Efficacy Of Lidocaine And Xylometazoline Intranasal Spray In Anesthetizing Maxillary Teeth: An Open Label Randomized Controlled Trial

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Abstract

BACKGROUND: The most commonly used technique to anesthetize maxillary teeth is the infiltration anesthesia that currently is the gold standard. However, infiltration uses a dental needle that is associated with its de merits also. This led to the discovery of novel methods to anesthetize teeth. We in our study have used lidocaine with xylometazoline in the form of an intranasal spray to achieve local anesthesia of maxillary teeth for restorative procedures. The most commonly used technique to anesthetize maxillary teeth is the infiltration anesthesia that currently is the gold standard. However, infiltration uses a dental needle that is associated with its de merits also. This led to the discovery of novel methods to anesthetize teeth. We in our study have used lidocaine with xylometazoline in the form of an intranasal spray to achieve local anesthesia of maxillary teeth for restorative procedures. A total of 60 patients were enrolled in the study. Thirty patients were randomized each to lidocaine/Xylometazoline or to control local anesthesia group. Group A participants received 4% Lidocaine and 0.1% Xylometazoline solution as intranasal spray while Group B participants received injectable local anesthesia. Local anesthesia was then assessed and reading was taken on the Visual Analog Scale. If the reading was '0' the cavity preparation was performed. If the VAS reading was more than '0' a third dose of intranasal spray anesthesia was delivered. If profound local anesthesia was still not achieved the case was labeled as failure of intranasal spray anesthesia and local anesthesia was achieved by conventional infiltration anesthesia. For Group B participants, local anesthesia was achieved by means of conventional infiltration anesthesia. SPSS v.16 was used to analyze the data with level of significance set at $p<0.05$. Demographic data were analyzed upon the basis of frequency and percentages. Chi-square test and Fischer exact test were applied to see the difference of efficacy among the two groups and any influence of variables on the efficacy.

RESULTS: 21 out of 30 (70%) patients from Group A were anesthetized by intranasal spray anesthesia while all 30 (100%) patients from Group B had successful anesthesia by conventional infiltration. The p value computed is <0.05. No statistically significant effects of age group, gender, tooth location or the number of sprays was observed on the efficacy of intranasal spray anesthesia ($p>0.05$). There was a statistically significant effect of ICDAS score on the efficacy of intranasal spray anesthesia ($p<0.05$).

CONCLUSION: Lidocaine xylometazoline intranasal spray solution was fairly efficacious in anesthetizing maxillary teeth with smaller carious lesions for restorative procedures in patients with a stable medical history. Intranasal spray solution can be used for patients with needle phobia.

TRIAL REGISTRATION: The study is registered on clinical trials website via NCT04732104 on 26/01/2021.

Background

According to The International Association for the study of Pain (IASP), Pain has been defined as an unpleasant sensory or emotional experience, having an association with actual or potential tissue damage, or one that is described in terms of such damage.[1]

Pain arises as a result of stimulation of pain receptors that are sensitive to a noxious stimulus, or to a stimulus that has a tendency to become noxious if prolonged to a certain extent. When this noxious stimulus reaches the cerebral cortex, it is perceived as pain. Pain is regarded as a fifth vital sign[2] and should be addressed accordingly. The majority of tooth pain is thought to be nociceptive and of dento-alveolar origin.[3] Odontogenic pain may be derived either from pulpal tissues or neighboring periodontal tissues.[4] The healthy pulp possesses a good microcirculation which in turn plays an important role in initiating a cascade of inflammatory events against pulpal damages.[5]

The state of local Anesthesia is defined as a local loss of sensation in a circumscribed area of the body without loss of consciousness. It is brought about by a depression of excitation in nerve endings or due to an inhibition of the conduction process in the peripheral nerves.[6] The development of safe and effective anesthesia is regarded amongst the most important advancements made in medical and dental practice.[7]

Pain control has never been as efficacious as it is today. Mankind has been testing various methods to provide pain control. One of the earliest methods to control pain have been to compress the peripheral nerves to provide limb pain relief, as depicted in ancient drawings dating back 4500 years ago from Egypt.[8] Humans have been using herbal medicines for pain relief since thousands of years. Plato and Aristotle documented cases of using electricity as a means of reducing sensitivity to pain.[9] Around the year 1050 another means of anesthesia was discovered by Anglo-Sexan monks. They used cold water as a means of anesthetic agent.[10] Ice and various other coolant agents are still used as an inexpensive means to aid successful local anesthesia.

Local anesthesia has evolved over centuries. Two dentists were credited for first introducing anesthesia, namely Horace Wells who successfully used nitrous oxide in 1844,[11,12] and William Thomas Green Morton who discovered ether in 1846.[13] The development of local anesthesia was made much later.

The breakthrough came in 1943 when Nils Löfgren and Bengt Lundqvist in Stockholm, Sweden, discovered a new compound labeled LL30, which would later become the first amide local anesthetic: Lidocaine.[14] Compared to Novocain, Lidocaine featured less allergenicity, a longer duration of action, better potency, and less tissue irritation. In November 1948, Lidocaine, marketed as Xylocaine (Astra), was approved by the Food and Drug Administration for use in the United States.[15]

Many different techniques have been used to induce local anesthesia. They may range from regional nerve blocks to simple infiltration techniques. The gold standard of care for providing pulpal anesthesia to maxillary anterior and premolar teeth is by the help of buccal mucosa infiltration that eventually anesthetizes branches of anterior and middle superior alveolar nerves.[16]

The maxillary anterior teeth receive their nerve supply from anterior superior alveolar nerve while middle superior alveolar nerve supplies the maxillary premolars and the mesio-buccal root of maxillary first molar. The frequency of presence of middle superior alveolar nerve is only 72% in the general population. When this nerve is not present anatomically, second premolar receives its nerve supply by the posterior superior alveolar nerve.[17, 18]

Modern methods of anesthesia delivery include CompuDent System, Single Tooth Anesthesia System and Comfort Control Syringe.[19] These novel methods are aimed at precise location of delivery of the anesthetic, slower rate of injection and use of smaller needles to reduce pain and accompanying dental anxiety. However, anticipation of injection creates more anxiety than the injection itself,[20] therefore there was a need for an injection less system to anesthetize the teeth for dental restorative procedures.

