Effect of Diode Laser and 20% Benzocaine Anesthetic Gel on Pain Reduction following Tooth Separation with Elastomeric Separators in Fixed Orthodontic Patients: A Randomized Trial in Karachi-Pakistan

Muhammad Ashfaq
588981

List of investigators

Syed Iqbal Azam

Rashna H Sukhia

Muhammad Ashfaq

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TITLE: Effect of Diode Laser and 20% Benzocaine Anesthetic Gel on Pain Reduction following Tooth Separation with Elastomeric Separators in Fixed Orthodontic Patients: A Randomized Trial in Karachi-Pakistan

Introduction: Fix Orthodontic treatment can play a vital role in improving dentofacial esthetics and masticatory function, but some untoward effects like discomfort and pain are associated with it. In previous studies it is found that there is some sort of pain that is experienced by 90% or more of orthodontic patients post elastomeric separators , initial arch wires activations or insertions.(1-2) . The pain of elastomeric separators initiates after 4 hours of the placement and touches its peak at about 24 hours and then gradually subsides by day 7. (3,4)

Fix orthodontic treatment initiates with 1st step is placing separators which are placed to make space for cementing bands molar teeth. Separator placement cause tooth to displace which consequently results in the emergence of certain biochemicals in the gingival cervicular fluid, which is further followed a rise in the prostaglandins E2 and interleukin-1 levels, almost 24 hours of placing separators(5) This is why pain intensity is highest after 24 hours and there is some trouble for the next 3 days. The pain then in the next 6 to 8 days subsides.(1,4,6,7).

As orthodontic pain is inflammatory in nature, nonsteroidal anti-inflammatory drugs should be the gold standard for it.(8) But there are some systemic effects of these drugs which includes effecting the rate at which tooth moves in a negative way and requiring patient compliance for taking the medications, which should be considered before using these medications.(9) There are various other methods for relieving pain which includes low level laser, bite wafers, vibratory stimulation, transcutaneous electrical nerve stimulation, anesthetic gel and chewing gums. These methods have shown to reduce pain levels to various degrees and they have highly variable effects.(10-13)

Out of these modalities Low-level laser therapy (LLLT) is studied to be effective as anesthetic agent in various clinical situations.(14) there is a debate regarding the mode of actions of lasers in its use in different situations, but researchers claim its analgesic effects with anti-inflammation and neuronal effects. Studies have shown that low level laser acts by exciting neural cells and lymphocytes,which results in release of neurotransmitters into inflammatory tissues. Laser also acts by inhibiting neural signals which as a result decreases pain perception.(14,15) They also increase circulation of local blood which helps remove the pain-inducing inflammatory mediators and increases the cellular activities (biostimulation).(16)

Another modality which is less expensive and easily available is Benzocaine (ethyl 4-aminobenzoate) which is given as topical anesthetic with very few systemic adverse adverse-effects (17). Benzocaine is different from other anesthetics modalities as it is not injected and is directly applied to the area which is to be anaesthetized. It tend to acts locally and metabolized rapidly by esterase into an inactive compound (18), which results in blockage of the initiation and conduction of nerve impulses which is due to decrease in neuronal membrane permeability to sodium ions(19), as a result of which pain threshold increases.(20,21). Benzocaine has been used locally as a wax (22) or gel (23) to decrease the pain induced by orthodontic appliances.

Every patient desires painless dentistry due to which there are several studies that have been done globally, regionally and locally. In a study by Mirhashemi (24) a trial was done on 30 patients in a split mouth design were laser was used against a placebo. It was found that the laser group had low pain scores. However in this study laser was not compared directly with any other modality.

In another study by Eslamian(25) a randomized controlled trial with split mouth design of 30 patients with benzocaine gel and placebo for orthodontic pain reduction following orthodontic pain

reduction, it was found that benzocaine significantly reduced orthodontic pain after separator placement cross over design was used on 20 patients in which three gels were used to test pain levels during fix orthodontic treatment. This study didn't compare any other correct modality with the benzocaine gel directly in a split mouth design.

