from true cases based on clinical symptoms using machine learning [9].

4.2. Limitations of the Study. At the time of conceptualization and data collection, the review protocol and study design were not registered with any databases that indexed ongoing reviews. Past literature suggests that such registrations can guard against reporting biases and validate the integrity of the published protocol [49]. In addition to the aforementioned, the current study was limited by several other factors. Firstly, foreign articles without a formal translation were not manually translated in order to prevent misinterpretation of the technical content and, therefore, may indicate a certain degree of publication bias. Secondly, this review did not internally analyze the different machine learning models and their respective algorithms and primarily focused on the clinical parameters. Furthermore, the current study did not account for the confounding variables and factors responsible for shaping the orofacial disorders responsible for eliciting pain. The difficulty in quantifying pain encouraged focusing on specific target conditions commonly, but not solely, responsible for pain. Finally, while the diagnostic comparisons yielded high certainty and low bias, the risk of bias and quality of evidence were not evaluated across the remaining 26 studies due to missing standard reference (human clinicians) comparison.

4.3. Conclusions and Future Recommendations. Machine learning in orofacial healthcare is still emerging and has shown modest results in diagnosing oral diseases. However, such technology is far from replacing clinicians in rendering healthcare and can possibly serve as an "add-on" to the existing diagnostic tools. Various workflows and methods exist for diagnosing dental diseases that can benefit from future crossovers and randomized trials on larger pools of patients in the future.

Data Availability

All the supporting data have been provided as supplementary materials with the manuscript.

Conflicts of Interest

The authors declared no conflicts of interest.

Acknowledgments

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Supplementary Materials

Supplementary Table S1: summary findings of literature for dental diseases. Supplementary Table S2: summary findings of literature for periodontal diseases. Supplementary Table S3: summary findings of literature for dental trauma and neuralgias. Supplementary Table S4: summary findings of the literature on cystic and neoplastic lesions. Supplementary Table S5: summary findings of the literature on glandular disorders. Supplementary Table S6: summary findings of the literature on bone and joint disorders. Supplementary Material S7. (*Supplementary Materials*)

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Review Article

The Use of Technology in the Management of Orthodontic Treatment-Related Pain

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Orthodontic pain is one of the negatives associated with fixed orthodontic treatment that cannot be avoided. This pain usually comes around the wire placement period and gradually decreases once the endogenous analgesic mechanisms start functioning. Over the years, several treatment modalities have been utilized for relief from orthodontic pain, and these include mechanical, behavior modification, and pharmacological methods. However, in the last decade, there are several newer methods employing the use of technology that have come up and are being used for alleviating pain. From computerized indirect bonding to virtual treatment planning, technology has slowly become a vital part of an orthodontist's repertoire. The digital age is here, and orthodontics must embrace the use of technology to help improve the quality of life of patients.

1. Introduction

Orthodontic pain is one of the negatives associated with fixed orthodontic treatment that cannot be avoided. It is caused by vascular occlusion brought about by orthodontic forces and involves the release of inflammatory mediators that regulate the movement of inflammatory cells around the teeth. This pain usually comes around the wire placement period and gradually decreases once the endogenous analgesic mechanisms start functioning. Over the first 24 hours, this pain is usually found to increase and then taper down within a week after initial bonding [1]. This is an important aspect to consider because over this period, the patient's quality of life is impacted in terms of impaired speech, oral ulcers, difficulty in mastication, tooth mobility, and gum inflammation [2].

Previous research has shown that the periaqueductal grey and dorsal raphe maintain an important role in the management of orthodontic pain. Over the years, several treatment modalities have been utilized for relief from orthodontic pain, and these include mechanical, behavior modification, and pharmacological methods. However, in the last decade, there are several newer methods employing the use of technology that have come up and are being used for alleviating pain. Many of these methods are currently being researched to understand their precise benefits as well as effectiveness in managing pain. Some of the newer pain alleviation techniques are explained in this article.

2. Low-Level Laser Therapy (LLT)

This has found considerable use for pain management in both medical and dental fields. This involves the laser irradiation of both the arches using a low-level laser. The expansion for the acronym "laser" is "light amplification by stimulated emission of radiation." The main point of difference between lasers and other light sources is their coherence which helps narrow their focus to a specific area, even over long distances [3]. There are two types of lasers in use: high-intensity and low-intensity, and these differ in terms of their working action and potency [4]. The low-intensity laser also known as a cold laser does not have any

destructive potential and rather stimulates anabolic activities and bone remodeling and enhances tooth movement [5]. Commonly employed low-energy lasers include gallium-arsenide (904 nm wavelength), semiconductor (780–950 nm wavelength), helium-neon (632.8 nm wavelength), and gallium-aluminium-arsenide (805 nm wavelength) [6]. Previous research has shown that the gallium-aluminium-arsenide laser has greater penetration and is therefore more effective in managing pain associated with orthodontic treatment [7–10].

It has been seen that low-level laser therapy induces cellular proliferation which results in differentiation of osteoblasts bringing about bone formation [11–13]. Low-energy lasers have also been found to help enhance orthodontic tooth movement, but more research is still being conducted on the same [14].

2.1. Light Emitting Diodes (LEDS). Photobiomodulation has become popular in recent years, and it involves the use of light-emitting diodes to enhance healing, control inflammation, and reduce pain and discomfort across different scenarios [15]. Generally, when LEDS are applied to human body tissues, they elicit different reactions such as photothermal, photomechanical, and photochemical reactions which result in various effects [16]. LEDs (in the range of 670 nm) have been shown to be highly beneficial in cancer patients for the management of oral mucositis, but the near-infra-red region light (in the range of 850 nm) has been shown to help in release of growth factors and vasodilation, thereby helping promote wound healing [17, 18]. In recent years, there have been studies conducted on the use of LEDS after lower third molar surgical extractions and have delivered promising results by helping to reduce edema, pain, and swelling [19, 20]. In studies involving rats, it has been seen that the use of LED significantly reduces the quantity of osteoclasts in the periodontal ligaments and enhances orthodontic movement of teeth [21]. In the past few years, there have been various studies conducted on the use of LEDS with many conflicting results in terms of findings. As such, further research is needed to help get more predictable and consistent results.

2.2. Micropulse Variations. Pain is a complex phenomenon affected by a multitude of factors and is directly influenced by the amount of force applied. For orthodontic tooth movement to occur, there is inflammation in the periodontium caused by forces which results in the release of inflammatory mediators such as histamine, prostaglandins, and serotonin [22]. These inflammatory mediators act on the nerve endings, and the sensation of pain is transmitted to the brain via the neural pathway. Previous studies have shown that vibration decreases the pain originating from the dentoalveolar complex [23]. The rationale behind the use of vibration devices is the application of the gate control theory according to which pain reduction can be achieved by simultaneously activating nerve fibers with nonnoxious stimuli [24]. One device that generates micropulse vibrations and has become popular in recent times is AcceleDent. There have been studies conducted using this device that have demonstrated a reduction in pain following application during orthodontic therapy [25]. Also, clinical trials have shown that there was reduced overall and biting pain on the use of this device which makes it a highly effective means of pain control during fixed orthodontic therapy. However, more studies are required to understand the precise relationship between generating vibrating stimuli and pain control [26].

2.3. Transcutaneous Electrical Nerve Stimulation (TENS). Pain is one of the commonly associated problems with fixed orthodontic treatment, and previous studies have shown that it is one of the major reasons for patients discontinuing their treatment [27]. TENS is a noninvasive, non-pharmacological technique that utilizes electrical stimulation to reduce periodontal pain. Research conducted using TENS therapy has shown that its main action is to block nerve depolarization, thereby impeding the initial neuropeptide release as well as blocking the positive feedback loop [28]. For TENS therapy to work effectively, clinical studies have shown that simulation must be applied to multiple teeth and both the arches [29]. It was also observed that individual teeth required more than 10 seconds of stimulation to achieve the desired result.

2.4. Biofeedback Therapy. This method involves the use of electromyography to alter the physiologic reaction of a patient by neuromuscular manipulation [30]. Using electromyography, a patient's biologic reactions can be recorded, analyzed, and even controlled. The patient's reactions are recorded and then converted to auditory or visual, but the patient may try to influence such reactions [31]. Therefore, the patients are provided training to be able to control their reactions and achieve a relaxed status [32]. The recordings are obtained by placement of electrodes on the skin or by insertion of a needle subcutaneously. The placement depends on whether recordings are desired superficially or from a target group of muscles. Tension is usually recorded in microvolts, and the usual range is from 5 to 40 μv, and baseline data must be obtained prior to obtaining situational data [33]. Previous studies have shown that electromyographic feedback does provide significant pain relief, but the extent of relief is much lower when compared to other pharmacological and non-pharmacological interventions [34]. Therefore, further studies are required to gauge the effectiveness of this modality especially in the management of orthodontic movement-related pain.