This study therefore aimed to find an alternative to the use of a dental needle by assessing the efficacy of intranasal Lidocaine Xylometazoline combination in the form of an intranasal spray to achieve pulpal anesthesia of maxillary anterior and premolar teeth for restorative procedures.

Intranasal spray anesthesia is the newest way of achieving maxillary pulpal anesthesia by delivery of local anesthetic agent into the nasal cavity. It may be of great help to patients who are afraid of conventional dental needles and injections and may pave way for achieving anesthesia without the use of needle.

Lidocaine is a synthetic Aminoethylamide which is enriched with local anesthetic and antiarrhythmic properties. Lidocaine stands out as a prototype amide local anesthetic.[21] The drug possesses a rapid onset, usually within 2-4 minutes, with moderate potency and a duration of action that may last somewhere between 60-190 minutes. It possesses negligible side effects when compared to ester anesthetics.[15, 22] The drug commands the position of most versatile and the most commonly used local anaesthetic by virtue of its potency, the tendency to attain a rapid onset and a sufficient duration of action and its ability to produce adequate topical anaesthetic action.[23] The local anesthetic agent is rapidly absorbed from the airways into the blood stream. This property of lidocaine opens its avenues for use as an intranasal spray solution. Lidocaine is used for the attainment of infiltration anesthesia and for local anesthesia via different nerve block techniques. The agent acts primarily on sodium ion channels that are morphologically present on the internal surface of nerve cell membranes.[24]

One of the primary concerns with tetracaine as with other local anesthetics is CNS toxicity when administered beyond and above its therapeutic dose. Allergic reactions to tetracaine can occur. While allergy to local anesthetic is rare, it is more common with aminoesters than aminoamides. This reaction is thought primarily to be due to para-aminobenzoic acid (PABA).[25]A major factor precluding use of tetracaine for comparison purposes in our study was that tetracaine is commercially unavailable in Pakistan.

The first and second intranasal sprays are administered at the inferior and middle meatus of the nose. The nasal spray molecules then reach the anterior wall and floor of the maxillary sinus and penetrate the Schneiderian membrane and/or the bony cortex. This results in anesthetizing the anterior superior alveolar and middle superior alveolar nerves before they supply the apices of anterior and premolar teeth. The ASA and PSA nerves are always present but the MSA nerve is present in only 37% to 82% of the population.[26] If the MSA nerve is anatomically absent, pulpal innervation to the maxillary premolars is supplied by a plexus of nerve branches from both the PSA and the ASA nerves.

Lidocaine xylometazoline solution possesses potent vasoconstrictor and anesthetic properties for performing intranasal operative procedures.[27] The combination solution is used as a topical anesthetic during flexible transnasal endoscopy, nasogastric intubation and during nasal fibreoptic procedures in department of otorhinolaryngology. The combination solution is aimed at increasing patient comfort, reducing the chances of epistaxis and prolonging the duration of anesthesia.[28] Till date no published literature regarding the dental anesthetic effect of lidocaine xylometazoline combination exists.

Lidocaine is easily available, cheaper and safer anesthetic as compared to tetracaine. On the other hand, esters have a higher incidence of sensitivity reactions[29] and have a propensity to cause methemoglobinemia if overdosed.[30] Due to these negative effects amides have surpassed esters in terms of popularity. Therefore, the aim of this study was to test the efficacy of lidocaine xylometazoline intranasal solution in achieving sufficient pulpal anesthesia to perform dental restorative procedures on teeth numbers 4 till 13 (Universal tooth numbering system).

OBJECTIVE OF THE STUDY

To compare the efficacy of 4% lidocaine and 0.1% xylometazoline intranasal spray solution as compared to injectable 2% lidocaine with 1:100,000 epinephrine solution in anesthetizing maxillary anterior and premolar teeth for dental restorative procedures.

Methods

RESEARCH DESIGN AND SETTINGS

STUDY DESIGN:

Open Label Randomized Controlled Trial.

STUDY SETTING:

Department of Operative Dentistry, Dr. Ishrat-Ul-Ebad Khan Institute of Oral Health Sciences, S, Karachi.

STUDY DURATION:

The study was conducted between July 2018 and June 2020.

INCLUSION CRITERIA

- Adults aged 18-40 years,
- Patients having a vital maxillary premolar, canine or in
- Patients having Class 1,2,3,4 or 5 restorations (G.V. Black).[31]
- Patients having heart rate between 55 and 100 beats per
- Patients with a seated Systolic blood pressure between 95 and 150 mm Hg and diastolic blood pressure between 60 and 100 mm of Hg.
- Teeth with no radiographic evidence of pulpal or periapical pathosis.
- Patients having ICDAS caries detection score of 4, 5 or 6.
- Patients who fulfilled alcohol sniff test criterion.

EXCLUSION CRITERIA

- Patients with Upper respiratory tract infection.
- Patients with Uncontrolled thyroid disease.
- Patients having a known allergy to any of the components used in the solut
- Pregnant or breast feeding patients.
- Those patients having 5 or more nosebleeds per month.
- Patients who received any local anesthetic/analgesic within 24 hours of study drug administra

SAMPLING TECHNIQUE

Consecutive sampling was done for the study participants who met the inclusion criteria. 30 patients were randomly allocated each to lidocaine /xylometazoline group and to control group.

RANDOMIZATION: Randomization was done with lottery method. Simple random method was used for group allocation via computer software (MS Excel).

The study was designed in accordance with CONSORT 2010 guidelines. CONSORT flowchart is shown in Figure 1.

STUDY DURATION

The study was conducted between July 2018 and June 2020.