A study in 2020 in India by Oza(26) a randomized control trial was done on 120 patients in 4 groups in which a control group, laser , anesthetic gel and transcutaneous electric nerve stimulations were compared. It was found in this study that anesthetic gel group had the least immediate pain. However this again was not a split mouth design and patient related factors could affect the results of this study.

In Pakistan recently a cross sectional study was sultan et al(27) related to pain caused by separators, and it found that pain was associated with female sex and more in the age group between 21 and 36 years than in the younger ones. A randomized control trial was also done in Pakistan by Qamruddin et al(28) concluded reduction of postoperative pain after separator placement can be achieved with a single dose of low-level laser therapy

RATIONALE: It is important to establish whether Benzocaine is at least as effective as new modality low level laser therapy(LLLT). Demonstrating equivalence between these two treatments would provide clinicians and patients with a reliable, alternative option for managing pain.
Multiple studies globally have evaluated the pain reducing effects of each of these modalities individually after separator placement But no study has been conducted which compare both these modalities in a split mouth design to the best of our knowledge.
Local literature shows cross-sectional studies related to pain perception following separator placement and a randomized trial for low level laser therapy(LLLT) but that study was also not comparing different modalities together in a split mouth design which itself counters many confounders and biases.
This study aims to compare the effectiveness of anesthetic gel and low level LASER therapy in controlling pain, after placing the elastomeric separators in a split mouth design which would help clinicians to have both of these options for pain management as per the availability of resources. as laser is not easily available at any typical clinical practice and requires a huge budget for a practice to have laser at its disposal.

Research Question: Is there any difference in mean pain scores with Low Level Laser Therapy (LLLT) and 20% Benzocaine anesthetic gel of patients receiving elastomeric separators in fixed orthodontic treatment?

OBJECTIVE: To evaluate whether low level laser therapy is equivalent to anesthetic gel in pain score reduction after placement of elastomeric separators in fixed orthodontic patients of Karachi, Pakistan.

HYPOTHESIS:
NULL HYPOTHESIS: The difference in the mean pain score of LLLT and anesthetic gel is at least 12%[26] after elastomeric separators in fixed orthodontic patients
ALTERNATE HYPOTHESIS: The difference in the mean pain score of LLLT and anesthetic gel is less than 12% after elastomeric separators in fixed orthodontic patients

Study Design

It will be a randomized control trial in which site of treatment will be randomized. It will be an equivalence trial with split mouth approach. This design was selected as it is the gold standard for evidence based practice. This design also established causality. It reduces bias and counfounders like baseline pain, age, gender , baseline anxiety, as each participant would have both the

treatments Blinding would be possible with this approach as patient will not know which side was applied actual laser and which side was given placebo.

Study setting

Study will be conducted at department of orthodontics, Dow Dental College. It is a public sector institute with seven outpatient departments. It serves middle to low socioeconomic patient demographic. It has access essential dental equipment and procedures at a very affordable price. This facility also has easy access to Laser. The orthodontic department have on average 25 new patients per month starting per month .

Study population

Our target population would be patients aged 18-25 years seeking orthodontic care in Pakistan. While our study population would be patients aged 18-25 years seeking orthodontic care in dental OPD at Karachi. Our sample population would be patient aged 18-25 years seeking orthodontic care in orthodontic department at Dow dental college, Karachi. This age group is selected deliberately as it commonly presents for orthodontic treatment and is developmentally reliable enough to record self-recording pain outcome. More than that individuals in this age range are less likely to have diseases like gingivitis and periodontitis which could ultimately effect the pain perception since our pain scoring is self-reported and this age group is considered appropriate to accurately and consistently report the scores.

Eligibility Criteria

Inclusion criteria

- Patient aged 18-25 years

- no history of previous orthodontic treatment

- healthy and complete erupted dentition including permanent second molars

- good periodontal health(on basis of periodontal index)

- Tight proximal contacts of all permanent first molars (both mesially and distally)

Exclusion criteria

- Patients with multiple fillings, root canal treatments, gingivitis,, missing teeth, or spacing between molars and premolars will be excluded from the sample

- Severely rotated teeth

- posterior open bite

- any systematic disease

Sampling strategy

Consecutive sampling technique would be used once the patient fulfils the inclusion and exclusion criteria. After enrollment, use of random allocation process (Block randomization) to determine which side of each patient's mouth receives LLLT and which side receives the anesthetic gel, adhering to the split-mouth design.