2.5. Low-Intensity Pulsed Ultrasound (LIPUS). LIPUS is a noninvasive modality that utilizes acoustic pressure waves with frequencies higher than the human threshold [35]. This method is widely utilized in the field of medicine for diagnosis as well as therapeutic purposes. It has been studied to have a biologically healing effect on tissues when the acoustic waves are passed through them [36]. The waves are of an

intensity that does not cause tissue destruction or generate heat. LIPUS has been researched for its use as a therapeutic modality, and it was found to have an accelerating effect on healing of bone fractures [37]. There are also studies that have explored the option of using a combination of low-level laser therapy and LIPUS, and the findings suggest that it could prove to be a particularly useful combination [38]. It was seen from the results that LLT stimulated the mitochondria and enhanced the energy cell cycle, while LIPUS initiated functional movements around the cell membrane, thereby resulting in a synergistic action [39]. Their combination improved histological bone formation and accelerated tooth movement which should be of considerable importance in the field of orthodontics. Like other newer methods, LIPUS and its combination with other modalities must be explored further to arrive at a conclusion as to how it can help alleviate orthodontic pain.

2.6. Iontophoresis. This is a noninvasive modality that helps deliver charged as well as uncharged drugs across a membrane using electrical currents [40]. This technique relies on various mechanisms such as electrophoresis, electropermeabilization, and electro-osmosis [41]. It relies on the movement of positively charged ions from the anode to the cathode and the movement of negatively charged ions from the cathode to the anode [42]. This has been found to be a particularly useful technique in the field of medicine for delivering ionic drugs. The process involves the placement of a drug-delivering electrode at the site of drug administration and a return electrode on another area of the body to form an electrical circuit. These electrodes are then connected to a device that generates 4 mA current which is sufficient for ionic delivery of drugs [43]. This technique has been utilized in dentistry and oral care, and significant penetration of drugs has been seen in the oral mucosa [44]. Since the current oral drug delivery systems are not very convenient, this method should be researched further to establish a method for relieving pain, resulting from fixed orthodontic therapy.

2.7. Virtual Reality. This is the latest example of technology being used to create a realistic appearing simulation. Sensory illusions can be framed to promote behavioral changes in an environment that can be augmented using digital information [45]. Commonly used devices for sensory stimulation are helmets, headphones, and actuators with sensors that can change the simulation depending on the patient response. The major benefit of virtual reality over the other methods is that patients would feel a psychological presence in the simulated environments because of the sensory immersion [46]. Augmented reality can help alleviate pain by distracting the patient's attention away from pain due to orthodontic treatment. There have been studies done using image-based methods for tracking teeth across a video image 47. CT scans were used in these studies to achieve an approximation of the gingival line. Following this, back-projections of older video frames were used to account for bracket positions [47]. Results from these studies have demonstrated the utility of augmented reality for specific orthodontic interventions though much research into this area is still required.

There have also been research studies conducted on the efficacy of virtual reality for helping control dental pain which have demonstrated the presence of analgesic potential. Patients participating in these studies were subjected to various dental procedures in conjunction with virtual reality distractions [48–50]. The patients were found to experience lesser pain on the rating scale when they were distracted virtually. The same patients reported much higher scores on the pain rating scale in the absence of any virtual distractions, thereby showcasing the adjunctive analgesic potential of augmented reality [48, 49]. With the popularity of augmented reality systems growing with each passing day, it is only a matter of time when specific systems dedicated to various painful conditions are developed and put into practice.

2.8. Other Less-Explored Technological Methods for Pain Relief. In the current digital age, there are many methods that are being researched for their use in management of pain. There have been studies conducted on the use of SoLux lamps to deliver heat especially in cases with arthropathies and rheumatic diseases, and the results have been promising [51]. Another noninvasive modality that can be explored for the management of orthodontic treatment-related pain is transcranial magnetic stimulation (TMS). Using this method, alternating magnetic fields are passed through the scalp region which stimulates electrical currents in the neurons. In previously conducted studies, low-frequency stimulation has shown significant pain relief in patients with varying degrees of pain [52]. Another similar method to TMS is transcranial direct current stimulation (tDCS) which stimulates the neurons in the cortex using weak electrical current. Its major advantage over its magnetic counterpart is that its stimulators are small making it preferable for home use [53]. Optogenetics is another futuristic method using which pain modulation can be carried out using brain-stimulation. This can enable action on specific groups of cells to help alleviate pain by means of neuromodulator and neuropeptide pathways [54].

3. Conclusion

With the advent of technology, the field of orthodontics is slowly but surely treading the digital path. From computerized indirect bonding to virtual treatment planning, technology has slowly become a vital part of an orthodontist's repertoire. The said pain is one of the few negatives that are associated with fixed treatment starting from the placement of separators. Pain management is an immensely difficult task especially because of the complex systems involved in causing pain. What is needed in the future is a combination of technology and therapy that is planned using data from various clinical trials and experiments. The problem with current modalities is that even being effective, they are not based on a precise neurobiological principle.

This is one of the reasons why pain management is still an area of concern when it comes to orthodontics specifically and medicine generally. Pain resulting from orthodontic treatment varies from one individual to another, and it would be a good idea to evaluate a patient's general pain susceptibility during initial diagnosis to be able to plan treatment more effectively. The digital age is here, and orthodontics must embrace the use of technology to help improve the quality of life of patients.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Revisiting the Corneal and Blink Reflexes for Primary and Secondary Trigeminal Facial Pain Differentiation

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Trigeminal neuralgia is often misdiagnosed at initial presentation due to close connotation with dental pain and is often over diagnosed for the very same reasons leading to numerous unnecessary surgical procedures such as peripheral neurectomy and alcohol injections, while the actual cause may remain elusive for decades. Evaluation of the neurosensory system may disclose the correct anatomical location of the etiology. The neurological examination may be clouded by the sensory deficits subsequent to previous peripheral surgical procedures. The corneal and blink reflexes are integral measures of the trigeminal and facial neurosensory assessment, and their abnormal function may facilitate the identification of intrinsic disease of the brain stem. These reflexes can be employed to discover pathological lesions including intracranial space-occupying trigeminal, lateral medullary, cerebral hemispheric lesions, and degenerative diseases of the central nervous system. Dental surgeons and oral and maxillofacial surgeons should consider corneal reflex in neurological assessment of patient presenting with trigeminal neuralgia-like symptoms. Failure to evaluate corneal sensitivity may lead to delayed or inaccurate diagnosis and unsuitable or redundant treatment interventions. This simple noninvasive reflex can be performed by chair-side and may provide significant information regarding the origin of facial pain and is an invaluable part of clinical methods especially in remote and peripheral healthcare center practitioners where sophisticated radiographic investigations such as computed tomography and magnetic resonance imaging may not be available.

1. Introduction

The human eye is covered by a thin and transparent layer of tissue called cornea which contains the highest number of nerves in the whole body [1]. These nerves convey the touch, pain, and temperature sensations and perform a fundamental part in corneal reflexes [2]. The human cornea is three to six hundred times more sensitive than the skin with a density of seven thousand nociceptors per square millimeter approximately at the center. Unintentional eyelid shutting that can be induced by stimulating the corneal surface or by flickering direct light serve primarily as a shielding purpose constitute the corneal reflex. The blink reflex, on the other hand, essentially preserves the thin film of lacrimal fluid over the eye surface, occurring impromptu, or conversely is induced by various trigeminal or spinal stimulations [3].

Corneal and blinks reflexes have several common features, and each results in excitation of orbicularis oculi motor units and lid closure. The nasociliary and supraorbital branch of the ophthalmic division of the trigeminal nerve gives origin to the afferent innervation for the corneal and blink reflexes, respectively, while the efferent motor response is interceded via branch of the facial nerve to the orbicularis oculi muscle. Hence, these reflexes are essential instruments for assessment of the integrity of the trigeminal and facial cranial nerves which comprise the reflex arc [4] (Figure 1).