SAMPLE SIZE ESTIMATION

Total 60 participants were enrolled in the study. Using PASS v11, 2-sample independent proportion with 99% power of test and 99% Confidence interval; 88% success rate of tetracaine[17], 28% success rate of placebo[17], sample size calculated was 28 each group which I had increased up to 30 each group.

DATA COLLECTION

ELIGIBILITY

Thorough medical and dental history, Intra oral and Extra oral examinations were carried out if the patient required a dental restorative procedure on teeth numbers 4 to 13 (universal tooth numbering system). Teeth having ICDAS cavity score of4, 5 or 6, had electric pulp vitality testing done by Digitest II, Parkell Inc., NY, USA. A peri-apical radiograph was also taken for radiographic assessment taken.

The researcher then conducted an alcohol sniff test, to assess baseline olfactory sensation of the patient since a person with altered olfactory sensation would not be able to inhale and absorb the required amount of spray solution for its desired anesthetic effect.[32]

A pad of 70% isopropyl alcohol was used for the nostril ipsilateral to the tooth that was to be treated. The research participant closed his/her eyes and the contralateral nostril while inhaling through the other nostril. The alcohol pad was placed at 30 cm from the nostril and with each expiration was brought closer by 1-2 cm to ascertain at what distance did the patient sense the odor. Patient with a normal olfactory function sensed it at 14 centimeters (cms.) while one with reduced olfactory sensation sensed it at approximately 8 cms. The procedure is shown in Figure 2 (i and ii).

CONSENT

The research participant was explained about the procedure, efficacy and safety of the materials used, possibility of receiving either treatment options (i.e. intranasal spray or injectable local anesthesia), the patient was asked to sign a consent form (Appendix II & III).

RANDOMIZATION

The research participants were then randomized into two groups. Group 'A' participants received 4% Lidocaine and 0.1% Xylometazoline intranasal spray solution while Group 'B' participants received injectable local anesthesia (2% Lidocaine with 1:100,000 Epinephrine).

INTRANASAL SPRAY SOLUTION PREPARATION

Equal volumes of Lidocaine 4% solution (Xylocaine, Barret Hodgson Pakistan Pvt. Ltd) and Xylometazoline 0.1% solution (Xynosine 1:1000, Zafa Pharmaceutical Laboratories Pvt. Ltd.) were dispensed in a single pilferproof bottle of XYNOSINE. With each puff the bottle delivers a standard dose of 0.2 ml. A separate bottle of intranasal spray anesthesia was used for each participant so as to minimize the possibility of cross infection.

ADMINISTRATION OF INTRANASAL SPRAY ANESTHESIA

For Group 'A' participants, the researcher administered a single puff of the intranasal spray while the patient sat upright in the dental chair with the device positioned inside the nostril up to the edge of the nasal valve[17]. (Figure 3) The dose was then given with a single puff as a plume of mist. The second spray was delivered approximately 4 minutes after the first one with the tip of the spray positioned at 45 degrees to the horizontal[17]. (Figure 4)

ASSESSMENT OF SPRAY ANESTHESIA

The operator waited for ten minutes after administering second dose of spray anesthesia, and then assessed anesthesia by probing the soft tissue adjacent to the tooth and reading was taken on the VAS (Visual Analog Scale) (Figure 5). If the VAS reading was 0, the cavity preparation procedure was initiated. If the VAS reading was more than 0, a third dose of the intranasal spray was delivered in a similar way as the second one. The operator waited further ten minutes before beginning to use hand piece. VAS reading was taken again at this moment. If the patient still experienced any sensation of pain (VAS reading more than 0), the procedure was halted and standard buccal infiltration anesthesia was given with 2%lidocaine with 1: 100,000 epinephrine (Medicaine Inj., Huons Co. Ltd, Korea). Some patients experienced pain on cavity preparation stage, such patients were also administered infiltration anesthesia and the case was labeled as a failure of spray anesthesia. The need for a rescue injectable local anesthetic was considered as study drug failure. The ability to carry out the restoration after 2 or 3 sprays was considered as the study drug success.

CONVENTIONAL INFILTRATION ANESTHESIA

For Group B participants and those who could not be anesthetized by spray anesthesia, anesthesia was achieved by the help of injectable local anesthetic (Figure 6).

After application of topical anesthetic lidocaine (Lidocaine ointment USP 5%, Septodont Inc. Lousville), local infiltration anesthesia was given by means of an aspirating syringe with 2%lidocaine with 1: 100,000 epinephrine (Medicaine Inj., Huons Co. Ltd, Korea). A 27 Gauge infiltration needle was used for the procedure (S-Dent, 27 G, 0.4*25mm.) and was discarded according to the standard sharps protocol after the procedure was completed. Anesthesia was then assessed by the the similar method as in Group A participants and reading was taken on the VAS. If the VAS was ‘0’ cavity preparation and restoration steps were undertaken. If not another infiltration injection was given and after achieving satisfactory anesthesia, restorative procedure was undertaken.

CAVITY PREPARATION AND RESTORATION

After achieving sufficient anesthesia, the cavity preparation and restoration was done as per standard recommendations according to material selection (i.e, Amalgam or composite).

POST OPERATIVE INSTRUCTIONS

After completion of the procedure, the patient was given standard post-operative instructions for restoration maintenance and was recalled for finishing and polishing procedure at 24 hours. After satisfactory outcomes, the patient was discharged with postoperative instructions and re emphasis on oral hygiene. The patient was also prescribed analgesic according to the analgesic hierarchy if needed.

FOLLOW UP VISIT

The patients were recalled at 24 hours for finishing and polishing of the restoration. At the same visit they were also asked about any adverse effects following local anesthesia administration. The amalgam restorations were polished by autoclavable silicone polishing points (SHOFU Dental GmbH). The composite restorations were polished by Sof-lex finishing and polishing discs (3M ESPE).