Sample size

To achieve an 80% power to detect equivalence within a margin of 1.17(26) with a significance level of 0.05,keeping standard deviation of 2.50, a total sample size of 79 participants will be required. Sample size was calculated using an online calculator for sample size of equivalent trials named 'Sealed Envelop power Sample size calculator.

Recruitment Plan

Participants will be recruited after the approval of ERC based on the inclusion and exclusion criteria. Once recruited random allocation process (block randomization) would be used to allocate the side receiving laser application and the side receiving anesthesic gel in each participant. Since it is a single blind study in order to blind the patient, placebo gel and placebo laser application would be given to the sides opposite to the side receiving the actual modality. To ensure allocation concealment, treatment assignment to the left or right side of the mouth (laser vs. gel) will be determined using a computer-generated randomization list to be prepared by an independent statistician. Sequentially numbered, opaque, sealed envelopes will be used to conceal allocation until the point of treatment. The investigator enrolling the participant will not be involved in the allocation process.

Numeric rating scale will be used record pain level on days 1 to 7 days on a log that will be provided to the participants.

Study variables

Our outcome variable will be pain scores which will be measured by patients themselves on a given log for seven days. Pain scores will be measured on a numeric rating scale which ranges from 0-10 based on increasing severity.

Exposure of interest variable

Our exposure will be the application of low-level laser and benzocaine anesthetic gel. One of these modalities will be applied on either side of a mouth randomly in this split mouth design. Laser therapy will be applied using a 940- nm gallium-aluminum-arsenic diode laser on continuous mode with power set at 200 mW. The laser was applied buccally on 3 points: mesial, distal, and middle of the root of the permanent first molar for 20 seconds each.

20% Benzcaine gel will be applied by the patient himself with a applicator tip. The gel will be applied to the buccal mucosa on the attached gingiva in relation to the first molars, covering an area of about 1.5 cm in diameter

Other risk factors and potential confounders

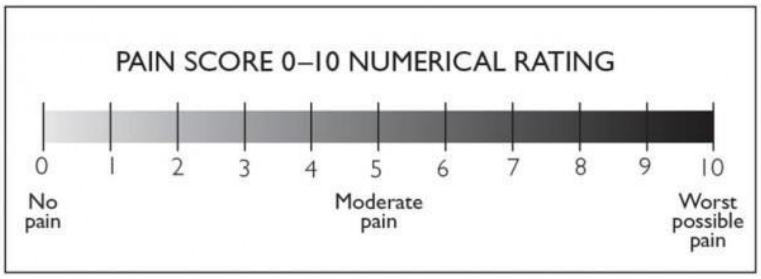
Age, gender, baseline pain perception, dental Anxiety and socioeconomic status are the potential confounders which will be catered at the analysis level.

Data Collection methods and data collection tools

Data will be collected on paper based CRFs with predefined instructions and coding schemes.Once patients will be recruited on the basis of eligibility criteria, demographics will be recorded. Patients will be provided with laser application and benzocaine gel one on each side of the oral cavity. Records of the random allocation will be maintained which side of the oral cavity Baseline pain assessment, dental anxiety scores and indicator of socioeconomic status would be recorded. (annexure). A log will be given to the patient to record his/her pain scores on a daily basis for 7 days on a numeric rating scale. An adherence log will be given to the patient for proper application of benzocaine gel. This will a paper-based log and reminder messages will be sent to the patients to ensure timely entries into the log.

Double data will be entered to control the discrepancies by two independent personnel.The data will be verified for any missing values, or inappropriate entries, its completeness, and accuracy (by random unique pateint ID)

Data would be stored with password-protected database with regular backups, unique id numbers would be given. Data will be stored at a back up site with limited access to PI and Statistician only. Data will be stored for 7 years applying institutional policy after which it will be destroyed.