Trigeminal neuralgia, also known as tic douloureux, is a bursting painful condition that is characterized by agonizing, piercing paroxysms, inflicting one or more divisions of the trigeminal nerve, with less than 5% of the cases involving the ophthalmic division, while the mandibular division is affected in 70% of the cases. The attack can transpire suddenly as brief electric current-like contraction lingering for a

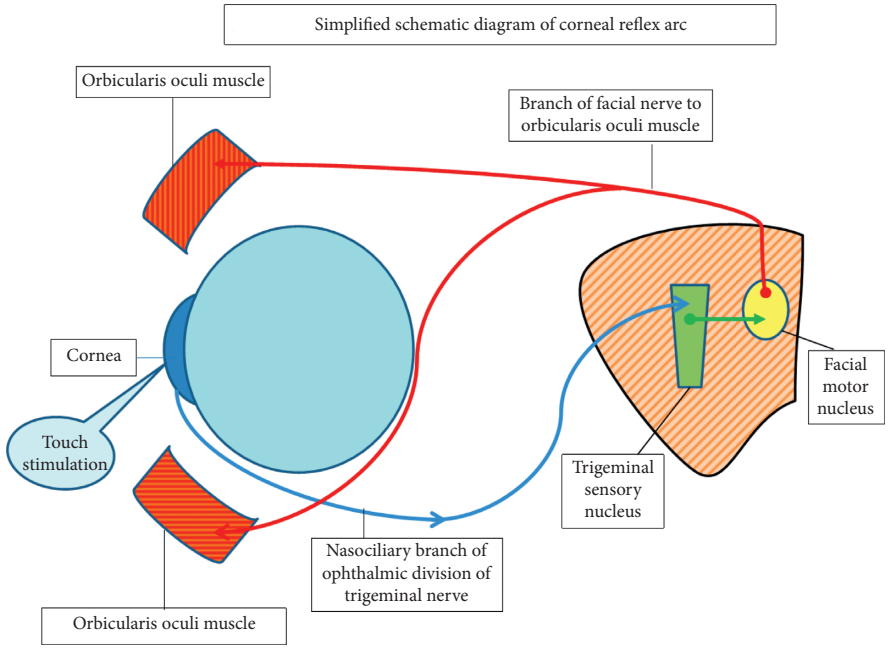


Figure 1: Simplified schematic diagram of corneal reflex arc.

few seconds to few minutes, or conversely, it is triggered by slight stimuli touching the facial skin including mild wind or even sound vibration rendering the patient unable to chew, eat, drink, shave, or brush their teeth for fear of impending attack. Trigeminal neuralgia is not characterized by objective sensory or motor deficits, but the patient may present with a subjective hypesthesias or numbness over the facial skin in the distribution of trigeminal nerve branches. The diagnosis is based on history alone; however, primary disorder must be differentiated from similar symptoms secondary to other more ominous causes. Documenting the age of commencement of symptoms is significant in such cases as the advent of trigeminal neuralgia in a young patient should raise the suspicion of secondary causes including multiple sclerosis or intracranial space-occupying lesions that may lead to compressive demyelination of the trigeminal root entry zone at the lateral pons [5]. Trigeminal neuralgia is often misdiagnosed at initial presentation due to close connotation with dental pain causing various unnecessary procedures directed to relieve the supposed dental origin of pain. Paradoxically, this disorder is often over diagnosed for the very same reasons leading to numerous unnecessary surgical procedures such as peripheral neurectomy and alcohol injections, while the actual cause of symptoms may remain elusive for many years from general clinicians. A meticulous and focused evaluation of the neurosensory system discloses the correct anatomical location of the correct etiology. The neurological examination may be clouded by the sensory deficits subsequent to peripheral surgical procedures performed in pursuit of providing long-lasting relief from primary trigeminal neuralgic symptoms [6, 7]. In this study, I have reviewed the role of the corneal and blink reflexes in differentiation and diagnosis of the primary idiopathic trigeminal neuralgia from the secondary neuralgia.

1.1. Role of Corneal and Blink Reflexes in Neurological Examination. The corneal and blink reflexes are not only integral measures of the trigeminal and facial neurosensory assessment, but the abnormal function may facilitate the identification of intrinsic disease of the brain stem as well. These reflexes can be employed to discover a range of different pathological lesions including intracranial space-occupying trigeminal, lateral medullary, cerebral hemispheric lesions, and degenerative diseases of the central nervous system [1, 4, 5] (Table 1).

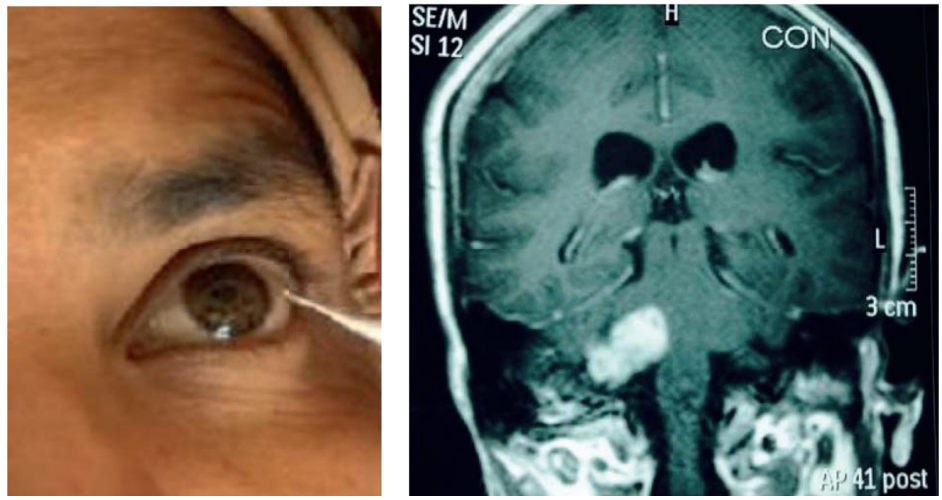
1.2. Role in Localization of Trigeminal Nerve Lesions. Measurements of delays in these reflexes have been reported as reliable in localization of supranuclear, nuclear, or peripheral nerve lesions. Trigeminal nerve may become compressed anywhere in the region brain-stem nuclei, the gasserian ganglion, or in the root entry zone at the cerebellopontine angle region and reveal symptoms of diminished sensations on the facial skin in association with hearing loss, facial muscle weakness, and complete loss or delay in reflex [4] (Figure 2).

The provoked reaction permits measurement of the delay in reflex after the stimulation of the afferent or the efferent nerve and noting the time taken by orbicularis oculi muscle contraction bilaterally [5].

1.3. Technique of Corneal Reflex. Lightly touching the surface of the cornea with a delicate material such as a cotton swab or wisp induces a rapid bilateral blink. Corneal reflex evaluation can be made while the patient looks to the side and the cornea is mechanically stimulated approaching from the temporal direction with a saline-soaked cotton tip or a droplet of saline or air ejected with an empty disposable syringe tip. The direct gaze on the oncoming object may

Table 1: Lesions and conditions that can present with trigeminal neuralgia-like pain with loss of corneal reflex.

Viral infections	Herpes zoster
Intracranial space-occupying lesions	Meningioma, schwannoma, acoustic neuroma, and AV malformations epidermoid tumors/cyst
Demyelinating disorders	Multiple sclerosis
Inflammatory disorders	Tolosa–Hunt syndrome Gradenigo's syndrome
Others	Arnold–Chiari 1 malformation



(a) (b)

Figure 2: A 50-year-old female presenting with electric shock-like pain on the right side of the face for last 10 years. Patient had a history of multiple neurectomy of the infraorbital, mental, and inferior alveolar nerve with temporary relief followed by recurrence of symptoms. Corneal reflex was found absent. MRI revealed $2.2 \times 2.2 \times 2.7$ extra-axial mass in the right cerebellopontine angle cistern suggestive of acoustic neuroma.

cause the patient to blink in response to visual threat and may lead to misinterpretation of the reflex [6, 7]. The stimulus application to the corneal surface is fundamental to maximize the reflex yield. It has been reported that normal volunteers with healthy cornea can reliably distinguish the stimulus; nevertheless, the strength and sensitivity of corneal stimulation is considerably greater than the temporal conjunctiva [8]. The reflex is achieved preferably with approaching from the periphery to the middle portion of the cornea while avoiding the pupil and the field of vision in the center. It is preferable to use the noninjurious objects such as a slight saline jet emission from the syringe tip to prevent any chance of scratching the cornea during the process [9]. If gentle techniques fail to provoke the reflex, then the evaluator may continue with intensifying stimuli strength to acquire a conclusive response or confirm the lack of the response [10]. Slightly and steadily touching the cornea with a cotton-tipped applicator is considered the most effective method to achieve maximum stimulation of corneal nerve endings [4].

1.4. Technique for Blink Reflex. The blink reflex is considered the electronic equivalent of the corneal reflex that is utilized to serve the same diagnostic purpose. An electrical stimulus is applied to the supraorbital nerve, and evoked responses are recorded over various muscles innervated by the facial nerve. The blink reflex requires the electromyographic or nerve conduction study machine with at least two-channel recording capabilities and recording and dispersive electrodes [11]. The cathode (i.e., the negative electrode) of the transcutaneous electric nerve stimulator is placed exactly on the supraorbital notch region which indicates the path of the supraorbital branch of the ophthalmic division of the trigeminal nerve. The rest of the electrodes are placed on the face, with two on the inferior part of both orbicularis oculi just below the lower eyelids, while one electrode is placed on the zygomatic arches as reference. One dispersive electrode is placed either over the forehead or below the chin for prevention of any possible thermal injury to the underlying tissue. Transcutaneous electric stimulation of the supraorbital nerve elicits two responses in the orbicularis oculi muscles: the early (R1) component in the ipsilateral muscle and the late (R2) component bilaterally. The pattern of abnormal responses (early and late, direct and crossed) indicates which part of the reflex circuit is affected [12].