STATISTICAL ANALYSIS

Data were analyzed using SPSS v.16 (SPSS Inc., IBM). Demographic data was analyzed upon the basis of frequency and percentages. Descriptive statistics were calculated for efficacy of intranasal spray and injectable anesthesia as frequency and percentages. Chi-square test was applied to see the difference of efficacy among the two groups and any influence of age group, gender, tooth location, cavity classification, ICDAS score or the number of sprays required to produce anesthesia, on the efficacy. A p-value of 0.05 or less was considered as significant.

Results

Table 1 enlists demographic data of the study participants

TABLE 1: DESCRIPTIVE STATISTICS OF DEMOGRAPHICS

Basic characteristics	N (%)	
Group		
Injectable anesthesia	30 (50%)	
Spray anesthesia	30 (50%)	
Total		60 (100%)
Age (years)		
18-25	11 (18%)	
26-40	49 (82%)	
Gender		
Male	22 (37%)	
Female	38 (63%)	

EFFICACY OF INTRANASAL SPRAY ANESTHESIA AS COMPARED TO CONVENTIONAL LOCAL ANESTHESIA

Our study had 30 patients from Group A, who received intranasal spray local anesthesia, out of which 21 patients had successful anesthesia by 2 or 3 intranasal sprays while the remaining 9 patients could not achieve anesthesia. These patients were anesthetized using conventional means of injectable anesthesia.

Group B had 30 patients and all of them were successfully anesthetized by conventional infiltration anesthesia.

Since the p value computed is less than 0.05, there is a significant difference in efficacy of anesthesia between the two groups, as shown in Table 2. **This value therefore illustrates that there is a statistically significant difference in anesthetic efficacy of lidocaine xylometazoline intranasal spray v/s injectable lidocaine epinephrine infiltration in anesthetizing maxillary anterior & premolar teeth for restorative procedures, thereby rejecting the null hypothesis.**

TABLE 2: EFFICACY OF LOCAL ANESTHETIC AGENTS

Variable	Efficacy		Total	P-value
	Yes n (%)	No n(%)		
Spray anesthesia	21 (70%)	09 (30%)	30	**0.02$^{*\alpha}$**
Injectable anesthesia	30(100%)	00(00%)	30	

*= significant at 0.05

α= Fischer exact test

EFFECT OF AGE ON THE EFFICACY OF INTRANASAL SPRAY ANESTHESIA

Since the p value is greater than 0.99, there is no association of age on the efficacy of intranasal spray anesthesia, as shown in Table 3.

Table 3: EFFECT OF AGE ON THE EFFICACY OF INTRANASAL SPRAY ANESTHESIA

Variable	Efficacious		Total	P-value
	Yes (n=21)	No (n=09)		
Age				
18-25 years	03 (75%)	01 (25%)	04	**> 0.99$^{\alpha}$**
26-40 years	18 (69%)	08 (31%)	26	

*= significant at 0.05
**= significant at 0.001
$^{\alpha}$ = Fischer exact test

EFFECT OF GENDER ON THE EFFICACY OF INTRANASAL SPRAY ANESTHESIA

Since the p value calculated is 0.691, there is no statistically significant association of gender on the success of intranasal spray anesthesia (Table 4).

Table 4 EFFECT OF GENDER ON THE EFFICACY OF INTRANASAL SPRAY ANESTHESIA

Variable	Efficacious Yes (n=21)	No (n=09)	Total	P-value
Gender				
Male	10 (77%)	03 (23%)	13	**0.691**$^{\alpha}$
Female	11 (65%)	06 (35%)	17	

$^{\alpha}$ = Fischer exact test

EFFECT OF TOOTH NUMBER ON THE EFFICACY OF INTRANASAL SPRAY ANESTHESIA

Since the p-value calculated is 0.637, we conclude that there is no difference in efficacy of spray anesthesia between second premolars, first premolars and anterior teeth (Table 5).

Table 5: EFFECT OF TOOTH NUMBER ON THE EFFICACY OF INTRANASAL SPRAY ANESTHESIA

Variable	Efficacious Yes (n=21)	No (n=09)	Total	P-value
Tooth number				
Second premolar	03 (60%)	02 (40%)	05	
First premolar	05 (62.5%)	03 (37.5%)	08	**0.637**$^{\alpha}$
Canine and incisors	13 (76.5%)	04 (23.5%)	17	

$^{\alpha}$ = Fischer exact test

EFFECT OF ICDAS SCORE ON THE EFFICACY OF INTRANASAL SPRAY ANESTHESIA

Since the p-value is greater than 0.002 there is a statistically significant effect of cavity depth on the success rates of intranasal spray anesthesia. On the basis of frequency and percentage we conclude that the spray anesthesia was more effective in anesthetizing cavities with ICDAS score of ‘4’ where 91% of the patients were successfully anesthetized (Table 6).

Table 6: EFFECT OF ICDAS SCORE ON THE EFFICACY OF INTRANASAL SPRAY ANESTHESIA

Variable	Efficacious Yes (n=21)	No (n=09)	Total	P-value
ICDAS Score				
‘4’	10 (91%)	01 (9%)	11	
‘5’	11 (73%)	04 (27%)	15	**0.002**$^{**\alpha}$
‘6’	0 (0%)	04 (100%)	04	

**= significant at 0.001

$^{\alpha}$ = Fischer exact test

EFFECT OF CARIES CLASSIFICATION ON THE EFFICACY OF INTRANASAL SPRAY ANESTHESIA

The p-value is >0.05 therefore we conclude that there is no effect of caries classification on the efficacy of intranasal spray anesthesia. The details are shown in Table 7.