Plan of analysis

Since our observations will be paired within same individual demographics and clinical variable will remain same both treatment modalities. However, for categorical variable like gender, socioeconomic status, dental anxiety, frequencies and percentages will be reported. Similarly for quantitative variables we will assess the symmetry of distribution and will report means and standard deviations for symmetrically distributed data and inter-quartile ranges for skewed data.

Data will be analyzed using linear mixed-effects model to compare the mean difference in pain scores between the two treatments (LLLT and benzocaine gel). Potential confounders like dental anxiety, socioeconomic status and side of mouth will be adjusted.

We will be using last observation carried forward (LOCF) methods or imputation for missing pain scores, ensuring that missing data does not introduce bias. Significance Level (α) will be Set at 0.05 for hypothesis testing.All data will be analysed using STATA software version (17.0)

Ethical concerns- Consideration of ethical issues

Informed Consent: Study purpose explained and informed consent will be taken from participants.Voluntary participation and rights of refusal and consent withdrawal will be stressed upon.

consent form.docx

Data Privacy and Confidentiality will be maintained by assigning unique code to each participant. Data will be used exclusively for research purposes and If required for publication, unidentifiable data will be used. Study will commence after ethical approval from participating institutes. Selection bias will be taken care of through consecutive sampling. Besides that block randomization along with allocation concealment will be implemented. We will also ensure the outcome assessor is blinded to treatment allocation. External validity will be maintained using the site (Dow dental college) where patients from various regions report for treatment. To increase external validity, participants will be recruited from a general orthodontic outpatient population from public sector OPD. Commonly used laser and benzocaine gel protocols will be employed as in any typical clinical conditions.

All participants will be monitored for any untoward or adverse events from the day of separator till day 7. Although low level laser therapy and 20% benzocaine gel are considered safe and are routinely used in dental practice, patients will be advised to report any sort of sensitivity, irritation or burning sensation at laser application site. Patient will be given contact number of the data

collecting team to report any event on phone call. In case of any severe event treatment will be discontinues and patient will be referred for appropriate clinical care.

Outcome measures will be standardized, and timings of pain record will be based on the clinical pain trajectory following separator placement, which will allow generalizability to similar dental practice settings. Besides that, pain scores will be recorded by the patients using a validated scale like NRS with clear instructions.

Public health implications

Since this the era of evidence-based practice this study will help clinicians to confidently use either of the two modalities at their practice. This trial is basically for pain management in the initial phases of fix orthodontic treatment and since essential pain management is important to execute orthodontic treatment plans and increases adherence of the patient. Since this study is a split mouth design it itself controls for interpersonal confounding such as baseline pain, anxiety, age, gender and socioeconomic status. However, there are certain possible limitations of our study which would include, blinding either participants or administrator is not fully possible and it may have limited generalizability.

As per as cost effectiveness is concerned if benzocaine gel is found equivalent to laser it would be a affordable pain managing modality specially in low resource as laser is an expensive technique and requires a huge budget and it is not possible for every typical clinical practice to have this facility at their disposal.

Gantt Chart- Timeline of the Study

Muhammad Ashfaq(MA) Msc Thesis Gantt chart

Supervisor: Sir Iqbal Azam(IA) , Committe member : Dr.Rashna Shukia(RS)

Study Setting: Dow Dental College

Sno	Task	Carried out by	January	February	March	April	May	June	July	August	September	October
1	DRC and ERC	MA, AKU DRC&ErC										
2	Training of Data C	MA										
3	Data colllection	MA supervised by IA &RS										
4	Data analysis	MA supervised by IA & RS										
5	Thesis presentati	MA										
6	Thesis writeup an	MA supervised by IA &RS										
7	Thesis Defence	MA										

Proposed Study Budget

Muhammad Ashfaq Msc Thesis Data Collection

PI: Iqbal Azam

Sno	Budget Head	No of Units	Unit Price	Total	
1	Data collector	2	in-kind	-	
2	laser application	80	2000	160000	
3	benzocaine gel	80	1200	96000	
4	Print out (consent/lo	50	80	4000	
				260000	(Direct cost)
				26000	(Indirect cost 10%)
				286000	Total

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