1.5. Significance in Trigeminal Neuralgia. All of the trigeminal reflexes and sensations of touch, two point discrimination, pressure, temperature, and pain are reported to be unaffected in classic or typical trigeminal neuralgia cases unlike the secondary type; therefore, the neurophysiologic examination and trigeminal reflex testing represents the

Table 2: Situations of corneal sensation alterations that may limit the use of corneal reflex if present concurrently with trigeminal neuralgia.

Infectious diseases
Type 1 herpes simplex
Varicella zoster virus
Mycobacterium leprae
Fungal infections
Autoimmune disorder
Diabetes mellitus
Grave's disease
Sjögren's syndrome
Ophthalmic procedures and surgeries
Corneal transplant
Laser and other ocular surgeries including laser-assisted in situ keratomileusis (LASIK)
Photorefractive keratectomy (PRK)
Ophthalmic medication
Antiglaucoma topical medication especially topical beta-adrenergic antagonists
Benzalkonium chloride
Age
Advanced age

paramount and the most valuable and dependable measure for the diagnosis and differentiation of primary and secondary TN [10]. This differentiation is important as the treatment is different in both cases and early identification can guide the clinician to correct and timely treatment options. TN patients are often subjected to unwarranted and repeated peripheral neurectomies and alcohol injections, and in such patients, if neurosensory evaluation reveals abnormal sensation or numbness over the face in the distribution of the trigeminal nerve region, it cannot be confirmed weather it is secondary to previous neurectomy and alcohol injection or a manifestation intracranial lesion or underlying the disease process. Corneal and blink reflex remains intact despite previous failed attempt for treatment of patient's symptoms by peripheral neuroablative procedures [13, 14]. The abnormalities found in these reflexes can facilitate in the diagnosis of various intracranial space-occupying lesions as discussed previously, which can be of utmost significance in early differentiation between primary idiopathic trigeminal neuralgia and secondary trigeminal neuralgia caused by space-occupying or vascular lesions of the cerebellopontine angle or inside the semilunar trigeminal ganglion that can mimic primary trigeminal neuralgia symptoms, and the pain in such situations is more enduring and assiduous accompanied with diminution or absence of corneal reflexes as a reliable sign pointing to a secondary cause of pain in such cases [5].

1.6. Conditions of Corneal Innervation and Sensation Alterations. There are various conditions and situations that may alter corneal innervation and sensation which may subsequently limit the utility of corneal reflex in differentiation of primary and secondary trigeminal neuralgia (Table 2).

1.7. Infection. Various infections including type 1 herpes simplex virus and varicella zoster virus, *Mycobacterium leprae*, and fungal infections can harm both the parenchyma and nerves of the cornea which subsequently alter the corneal reflex and limit its use in such situations.

1.8. Herpes Infection. Herpes zoster virus affecting the ophthalmic region is an agonizing and overwhelming situation arising due to reactivation of virus in the trigeminal ophthalmic division. Ophthalmic involvement may involve any portion between the conjunctiva and the optic nerve and is accompanied by a wide variety of inflammations causing ulceration and corneal perforation. Numerous research studies have observed the physical damage of nerves of the cornea due to infection of zoster virus, associated with reduced sensation which can consequently hamper the utilization of corneal reflex in postherpetic neuralgia cases [15]. Similarly, type I herpes simplex virus can also infect the ophthalmic region, and in such cases, changes below basal plexus has been reported in both eyes of patients that associate congruently with corneal sensation reduction related to length of the infection period and episodes of recurrences [2].

1.9. Leprosy. Leprosy has been reported to be associated with variations in nerve density of the stroma, abnormalities in epithelial nerves, and swelling, twisting, and convolution of the corneal nerve, supplemented by reduced sensations [16].

1.10. Corneal Transplant, Laser, and Other Ocular Surgeries. Several studies have reported a significant reduction in corneal sensation many years subsequent to transplantation. The most common corneal corrective surgical procedures include laser-assisted in-situ keratomileusis (LASIK) and photorefractive keratectomy (PRK) that utilize excimer photoablation for tissue removal. The magnitude of post-surgical corneal sensation reduction depends on the amount of tissue removal during the procedure [17, 18]. Laser panretinal photocoagulation for diabetic retinopathy or

central retinal vein occlusion has also been reported to reduce sensations of the cornea [19].

1.11. Antiglaucoma Topical Medication. Reduction in sensation is documented in patients on glaucoma medication particularly with topical beta-adrenergic antagonists, specifically with a preservative benzalkonium chloride [20].

1.12. Advanced Age-Related Changes. Corneal sensation appears to decrease with age including thermal sensitivity to a cooling stimulus [21]. However, the significance of corneal reflex in diagnosis of trigeminal neuralgia due to intracranial lesions remains unaffected, as in most of the cases, the secondary trigeminal neuralgia presents at an earlier age and often before the age of forty years [14].

1.13. Diabetes Mellitus. Diabetic neuropathy involving the unmyelinated C and A delta-fibers contribute to paresthesias and may reduce corneal sensation in diabetics [22, 23]. This can limit the use of corneal reflex for differentiation in primary and secondary trigeminal neuralgia in diabetic patients.

1.14. Thyroid Gland Disease. Any thyroid gland dysfunction especially Graves' disease may present with thyroid-related ophthalmological pathology that may lead to abnormal function of corneal nerve and associated reflexes [24].

1.15. Sjögren's Syndrome. This condition can compromise corneal nerve function as it causes distortion of microscopic architecture of the nerve. However, there is disagreement in literature, whether this distortion leads to corneal sensation reduction or causes increased sensitivity, which may affect the validity of various testing modalities used to assess the corneal sensitivity [25–27].

2. Conclusion

As the trigeminal neuralgia pain appears to be originating from structures of the face and oral cavity, patient primarily pursue a general dentist for pain relief. When such patients finally present at tertiary care centers seeking relief of pain, they have already endured multiple dental procedures that have caused irreversible damage. In contrast, vast majority of dental practitioners lack knowledge of facial pain due to various other causes and have a tendency to over diagnose trigeminal neuralgia, being the only other cause of pain apart from toothache with which they are acquainted. For general dentists and maxillofacial surgeons, thorough history and meticulous clinical examination with a special emphasis on comprehensive appraisal of cranial nerves are indispensable in eluding erroneous diagnosis and inappropriate interventions in patients presenting with facial pain. Dental surgeons and oral and maxillofacial surgeons should consider corneal reflex in neurological assessment of patient presenting with trigeminal neuralgia-like symptoms. Failure to evaluate corneal sensitivity may lead to delayed or inaccurate diagnosis and unsuitable or redundant treatment interventions. This simple noninvasive reflex can be performed by chair-side and may provide significant information regarding the origin of facial pain and is an invaluable part of clinical methods especially in remote and peripheral healthcare center practitioners where sophisticated radiographic investigations such as computed tomography and magnetic resonance imaging may not be available. Its use may be limited in some local and systemic conditions of corneal hypoesthesia.

Data Availability

No data were used to support this study.

Conflicts of Interest

The author declares that there are no conflicts of interest.

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Research Article

Injection of Lidocaine Alone versus Lidocaine plus Dexmedetomidine in Impacted Third Molar Extraction Surgery, a Double-Blind Randomized Control Trial for Postoperative Pain Evaluation

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Objectives. Administration of medications such as dexmedetomidine as a topical anesthetic has been suggested in the pain control in dentistry. This double-blind randomized control trial study evaluated postoperative pain and associated factors following impacted third molar extraction surgery. Lidocaine alone was taken as the control and lidocaine plus dexmedetomidine as the intervention. *Materials and Methods.* Forty patients undergoing mandibular third molar extraction entered the study and were randomly allocated to the control and interventional groups. 0.15 ml of dexmedetomidine was added to each lidocaine cartridge and the drug concentration was adjusted to 15 μg for the intervention group while only lidocaine was used in the control group. A visual analog scale was used to measure and record pain levels at the end of the surgery and 6, 12, and 24 hours after the surgery and number of painkillers taken by the patients after the surgery was also recorded. *Results.* Pain scores of the intervention group decreased significantly during the surgery and also 6, 12, and 24 hours after the surgery compared to the control group. The pain score was correlated significantly with our intervention during the surgery and also 6 and 12 hours after that (all P value < 0.05). There was a nonsignificant reduction in the number of painkillers taken by the patients at 6, 12, and 24 hours after surgery (all P value > 0.05). *Conclusion.* In patients undergoing molar surgery, administration of a combination of dexmedetomidine and lidocaine is beneficial for the pain control. *Clinical Relevance.* Compared to the injection of lidocaine alone, combination of dexmedetomidine and lidocaine can be used for a better pain control in molar surgeries.