Table 7: EFFECT OF CARIES CLASSIFICATION ON THE EFFICACY OF INTRANASAL SPRAY ANESTHES

Variable	Efficacious Yes (n=21)	No (n=09)	Total	P-value
Caries classification				**0.647**$^{\alpha}$
I	06(86%)	01(14%)	07	
II	02(33%)	04(67%)	06	
III	08(89%)	01(11%)	09	
IV	05(63%)	03(37%)	08	
V	00(0%)	00(0%)	00	

$^{\alpha}$ = Fischer exact test

NUMBER OF INTRANASAL SPRAYS REQUIRED TO ACHIEVE LOCAL ANESTHESIA

Since the p-value computed is 0.11, there is no effect of number of sprays on the efficacy of intranasal spray anesthesia. (Table 8)

Table 8: EFFECT OF NUMBER OF SPRAYS ON THE EFFICACY OF INTRANASAL SPRAY ANESTHESIA

Variable	Efficacious Yes (n=21)	No (n=09)	Total	P-value
No. of sprays required to achieve anesthesia				
Two	11 (100%)	0 (0%)	11	**0.110**$^{\alpha}$
Three	10 (53%)	09 (47%)	19	

$^{\alpha}$ = Fischer exact test

ADVERSE EFFECTS OF SPRAY LOCAL ANESTHESIA

Out of a total of 30 patients, only 4 experienced minor rhinorrhea after administration of spray anesthesia, that also subsided within a few seconds. No adverse effects were reported after discharge from dental office or at 24 hours recall visit. Those patients that did not turn up for recall were contacted over phone. They also did not report any adverse effects at 24 hours interval. Since the p value is 0.11, there is no significant difference in occurrence of adverse effects between the two groups. (Table 9)

TABLE 9:- ADVERSE EFFECTS OF LOCAL ANESTHESIA

	Adverse effects		
	Yes (04)	**No (56)**	**p-value**
Spray anesthesia	04 (13%)	26 (87%)	0.112
Injectable local anesthesia	0 (0%)	30 (100%)	

Discussion

Successful anesthesia ensures provision of dental treatment in a peaceful environment with least patient discomfort. All dental procedures, from routine restorative treatments to complex surgical procedures, need to be done under profound anesthesia, both for the clinician's ease and the patient's comfort.[33]

If local anesthesia is so effective, why then do we still have major difficulties in dental anesthesiology today? The answer from almost all dentists who will admit it and from the hundreds of thousands of potentially terrified patients is that fear and anxiety are as much a part of the overall problem as is pain and the management of pain itself. General anesthesia effectively manages all the components of the pain package but is beset with other inherent difficulties. Local anesthesia no matter how skillfully administered has no direct effect on reducing fear and anxiety. If anything, because a local has to be administered by needles applied intra orally, the problems are intensified in most patients. Administration of a dental injection also bears a risk of possible transmission of blood borne pathogens via a needle stick injury. In order to reduce this risk, a Needle stick Safety and Prevention Act[34] was passed by the US congress that encourages the use of needle-free technology whenever its use is possible. The law also provides incentives for the drug manufacturing companies to develop anesthetics that can be delivered via needle less technologies.

The whole concept of using needle less technologies paved way for the development of a solution containing 3% Tetracaine and 0.05% Oxymetazoline, delivered via an intranasal spray in order to perform restorative procedures on maxillary anterior & premolar teeth. In a study performed by Hersh et al. a comparison was done between the anesthetic efficacy of an intra-nasally administered solution of tetracaine and oxymetazoline (K305) with that of a placebo in adult patients who required restorative treatments on teeth numbers 4 to 13 (according to Universal tooth numbering system).[17] The primary outcome variable was the ability to complete the restorative procedure without the use of a rescue injection for dental anesthesia. The study reported overall success rates of 88% and 28% for K305 and placebo respectively. Participants in the K305 group experienced rhinorrhea (57.0%) and nasal congestion (26.0%). No serious adverse effects were observed in the study. The researchers concluded that K305 was effective and was well tolerated during restorative procedures in adult participants. The combination of Tetracaine/ Oxymetazoline (Kovanaze, St. Renatus USA) received FDA approval on June 29th 2016.

EFFICACY OF INTRANASAL SPRAY ANESTHESIA

In our study twenty one (21) patients had successful anesthesia by two or three intranasal sprays while in nine patients anesthesia could not be achieved by intranasal means. These patients were anesthetized using conventional injectable anesthesia. Success rates of 70% were computed for Lidocaine Xylometazoline combination spray in our study (Table 2).

SG Ciancio et al. compared the anesthetic effects of three different intranasal mists for anesthetizing maxillary anterior & premolar teeth for restorative procedures.[35] They compared the anesthetic success rates of tetracaine/oxymetazoline group with tetracaine only group and placebo. They concluded that the combination spray of tetracaine/ oxymetazoline yielded success rates of 84% in contrast to tetracaine and placebo groups, that yielded success rates of 27% each.[35] In another study Ciancio et al[36] reported success rates of tetracaine oxymetazoline combination at 83.3%.

In another study conducted by Hersh et al.[37], they reinstated the anesthetic success rates of tetracaine/ oxymetazoline combination to be in the range of 83-90% with fair tolerability. They concluded that intranasal 3% tetracaine plus 0.05% oxymetazoline provided sufficient dental anesthesia to complete restorative dentistry procedures in maxillary premolar, canine and incisor teeth.

Kumar et al. assessed the knowledge, attitudes and practices regarding the use of nasal spray anesthesia by dental practitioners in Chennai, India.[38] He reported that the knowledge and use of intranasal spray anesthesia amongst Indian practitioners was limited and further awareness/ publication of data was required to encourage practitioners to use newer modalities of achieving local anesthesia.

Capetillo J. et al. in their study (2019) studied the anesthetic efficacy of intranasal 3% tetracaine and 0.05% oxymetazoline (K305) in maxillary teeth. They had concluded that the anesthetic success for the Kovanaze nasal spray and mock infiltration (22%–37%) was significantly lower when compared to the anesthetic success of mock nasal spray and lidocaine infiltration (89%–91%).[26] More unwanted adverse effects (like nasal drainage and congestion, sensation of burning, pressure sensation, and sinus congestion) were reported by the study participants after the Kovanaze nasal spray and mock infiltration than after a mock nasal spray and maxillary infiltration. More study participants(56%) preferred anesthesia via the nasal spray route as opposed to a standard infiltration (44%) before participating in the study. Once the study participants experienced both the routes of administration, all of the study participants preferred to receive the standard infiltration anesthesia.