1. Introduction

Despite significant advances in pain management in dentistry, pain remains a major concern for many patients [1]. Surgical procedures for the extraction of impacted molar teeth are often associated with lots of discomfort and difficulty [2]. Since surgeons try to reduce postoperative complications, various approaches have been examined to minimize postoperative complications [3]. Pain is one of the most important complications in the extraction of molar

teeth which can even cause the patients not willing to seek further dental treatment. The pain after the surgery causes discomfort, delays the resumption of daily activities, and necessitates the use of sedatives [4]. Effective pain control can help to improve outcomes of the surgery, also result in shorter hospital stays, and, on the other hand, reduce the risk of chronic pain in the patients [5].

Becoming aware of the need for a surgery evokes feelings of fear and anxiety in many patients. Sedatives can increase pain threshold, exert antianxiety effects, and ultimately influence and control patients' pain [6]. Glucocorticosteroids, long-acting local anesthetics, and nonsteroidal anti-inflammatory drugs are commonly used for this purpose [7]. In addition to traditional analgesics, i.e., propofol and lidocaine, dexmedetomidine has been recently administered in the field of anesthetics [8, 9]. Dexmedetomidine is an $\alpha 2$-adrenoreceptor agonist which is highly selective. It triggers and also maintains the sleeping state by stimulating the densest region of $\alpha 2$-receptors in the central nervous system which is located in the locus coeruleus in the brain stem. Patients can be aroused by language or stimuli after sedation and respiratory depression does not occur during the surgery [10, 11]. Owing to its mild analgesic and sedative effects, dexmedetomidine can reduce not only stress and anxiety but also blood pressure and heart rate [12]. A comparison of pain relievers revealed that dexmedetomidine had fewer complications, e.g., lower frequency of amnesia and tachycardia and lower systolic and diastolic blood pressures, and no side effects, e.g., unstable oxygen saturation and respiratory rate [13]. Due to its limited side effects and efficacy in pain relief, dexmedetomidine can play an important role in surgical procedures. So, dexmedetomidine has been used in intraoperative sedations [14]. Dexmedetomidine can be administered intravenously and via inhalation [15]. Some researchers indicated the greater pain relief effects of dexmedetomidine plus lidocaine injection [16]. Studies also suggest that adding dexmedetomidine to lidocaine for the surgery will increase the time of nerve block and decrease the action onset; meanwhile, it improves the postoperative pain control. The vital parameters also reported to be stable after the surgery and no complications were observed [17]. But these results need to be confirmed before it becomes a routine practice in the dentistry.

The objective of this study is to see the effects of adding dexmedetomidine to lidocaine which is the routine nerve blocker for the extraction of third molar tooth, by comparing the postoperative vital signs and pain in a randomized control trial in patients referring to Torabinejad Clinic, Isfahan University of Medical Sciences (Isfahan, Iran), in 2018.

2. Materials and Methods

This double-blind clinical trial was conducted on the patients referred to dental clinics affiliated to Isfahan University of Medical Sciences for mandibular hard tissue surgery in 2018. The patients were included if they were aged 18–40 years, were ASA I-II, had no contraindication for dexmedetomidine use (hypotension, bradycardia, sinus disorder, unstable hypertension, arousability, tachyphylaxis, and liver disorders), and signed an informed consent form. The exclusion criteria were lack of analgesia with the administered dose, maxillary 3rd molar surgery, excessive fear of surgery, and not replying follow-up phone calls after surgery. All of the cases were also examined for the nature of impaction and expected difficulty level of the surgery by a senior maxillofacial surgeon based on the anatomical and radiological variables [18]. They were excluded if they were considered as very easy or very difficult.

To calculate the sample size, a preliminary study was performed on three patients in the case group and three in the control group, and the mean and standard deviation (SD) of pain score after 6 hours had been obtained to use for sample size calculation. The method of this preliminary study was the same as the main study which will be discussed later. These patients' data were not used in the main study results and analysis. In this preliminary study, the mean $\pm$ SD of the pain score after 6 hours in cases and control was 3.6 ± 2.5 and 6.35 ± 2.8, respectively. To reach the power of 80%, considering $\alpha = 0.05$ and ratio of the cases and control = 1, the number of participants in each group was calculated as 15 by the method of sample size for comparing two means [19]. However, considering the possible loss to follow-up of 25%, 20 individuals were selected for each group. The patients were provided with information about study objectives and asked to complete an informed consent form. In order to prevent the confounding effects of age and gender, equal numbers of men and women and equal numbers of individuals from different age groups, i.e., 18–25, 25–30, and 30–40 years, were recruited into the two groups. After the enrollment, from a pool of 63 patients, a patient was selected by generating a random number between 1 and 63 using MS Excel and sent to group 1. Another patient with the same sex and age group was selected from the pool to send to group 2. If the patients with those characteristics were not in the pool, we performed the selection once again. For selecting the second patient, a number between 1 and 61 was generated and this process continued until we reached 20 patients in each group. In summary, 157 patients were assessed for the eligibility but only 20 patients were allocated to each group and analyzed. The detailed CONSORT flow diagram can be seen in Figure 1.

Two identical sets of twenty cartridges were prepared. One set was lidocaine cartridge (Exir Co., Tehran, Iran) and for making the other set, 0.15 ml of dexmedetomidine (Daru Pakhsh Co., Tehran, Iran) was added to lidocaine cartridge and the drug concentration was adjusted to 15 μg. An anesthetist individually prepared the mixture. Using the same method of randomization by choosing a random number between one and two, one of the groups was assigned to one of the sets of cartridges. The surgeon and the consultants were not aware of the cartridge type. All surgeries were performed by the same surgeon. To avoid consecutive surgeries in each group, by using the same method of choosing random numbers, a number between one and forty was assigned to each person for the order of surgeries. The cartridge was also labeled by that number.

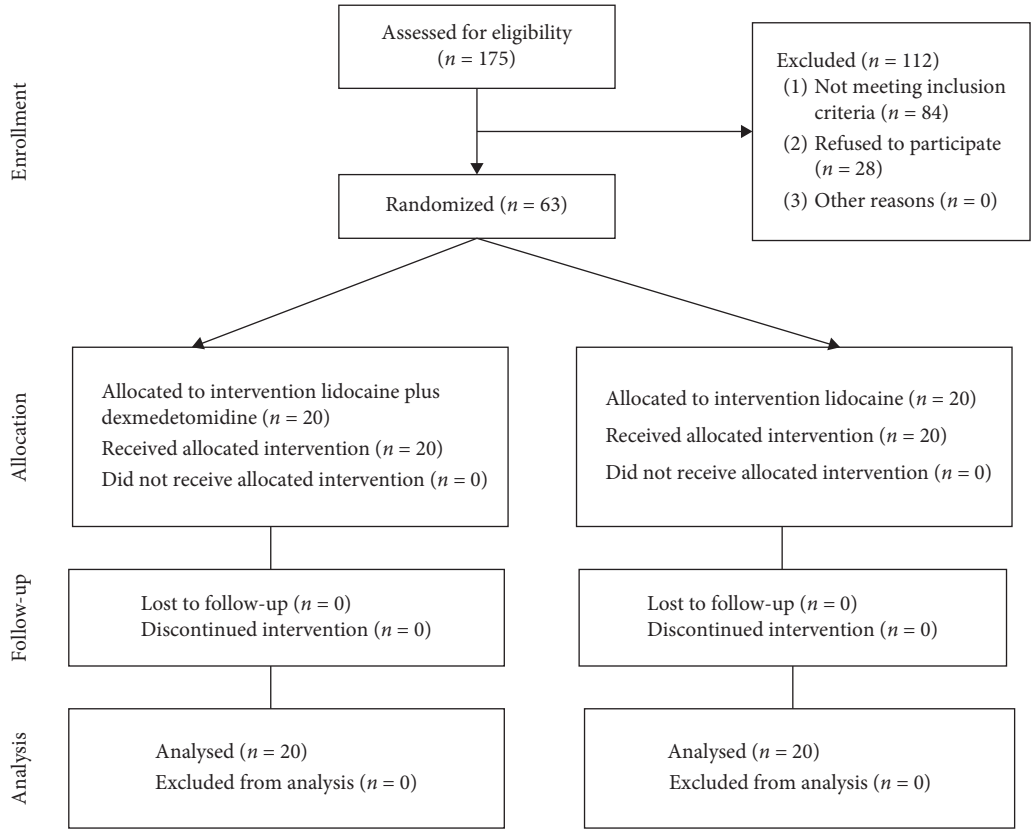

Figure 1: CONSORT flow diagram of the study participants.

The eligible patients were first briefed about the study objectives and methods and asked to sign an informed consent form. They were then asked to complete a questionnaire containing demographic information, medical history, medicine use, and smoking. During the surgery, patient information (e.g., gender, age, and blood pressure) was recorded in a specific data collection form. A visual analog scale was also administered to measure and record patients' pain levels at the end of the surgery and 6, 12, and 24 hours later in the scale of 0 to 10, 0 corresponding no pain and 10 the worse pain. Patients were allowed to take nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen after the surgery and they were asked by telephone about the number of postoperative painkillers taken. The patient's satisfaction and the surgeon's assessment of the surgical process in regards to the pain control was recorded as 3-scale questionnaire, high, intermediate, and low, for the patients' satisfaction and 4-scale questionnaire, good, fair, poor, and impossible, for the surgeon's assessment of the surgical process and pain control. The patient is marked good if he or she is fully cooperative with optimum degree of sedation, marked fair if the minimal interference is necessary due to over/under sedation, marked as poor if the operation is difficult due to over/under sedation, and marked impossible if actions such as general anesthesia are required.

All patient information was recorded anonymously and the participants were ensured about the confidentiality of the collected data. The patients paid no fees for pre- and postoperative tests. Informed consent was obtained from all subjects before the intervention. The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (ID = 397331).

Data collected through questionnaires were coded and analyzed using Fisher's exact test, ANOVA, or Mann–Whitney U test wherever appropriate. Spearman rank correlation analysis was performed by dichotomizing the pain score values using the 75 percentiles (third quartile) of the patient's pain scores as the cutoff value, between pain score and the intervention group, using the intervention group as 1 and the control group as 0. All analyses were performed using SAS version 9.4 (SAS, Cary, NC, USA) at a significance level of $P < 0.05$. After the results have been obtained, the power of the study was determined by using free online open source calculator OpenEpi, version 3, by the method of comparing two means for the pain score between the interventional and control groups [19].

3. Results

From the total of 40 patients, 17 were men (42.5%) and 23 were women (57.5%). Assessment of 36 patients (901%) was good and 4 patients (10%) was fair. Satisfaction rate of 35 patients (87.5%) was high and 5 patients had moderate satisfaction. Table 1 shows the characteristics of the patients in each group. Except pulse rate of the patients which is significantly higher in the intervention group, other vital signs are not different between the two groups.

Table 1: Patient characteristics in the intervention and control group.

Variable		Intervention group (dexmedetomidine + lidocaine)	Control group (lidocaine)	P value (test)
Age (year)		27.15 ± 5.54	27.05 ± 5.51	0.93
Gender	Female	12 (60%)	11 (55%)	0.50
	Male	8 (40%)	**9 (45%)**	
Assessment	Good	20 (100%)	16 (80%)	0.10
	Fair	0 (0%)	4 (20%)	
Satisfaction	High	19 (95%)	16 (80%)	0.34
	Intermediate	1 (5%)	4 (20%)	
Age (year)		27.15 ± 5.54	27.05 ± 5.51	0.93
SBP before injection		120.5 ± 10.99	113 ± 13.41	0.06
SBP after injection		122.5 ± 11.18	119 ± 13.37	0.37
SBP after surgery		120.5 ± 10.99	117 ± 13.41	0.37
DBP before injection		75 ± .5±6.86	72 ± 9.51	0.19
DBP after injection		77 ± 9.23	74.5 ± 8.25	0.37
DBP after surgery		75 ± 6.09	73 ± 7.32	0.35
O2 before injection		97.15 ± 1.95	97.8 ± 1.15	0.20
O2 after injection		96.85 ± 2.08	97.45 ± 1.19	0.27
O2 after surgery		96.55 ± 1.87	97.20 ± 1.05	0.18
PR before injection		86.75 ± 7.41	84.40 ± 9.32	0.38
PR after injection		90.50 ± 7.38	84.95 ± 8.16	**0.03**
PR after surgery		89.55 ± 7.97	84.55 ± 6.56	**0.03**

Assessment: surgeons' assessment of patient's pain control during surgery. Satisfaction: patients' satisfaction of pain control during surgery; SBP, systolic blood pressure; DBP, diastolic blood pressure; O_2, blood oxygen saturation; PR, pulse rate. $P < 0.055$

The two groups had no significant differences in the number of painkillers used at 6, 12, and 24 h after surgery. However, pain score was significantly lower in the intervention group at the time of surgery and also 6, 12, and 24 hours after that (Table 2). The third quartile of pain score was set as the cutoff value for high and low pain. The 75% quartile of pain score for the times 0, 6, 12, and 24 was 1, 8, 6.5, and 5. The Spearman rank correlation analysis for pain score in different times based on different groups (intervention or control) can be seen in Table 2. Pain score is negatively correlated with the intervention, during 6 and 12 hours after the surgery, but loses its significant correlation 24 hours after the surgery.

By considering the mean pain score and the SD in the intervention and control groups, the power of the study during the surgery and 6, 12, and 24 hours after the surgery was 61.47%, 98.56%, 9.53%, and 87.75%.

4. Discussion

The findings of this study demonstrated that adding dexmedetomidine to lidocaine cartridge increased the effects of lidocaine and reduced pain scores in patients immediately and 6, 12, and 24 hours after surgery. The correlation of pain score and the intervention is negative, meaning adding dexmedetomidine to lidocaine cartridge correlates with decreasing the pain score in the patients. This significant correlation had been observed during the surgery as well as 6 and 12 hours after that. After 24 hours although the patients had lower pain scores, the difference between two groups was not significant. We also found out that, although the intervention group used fewer painkillers, there were no significant differences between the two groups in terms of the mean number of painkillers used. So, the higher pain score did not result in taking significantly more painkillers.

Molar surgery and the associated pain lead to various complications including decreased quality of daily activities, excessive use of sedatives, and increased risk of polypharmacy [20]. Studies on the reduction of these complications and pain relief after dental surgery have focused on the use of steroidal drugs, such as glucocorticosteroids, and nonsteroidal anti-inflammatory drugs [17]. However, the use of topical and anesthetic treatments is also of paramount importance [21]. Lidocaine is an important agent used for pain relief after dental surgery [22]. Moreover, as a pain reliever and α2-adrenoreceptor agonist, dexmedetomidine plays a key role in reducing postoperative complications. The drug's mechanism of action is by inhibiting epinephrine and norepinephrine release and thus decreasing patient stress through eliminating the feelings of confrontation and escape [11, 23].

Several studies have evaluated the effects of dexmedetomidine and lidocaine on pain relief. In a study on healthy individuals in 2014, Yamane et al. [16] showed that dexmedetomidine injection increased pain threshold and decreased feeling of pain. They observed the highest increase in pain threshold at 10 minutes after injection. Furthermore, an increase in pain threshold and, thus pain relief, was maximized 20 minutes after the administration of lidocaine + dexmedetomidine. Dexmedetomidine administration did not alter levels of blood pressure, heart rate, and drowsiness in healthy individuals. Although all the patients in our study had normal and stable vital signs, the pulse rate of the patients was significantly higher in the intervention group and remained high after the surgery.

A double-blind study by Shetty et al. in 2016 [21] evaluated the levels of consciousness in 15 patients undergoing third molar extraction surgery. The results showed that pain severity and consciousness levels were significantly

Table 2: The mean pain scores and number of painkillers used in the two groups at different times.

Variable	Time	Intervention	Control	P value	Spearman (r)	Spearman P value
Pain scores (mean ± SD)	0	0.25 ± 0.44	0.8 ± 1.00	0.031	−0.33	0.03
	6	4.40 ± 2.50	7.55 ± 2.03	<0.001	−0.37	0.01
	12	2.80 ± 2.52	5.50 ± 2.39	0.003	−0.46	<0.01
	24	1.60 ± 2.37	4.00 ± 2.49	0.003	−0.17	0.26
Painkillers used (number ± SD)	6	1.4 ± 0.75	1.6 ± 0.75	0.313	—	—
	12	0.75 ± 0.55	1.1 ± 0.71	0.109	—	—
	24	0.45 ± 0.60	0.70 ± 0.80	0.348	—	—

Time, time after the surgery (hours); intervention, intervention group (dexmedetomidine + lidocaine); control, control group (lidocaine); Spearman (r): Spearman correlation (r).

lower in those receiving dexmedetomidine than in the placebo group. In contrast, in 2016, Mishra et al. [13] reported that dexmedetomidine administration reduced amnesia and systolic and diastolic blood pressure, but failed to relieve pain. In a clinical trial in 2007, Cheung et al. [24] compared the effects of dexmedetomidine and midazolam on third molar surgery. They noticed that dexmedetomidine injection lowered blood pressure and heart rate compared to midazolam but had no significant pain relief effects. In line with some previous studies, the overall results of this study indicated that dexmedetomidine injection relieved pain and, hence, reduces the use of painkillers to some extent. Some studies, however, showed that dexmedetomidine injection did not significantly affect pain levels. Although our observations are consistent with those of some previous studies, further clinical trials are recommended to confirm these results.