Jasdev Bhalla et al. in their study evaluated the effect of time on the clinical efficacy of topical anesthesia. They concluded that topical anesthetic use reduces the pain of needle insertion if left on palatal mucosal surface for 2, 5, or 10 minutes, but has no significant clinical pain relief for anesthetic injection.[39]

In another study conducted by Masoud Parirokh et al. evaluating the effect of topical anesthesia on pain during needle penetration and infiltration injection, published in Journal of Endodontics[40], they concluded that the use of topical dental anesthesia had no significant effect on pain during either needle penetration or injection.

Hence previous two studies enable us to state that topical anesthesia does not alleviate the need for an infiltration injection and thus cannot be considered an alternative to the use of intranasal spray anesthesia, which enabled us to perform restorative procedures on maxillary anterior teeth with ICDAS 4 and 5 lesions without the need for an injection anesthesia. Moreover the mechanism of action of topical anesthesia is numbing of the mucosa and submucosa[41] whereas intranasal spray anesthetic is up taken from the nasal mucosa and absorbed by the maxillary sinus leading to anesthesia of the ASA and MSA nerves.

Lidocaine/ Xylometazoline combination is commonly used in nasal cavity for various routine otorhinolaryngology procedures like transnasal fiber optic laryngoscopy and transnasal upper gastrointestinal endoscopy.[42] The dental anesthetic effects of this combination have not been assessed to date. Therefore we, in our study aimed to find the dental anesthetic effects of lidocaine/ xylometazoline combination. We could only compare the local anesthetic effects of intranasal lidocaine xylometazoline solution with that of tetracaine/oxymetazoline group (Kovanaze) or with conventional infiltration anesthesia. We can also assess the nasal anesthetic effects of lidocaine xylometazoline combination intranasal spray.

As displayed in Table 2, the results of our study showed that there is a statistically significant difference in the anesthetic effectiveness of lidocaine/xylometazoline combination when compared to conventional dental injection anesthesia. The spray anesthesia yielded success rate of 70% (21 of 30) while injectable anesthesia had a success rate of 100% (30 of 30). The p-value computed is 0.02 which illustrates that there is a statistically significant difference in anesthetic efficacy of intranasal spray anesthesia and injectable local anesthesia. Thus the null hypothesis of our study is rejected.

This is in contrast to the study carried out by Hersh et al. that showed success rate of 88% for tetracaine oxymetazoline spray anesthesia.[17] The higher success rates of tetracaine may be attributed to its composition, i.e., tetracaine being an ester as opposed to lidocaine belonging to amide group, which may have an effect on the greater efficacy of tetracaine. Higher success rates of tetracaine/ Oxymetazoline group were also recorded in a study carried out by G.C Sebastian et al. who reported that the combination spray was more effective in producing pulpal anesthesia for maxillary anterior & premolar teeth than tetracaine only spray or placebo.[35]

Higher success rates for infiltration anesthesia may be attributed to the deposition of anesthetic solution near the teeth apices. Since the thickness of buccal cortex is approximately only 0.7-1.8 millimeters[43], in case of an infiltration injection the local anesthetic is administered in proximity to the apices of the teeth. On the contrary, the distance of first premolar apices from the sinus floor is 8 to 9 millimeters[43] and the apices of anterior teeth apices are 19 millimeters distant from the nasal floor.[44] As is evident by the data, the local anesthetic delivered via an infiltration injection has to travel a much shorter distance in order to reach the apices of these teeth as compared to an intranasal spray, which is administered into the maxillary sinus. This may also be one of the reasons why we have observed a higher anesthetic efficacy of infiltration anesthesia than intranasal spray anesthesia in our study.

Noorily et al assessed topical nasal anesthetic effects of cocaine, lidocaine and tetracaine.[45] He concluded that tetracaine had greater decrease in pain perception in the nose than with cocaine or lidocaine.

Somewhat lower success rates of lidocaine xylometazoline combination in our study as compared to Tetracaine oxymetazoline combination (70% vs. 88%) are warded off by the merits offered by lidocaine.

Easy availability, cost effectiveness, fewer side effects and unavailability of tetracaine in Pakistan all make lidocaine a suitable agent to be used for intranasal spray use.[46]

EFFECT OF AGE ON THE EFFICACY OF INTRANASAL SPRAY ANESTHESIA

The study participants were categorized into two age groups, 18-25 years old and 26 to 40 years old. There was no statistically significant difference of age group on the efficacy of spray anesthesia ($p>0.99$), as shown in Table 3. This non-significant difference may be due to inclusion of a fewer number of patients who were in the age bracket 18-25 years. Amongst 30 patients from the spray anesthesia group, 04 were aged 18-25 years while 26 patients were aged 26-40 years. The range between 18-25 years is also smaller as opposed to 26-40 years.

The results from a study conducted by Hersh et al on intranasal tetracaine and oxymetazoline are in accordance with our study, who also concluded that there was no significant difference of age group on the efficacy of spray anesthesia.[17] In another study performed by Ciancio et al. they also reported no significant difference of age on the efficacy of intranasal spray anesthesia.[35] They compared the anesthetic success rates of three different intranasal mists for maxillary anterior & premolar teeth: tetracaine/oxymetazoline spray, tetracaine only spray and placebo.

EFFECT OF GENDER ON THE EFFICACY OF INTRANASAL SPRAY ANESTHESIA

In our study, the spray anesthesia group had 13 male patients while 17 female patients. Out of which 77% of the males and 65% females were successfully anesthetized by intranasal spray anesthesia (Table 4). Statistical analysis revealed that the gender had no statistically significant effect on the efficacy of intranasally delivered spray anesthesia (p=0.691). There is no literature available to compare gender variable on the success of intranasal spray anesthesia.