Our study had some limitations including a relatively small sample size (due to lack of access to further facilities and time and space limitations), although the power of our study was very high, especially 6, 12, and 24 hours after the surgery, regarding the pain scores. Using only one drug dose (rather than various doses) was another limitation of this study. Given more efficiencies reported in the coadministration of other pain relievers, further studies with larger sample sizes are recommended to use combinations of dexmedetomidine and other drugs. An advantage of this study was the control of factors affecting the final results, which can provide more realistic and reliable outcomes.

5. Conclusions

In patients undergoing molar surgery, administration of a combination of dexmedetomidine and lidocaine reduced pain scores to a significantly greater extent compared to lidocaine alone and decreased the number of painkillers compared to the control group. Therefore, a combination of dexmedetomidine-lidocaine is recommended for further pain relief and reducing the use of analgesics in patients undergoing such procedures.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

M. Esh. and J. A. conceptualized the study; J. A. developed methodology; SFV. W. prepared the software; K. J., P. R, and Z. Z. validated the study; J. A. did formal analysis; K.J. did investigation; P.R. prepared the resources; J.A. did data curation; K. J. wrote the original draft; J. A. reviewed and edited the article; SFV. W. visualized the study; N. K. supervised the study; M. Esh. did project administration; SFV. W. was responsible for funding acquisition. All authors have read and agreed to the published version of the manuscript. Javad Alizargar, Milad Etemadi Sh, Nasser Kaviani, and Shu-Fang Vivienne Wu equally contributed to this work.

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Review Article

Essential Attributes of Clear Aligner Therapy in terms of Appliance Configuration, Hygiene, and Pain Levels during the Pandemic: A Brief Review

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Fixed orthodontic treatment has been compromised at many levels during the pandemic period, as clinics underwent a prolonged lockdown and patients could not be treated regularly. With the end of the pandemic nowhere in sight, may be it is time to put newer tools, such as clear aligner therapy, for better use. Fixed orthodontic appliances by nature are not always self-limiting, which, if left unmonitored over a long period may cause undesirable side effects, pain, and discomfort. The undesired tooth movements that may occur with arch wire-guided mechanics in addition to problems with cut wires or removed brackets may be minimized with the use of aligners. While the benefits of using aligners are for all to see, they do require extensive planning and careful evaluation of the progress. This article reviews the advantages of using aligners during the pandemic period and how it can be beneficial in helping orthodontists resume their practice.

1. Life and Dental Practice in the COVID-19 Era

At the beginning of this year, one could not have predicted that the entire world and life as we know it would come to a standstill. The COVID-19 pandemic has caused widespread damage to both life and property unlike any other. The aggressive nature of this virus has made containment a difficult task, and the increasing number of people getting infected by this virus is an example of the ease with which it has spread across the globe [1]. While connectivity has been the cornerstone of many businesses throughout the world, it has also been one of the main reasons this virus has been able to spread across countries with such ease [2]. While science and medicine have made a lot of advances over the past few years, lack of knowledge pertaining to the transmission of such microbes has made it extremely hard to find a cure to this problem [1, 2].

A recent study conducted at the University of Nebraska Medical Center demonstrated that this virus is transmissible via direct contact as well as by means of fomites [3]. Contact transmission may occur from inanimate object surfaces or from one individual to another or even airborne transmission if two individuals are in proximity by means of droplets. This is the reason why dentists including orthodontists are at great risk of contracting this infection during various clinical procedures such as [4]:

1 Airborne transmission during treatment

2 Indirect transmission through a contaminated instrument or surface

3 Release of aerosols from high-speed handpieces or scalers

4 Asymptomatic carriers

5 Patients may be accompanied by family or friends who could be carriers themselves

2. How Will Dental Clinics Be Affected?

As on the date of this correspondence, many countries have eased their lockdowns. Dental clinics have gradually started to function with inadequate or overwhelmingly confusing guidelines and advisories to ensure no spread of infection while treating patients [2, 5]. Cross infection in the clinics may lead to an exponential rise in the number of cases in the locality, thereby putting at risk lives of many [6]. Also, such incidents may lead to litigations rising from inadequate infection control measures.

3. Reducing Risks and Moving Forward

As far as preventive options are concerned, there are many countries which have imposed strict lockdowns, while others have enforced guidelines regarding operations during this period. Vaccines are at various stages of trials, and it would take a while before these are freely available [7]. While the virus itself is here to stay, the time has come when dental and orthodontic practices will have to resume. Carrying out procedures under risk needs considerable thought and planning. Orthodontic treatment, especially fixed orthodontic appliances by nature, is not always self-limiting, which, if left unmonitored over a long period may cause undesirable side effects. This may cause varying degrees of "round tripping" and eventual delays in treatment [8].

Studies have suggested that pain associated with the use of fixed orthodontic appliances at different stages of treatment exerted a negative influence on the quality of life of the patients [9]. The fear of pain is considered a key factor dissuading patients from seeking orthodontic treatment in the first place [10]. Soft tissue lesions and wounds caused by orthodontic appliances may be one of the factors contributing to pain [11]. In a study of 161 patients aged 12 to 17 years, Kvam et al. [12] reported that lesions caused by fixed appliances were common (76%), while severe ulcers were present among 2.5% of these patients. In this current crisis of the pandemic, with very limited follow-up adjustments, it is obvious that many of the existing orthodontic patients with fixed appliances may have broken brackets, excess wire ends, detached attachments, or fixed functional appliances, that may impinge on the soft tissue causing a lot of pain and discomfort to the patients [8].

4. Why Clear Aligners?

Clear aligners are an esthetic alternative to fixed braces, primarily based on the esthetic demands of patients. They seem to have found a way to maintain the comfort level of a removable appliance and maintain control over specific tooth movements by means of tooth-colored attachments that are placed over the teeth and over which the aligners fit [13]. It is also important to know that even though aligners can be taken off for a few hours, the recommended daily wear time should be at least 20 to 22 hours for maximal tooth movement [14]. Aligners are being increasingly utilized in different kinds of complex cases, and their efficiency in two-phase therapies or simple cases has been previously documented [15, 16].

Usually, orthodontic patients need to return to the clinic for their routine follow-up sessions. Unfortunately, during the current situation of the pandemic, it is not possible for the patients' to always return on their scheduled appointments. Many may even miss their follow-up visits for a couple of months or more. This may cause a lot of unwanted effects during treatment and may delay the treatment time [8, 17].

Clear aligner therapy may offer some advantages in the COVID-19 era (Table 1), but an orthodontist must also be fully aware of the limitations of aligners over tooth movement control [18]. Movements such as rotations, extrusion, and correction of large overjets have been found difficult with clear aligners [19].

It is common that a series of aligners are provided to the patient to last for a defined period before returning to the practice for evaluation and additional aligners. Some orthodontists deliver all the aligners up-front, and then they may follow treatment progress using virtual visits online or with a monitoring system [8, 25]. Even though some aligner brands may prove to be very expensive, a low-cost alternative is to use inhouse aligners that may prove more economical over the long run, as well as ensure that the patients' treatment go on as planned with predictable tooth movements. One concern with inhouse aligners, however, is that they may be less effective compared to industrially manufactured aligners.

Through this communication, we would elicit the clinical nuances and considerations that make the use of clear aligner therapy in a post-COVID era plausible, at least until a vaccine or potential cure is in sight. It may also be a good idea to consider aligners in conjunction with fixed orthodontics to correct a part of the malocclusion initially or at the end to ease finishing [15].

4.1. Leveling and Alignment. Leveling and alignment is done at the start of orthodontic therapy, and normally, all teeth are moved at the same time to guide them into their proper positions [8, 26]. With fixed appliances, smaller gauge NiTi wires with considerable play in the bracket slots are used, thereby increasing chances of them slipping out from the buccal tubes at the back [27]. Once these wires slip-out, there may be trauma to the soft tissues in that area or even undesired movements. This may be the prime source of soft tissue lacerations that cause discomfort or pain instantly. The use of aligners at the start of the treatment can minimize this problem, as the teeth are covered on all five surfaces: occlusal, buccal, lingual, mesial, and distal, thereby offering good control over tooth movement [14]. Also, since there are no wires used, there is very less possibility of trauma or soft tissue impingement.