Although the difference between the two genders is not statistically significant, the difference in success rates, as evident from the percentages may be attributed to a number of reasons. Females have a lower pain threshold and greater dental anxiety than their male counterparts. Meechan et al[47] in their study compared the differences between male and female regarding their attitudes with respect to dental local anesthesia amongst students at a dental institute in UK. They concluded that female students had greater dental anxiety when receiving or administering local anesthesia as compared to their male counterparts.

Wahid et al[48] in their study also endorsed the fact that more female patients had severe dental anxiety as compared to male patients (9% vs. 5%). Thus the comparatively lower success rates of intranasal anesthesia in females may be attributed to this reason.

EFFECT OF TOOTH NUMBER ON THE EFFICACY OF INTRANASAL SPRAY ANESTHESIA

Another parameter of our study was to assess any difference of tooth number on the efficacy of intranasal spray anesthesia. Out of 30 patients who were administered spray anesthesia, 05 patients had a second premolar, 08 had a first premolar and 17 patients had either a canine or central/lateral incisor that had to be anesthetized by spray anesthesia. By spray anesthesia, 60% second premolars, 63% first premolars and 77% of the anterior teeth were anesthetized effectively. However data analysis revealed that there was no statistically significant effect of tooth number on the efficacy of intranasal spray anesthesia (p=0.637) as shown in Table 5, but the difference in success rates in terms of percentages is evident.

Ciancio et al[35] in their study also reported lesser success rates for premolar teeth. Hersh et al[17] also reported success rates of tetracaine oxymetazoline combination for second premolars in range of 60-66% as opposed to success rates of 88%[17] for this product in maxillary premolars and anterior teeth combined. This variation in anesthetic efficacy may be attributed to the fact that the MSA nerve is present in only 72%[49] of the population. When this is the scenario, the second premolars receive their innervation from the PSA and the first premolars are innervated via the ASA. Intranasal anesthetic delivery system is not as efficient in anesthetizing the PSA branch of the maxillary nerve owing to its farther distance from the maxillary sinus.

EFFECT OF ICDAS SCORE ON THE EFFICACY OF INTRANASAL SPRAY ANESTHESIA

In this study we also investigated whether the size of the cavity had any role on the efficacy of intranasal spray anesthesia. The spray anesthesia group had 11 patients who had a cavity with ICDAS score of ‘4’, 15 patients had cavities with ICDAS score ‘5’, whereas only 04 patients had cavities with ICDAS score of ‘6’. 91% patients with cavity classification ‘4’and 11% patients with cavity classification ‘5’ were successfully anesthetized by spray anesthesia. None of the patients with cavity sized ‘6’ were anesthetized by means of intranasal spray anesthesia. Statistical analysis also showed that there was a highly statistically significant difference of cavity classification on the effectiveness of intranasal spray anesthesia. The p-value computed was 0.002 (Table 6) which symbolizes that the result is significant at 1%. Hence, we conclude from the results, on the basis of frequency and percentages that the smaller sized cavities, i.e., ICDAS score 4 and 5 had a greater chance of getting anesthetized by intranasal spray anesthesia than larger sized cavity with ICDAS score 6.

None of the published literature on intranasal spray anesthesia has investigated any effect of cavity depth on the success of intranasal spray anesthesia.

Our study only had 04 patients with ICDAS cavity size ‘6’ thus reducing the number of larger sized cavities in the study to investigate its effects. Inclusion of fewer patients in this category may be due to our inclusion criteria that did not allow any patients with Irreversible pulpitis, since such large cavities usually invade the pulp space.

Failure of intranasal spray anesthesia in ICDAS ‘6’ cavities may be due to less remaining dentin thickness at the base of such cavities and during dentin instrumentation more of the odontoblastic processes are activated leading to dentin sensitivity and pain.[50]

EFFECT OF CAVITY CLASSIFICATION ON THE EFFICACY OF INTRANASAL SPRAY ANESTHESIA

The distribution of patients in different cavity classifications was homogenous apart from cavity classification V, which had none in the spray anesthesia group.

CLASS I CAVITY:

A total of 07 patients were administered intranasal spray anesthesia out of which 06 were successfully anesthetized yielding success rates of 86%. (Table 7)

CLASS II CAVITY:

A total of 06 patients were administered intranasal spray anesthesia out of which only 02 were successfully anesthetized yielding success rates of 33%. (Table 7)

CLASS III CAVITY:

A total of 09 patients were administered intranasal spray anesthesia out of which 08 were successfully anesthetized showing success rates of 89% for spray anesthesia

CLASS IV CAVITY:

A total 08 patients were given intranasal spray anesthesia out of which 05 (63%) were successfully anesthetized.

CLASS V CAVITY:

None of the patients with cavity classification V were part of the intranasal spray anesthesia group.

The higher success rates for intranasal spray anesthesia were reported in cavity classifications III with 89% and class I with success rates of 86%. This is the first study that has assessed the effect of cavity classification on the efficacy of intranasal spray anesthesia.

We assume that the higher success rates in class I and class III cavities may be due to the size of the lesion, restricting its proximity to the dental pulp thus increasing the prospects of successful achievement of local anesthesia by intranasal spray.

NUMBER OF INTRANASAL SPRAYS REQUIRED TO ACHIEVE LOCAL ANESTHESIA

In our study we administered two intranasal sprays spaced 4 minutes apart. Anesthesia was then assessed. If the anesthesia was found to be ineffective a third dose was given ten minutes after the administration of second dose. The results of our study revealed that out of 30 patients who were part of the study group, 11 patients were successfully anesthetized by two doses of spray anesthesia. The remaining 19 patients had to be given a third dose of spray anesthesia out of which 10 were successfully anesthetized while 09 had to be anesthetized by conventional injectable anesthesia. There was no statistically significant association of number of sprays on the efficacy of intranasal spray anesthesia ($p=0.11$).

No literature is currently available that has probed the effect of number of sprays and the efficacy of intranasal spray anesthesia.

From the results of this study we conclude that it is advisable to administer three doses of intranasal spray anesthesia to achieve adequate anesthetic effect since therapeutic dose of the drug is given in these three doses.