Table 1: List of advantages of using clear aligners.

Advantages of aligners	References
(1) Aesthetically pleasing	Drake et al. [14]
(2) Better oral hygiene	Zhao et al. [20]
(3) Removable	Kravitz et al. [21]
(4) Better in terms of comfort	Zhao et al. [20]
(5) Can be used for a variety of cases	Haoili et al. [22]
(6) Invisible attachments	Garino et al. [23]
(7) Beneficial for intrusion and expansion	Tepedino et al. [24]; Haoili et al. [22]

4.2. Deep Bites. Normally, with fixed orthodontic treatment, reverse curve wires, intrusion arches etc., it may be used for correction of deep overbites. Some of the side effects of using these unchecked materials would be proclination of the anterior teeth, lingual or distal tipping of the molars etc. [28]. In case of aligners, the curve of Spee is flattened by extrusion of premolars and molars using extrusive attachments or by intruding the anteriors using intrusive attachments [13]. Since the anterior and posterior teeth are covered on all surfaces, there is a better control over anterior proclination or reciprocal lingual or distal tipping of the molars as side effects. So, the patient can continue active treatment without having to worry much about side effects of unmitigated forces [29].

4.3. Space Management. During the current scenario, opening or closing spaces may be a little problematic because of the use of coil springs or power chains. With fixed brackets, the use of springs or chains needs to be continuously monitored as we need a specific amount of space that needs to be opened or closed [8]. Employing aligners during this stage has the added benefit of specific individual tooth movements that is fail-safe until the next aligner change [11]. Aligners can be used very effectively to open smaller spaces, although opening bigger spaces may require additional forms of anchorage.

4.4. Oral Hygiene, Ligation, and Bite Blocks. While the use of stainless-steel ties for holding the arch-wires in position may be beneficial in comparison with elastic modules in terms of maintaining hygiene and securing the arch wire, with aligners, these are not needed. No brackets, no wires, no ligatures, and the flexibility to remove aligners to clean the teeth make it extremely easy and effective to maintain proper oral hygiene during this period. It is well known that fixed orthodontic appliances can alter oral microbiology, whereas clear aligner therapy has minimal effect on the growth of oral bacteria [20, 30]. Previous studies conducted to compare the microbial colonization associated with aligners and fixed orthodontic therapy have shown that there is lesser presence of microbes and reduced risk of dental caries with the use of aligners [31–33].

Similarly, aligners can be designed with bite ramps anteriorly or posteriorly without the need to place composite or prefabricated bite blocks that may cause discomfort to the patient with fixed orthodontic treatment in case the patient is unable to visit the clinic for the next few months [12]. These bite ramps can be placed on a planned number of aligners and removed in the subsequent ones to ensure proper treatment progress.

4.5. Extractions and Expansion. While aligners offer no alternative for extractions, when required, these must be done under strict aseptic conditions with use of high-quality personal protective equipment. Space closure can be planned out with individual tooth movements using aligners to ensure that, even during the lockdown months, the space closure is carried out effectively. In terms of expansion, aligners are a highly efficient appliance as there is no need to use additional appliances for dentoalveolar expansion [13], although skeletal expansion may need additional tooth or bone-borne appliances. Expansion in each segment is planned and carried out stagewise so that once the desired expansion is reached, the aligner becomes passive. Also, occlusal and buccal coverage of the teeth offers an additional benefit in terms of maintaining control over undesired flaring [14] during the process. The passive aligners post-expansion may also offer effective retention phase due to complete the palatal coverage.

4.6. Space Closure. As mentioned earlier, with aligners, space closure movements can be planned extensively to ensure that teeth are moved as desired. The reduced dependability on power chains or closed coil springs makes lesser chances for patients' turning up with emergencies such as removed brackets, broken wires, or unwanted tipping due to excessive or unmitigated forces for a longer duration, in case the patient cannot visit the clinic regularly. With aligners, however, tooth movements must be small, and lesser teeth must be moved at the same time to ensure there are minimal side effects. Most aligners offer the option to use a virtual power chain for space closure, allowing spaces to be closed, but the orthodontist needs to plan the placement of attachments carefully so that the teeth do not tip instead of undergoing bodily movement [14, 29].

4.7. Miniscrews. There are many fixed orthodontic cases that require the use of miniscrews for maintaining control over anchorage during retraction, protraction, or even intrusion teeth movements [8]. If proper oral hygiene is not maintained during this period, it could lead to gingival inflammation and subsequent failure of the miniscrews which is where aligners are beneficial again [7, 21, 34]. Aligners can

carry many of the movements without employing the use of miniscrews. In cases that require anterior intrusion, arch distalization, or uprighting of molars etc., the use of miniscrews is unavoidable.

4.8. Finishing and Detailing. The number of orthodontists who employ aligners as a part of two-phase therapy is increasing because of the flexibility that comes with aligners [15, 35–37]. Aligners can be used at the beginning of the treatment, midtreatment, or even at the end to get an ideal finish. While conventional fixed orthodontics may require the use of various elastics and wire-bending to achieve a good finish, with aligners, the same can be achieved by the placement of attachments and planned individual tooth movements to ensure an ideal finish [38].

4.9. Delivering Torque. Most aligners can deliver positive or negative torque as desired by the treating orthodontist [35]. With fixed orthodontic treatment, it may be difficult to see the patients for the next few months and monitor the third-order changes, so using aligners with planned buccal or lingual torque depending on the stage is a good idea.

4.10. Interproximal Reduction. While aligners do offer a lot of benefits when it comes to interproximal reduction, the scenario is the same, but a plausible benefit is that reduction can be planned with aligners [39]. Interproximal reduction can be planned after a few aligner stages so that the patients do not have to visit the clinic physically for the next few months. With fixed orthodontics, this may be more difficult to accomplish as the orthodontist may not be able to postpone it without certain side effects.

4.11. Retention. After finishing a case with fixed orthodontics, normally, the brackets must be removed, and the teeth need cleaning and polishing to remove the bonding composite residue. In such a scenario, aligners again prove to be beneficial in terms of smaller attachments to clean or continued use of the last aligners that become passive once the desired movement has been achieved. Clear retainers may be fabricated using the software used for planning tooth movement, and these may be printed or formed on a cast using the treatment planning software [40]. It is always a good idea to have an additional pair of retainers made just in case the patient breaks one by accident.

4.12. Attachments. While fixed orthodontic treatments employ the use of brackets and wires, aligners also make use of attachments to maintain precise control over tooth movement [23]. Aligners have been utilized well in the management of Class II cases by distalization of the maxillary molars with the help of planned attachments and elastics [41]. In case any attachments are lost, a nonaerosol generating procedure may be employed to rebond the lost attachments.

4.13. Virtual Monitoring. With the advent of technology, a lot of virtual monitoring tools are available to orthodontists for being able to monitor patients currently undergoing treatment. With the ability to plan out the entire treatment with aligners using planning software, it may be comfortable to virtually monitor the cases and match the treatment progress with the planned tooth movement progress using the software [22, 24], in case the patient is not able to physically visit the clinic. Since fixed orthodontic movements employ a continuously adaptive treatment plan, it is difficult to gauge the progress using a virtual platform. Patients can be encouraged to take intraoral records with the help of someone at home, but the reliability and accuracy of these records taken without expertise may be questionable.

5. Limitations

While aligners may have several plausible benefits to offer in the current scenario, we would do well to also remember their limitations in three-dimensional tooth movement. Previous studies [24, 42] have shown that, while aligners are effective in maintaining control over intrusion of anteriors, they are less effective when it comes to extrusion. Also, they are more efficient in managing labiolingual inclination in the posterior segment compared to that in case of the anteriors. Clear aligners have also been found limited in their ability to control severe rotations especially that of rounded teeth [43].

6. Conclusions

No one could have foreseen the COVID-19 situation beforehand, and even now, there is no definite answer to this problem. The world as a whole and dentists as a group are in unchartered territory and to survive and come out of it better, we must adapt. Charles Darwin's theory of "Survival of the Fittest" may yet come to the fore, and as practicing orthodontists, we must employ making use of the technology available to us for our benefit as well as for minimizing the risk of cross infections. With all the plausible benefits and limitations of clear aligner therapy or fixed orthodontic treatment in mind, we must also always remember that it is not the aligners or the brackets that move teeth, but it is orthodontist with extensive training in carrying out physiological tooth movements, who have the ability and the skill to do so. We, as orthodontists, must incorporate more planning, provide better patient care, and make the most of the technology that is available today.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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