ADVERSE EFFECTS OF SPRAY LOCAL ANESTHESIA

The adverse effects of spray local anesthesia were also assessed in the study. Out of 30 patients who were part of the spray anesthesia group, only 04 patients experienced minor rhinorrhea after administration of spray anesthesia. Rhinorrhea was self-limiting and lasted only for a few minutes after spray dose administration. The vital signs in these patients remained within normal limits during and after the procedure. None of the patients from the injectable anesthesia group had any major complications. There was no statistically significant effect of either spray or injectable anesthesia group on occurrence of treatment emergent adverse effects ($p=0.112$) as depicted in Table 9.

In their study Hersh et al[17] reported nasal discomfort as an adverse effect that also is a known adverse effect for oxymetazoline that is commonly used as an over the counter nasal decongestant at doses similar to the ones used in this study. Another adverse effect seen in the study was the occurrence of rebound nasal congestion. K305 caused a modest but overall non-significant change in the cardiovascular parameters in clinical setting. The variations in Systolic and Diastolic Blood Pressure are most likely linked to the oxymetazoline component of the formulation, since it causes a vaso constrictor effect owing to its postsynaptic alpha 2 receptor agonist effects.

In the study conducted by Ciancio et al[35] they observed nasal discomfort, rhinorrhea, nasal congestion but fortunately, most of the effects were mild in nature. Most of the patients had regained their baseline parameters after 24 hours of drug administration. The mean deviation in blood pressure readings was significantly higher in the K305 group versus placebo. The differences may be linked to oxymetazoline's mechanism of action which is a sympathomimetic drug and causes selective agonization of α1 & in part α2 adrenergic receptors leading to an episode of vasoconstriction.[51]

The last two studies reveal that Oxymetazoline, being an α-2 receptor agonist, has its own share of demerits. Therefore, in our study we have investigated the role of Xylometzoline in conjunction with Lidocaine, for anesthetizing maxillary teeth for restorative procedures.

This solution of combination intranasal spray seems promising for use to anesthetize maxillary anterior & premolar teeth for restorative procedures in patients having a stable medical history.

LIMITATIONS

1. The sample size could have been increased to further assess the efficacy of spray anesthesia agent.
2. Blinding was not possible due to two different treatment modalities, i.e. intranasal spray and infiltration injection.
3. Since the dental anesthetic effects of Lidocaine/ Xylometazoline intranasal spray combination have not been assessed before for restorative procedures, we have limited literature available to compare the results of our study with those of others.

STRENGTHS OF THE STUDY

1. Our study is a randomized controlled trial where every possible step was taken to control confounders, e.g; Randomization was done between intervention and control groups.
2. This is the first study that has used lidocaine xylometazoline combination intranasally for` anesthetizing maxillary teeth for restorative procedures.
3. This study provides a needle less solution for anesthetizing maxillary incisors, canine and premolar teeth thus reducing dental anxiety in needle phobic patients.
4. The results of our study may help us pave way for anesthetizing maxillary teeth for smaller carious lesions with much ease, alleviating the need for an infiltration anesthesia.

5. This study has used intranasal spray containing lidocaine as key component, which is easily available, cost effective and besets the de merits of tetracaine (ester) that is a vital component of Kovanaze nasal spray anesthesia.

CONCLUSION

Lidocaine xylometazoline intranasal spray solution was fairly efficacious in anesthetizing maxillary anterior & premolar teeth for restorative procedures. The intranasal solution can be more predictably used for smaller carious lesions (ICDAS size 4 or 5) and for anterior teeth and premolars in patients with stable medical history. The combination spray of Lidocaine (amide) and xylometazoline was used in our study instead of tetracaine (ester) that yields fairly successful anesthetic rate, thus avoiding the harmful effects of esters. Intranasal spray solution can be promising for patients with needle phobia who avoid dental visits due to fear of getting an injection, and as a result deteriorate their oral health to a point of no return.

RECOMMENDATIONS

- The study can be done with a larger sample size to further assess the success rates of intranasal spray anesthesia.
- Further clinical trials should be performed to assess the anesthetic success rates of this intranasal solution
- Comparison of this intranasal spray may be done with Kovanaze as a control group.
- The study can be performed on pediatric patients since they are the subjects most vulnerable to needle phobia.
- Homogenous age and gender based groups may be formed so as to better assess any role of age group on the efficacy of intranasal spray anesthesia.
- Our study measured anesthetic efficacy on the basis of subjective assessment only (by means of VAS). Anesthetic efficacy in future studies may be assessed by means of an objective tool, e.g., an electric pulp tester.

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

-Ethical approval was obtained by Institutional Review Board Dow University of Health Sciences via Letter # IRB-1004/DUHS/Approval/2018/47. The same is attached in Appendix IV.

-Informed and understood consent was obtained from all study participants. Consent forms, both in English and Urdu (regional) language are appended in Appendix II & III.

-All methods were performed according to relevant guidelines and regulations.

CONSENT FOR PUBLICATION

Informed consent for publication of identifying images in an online open-access publication was obtained from the study participant whose pictures are presented in the manuscript.

AVAILABILITY OF DATA AND MATERIALS

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

COMPETING INTERESTS

The authors declare that they have no competing interests..

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AUTHOR'S INFORMATION

Umair Wahid has been serving as a lecturer in a public sector university of Karachi since last 8 years. He specializes in the field of Endodontics and restorative dentistry.

AUTHOR'S CONTRIBUTIONS

1. DR UMAIR WAHID: PRINCIPAL INVESTIGATOR AND MANUSCRIPT WRITING
2. DR FARAH NAZ: SUPERVISION AND GUIDANCE
3. DR ATHER AKBER: MANUSCRIPT DRAFTING AND FORMATTING
4. DR HIRA AKHTAR: LITERATURE REVIEW
5. DR ANUM TANWIR: RESULT INTERPRETATION
6. MR WAQAS FAROOQUI: STATISTICAL ANALYSIS

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Figures

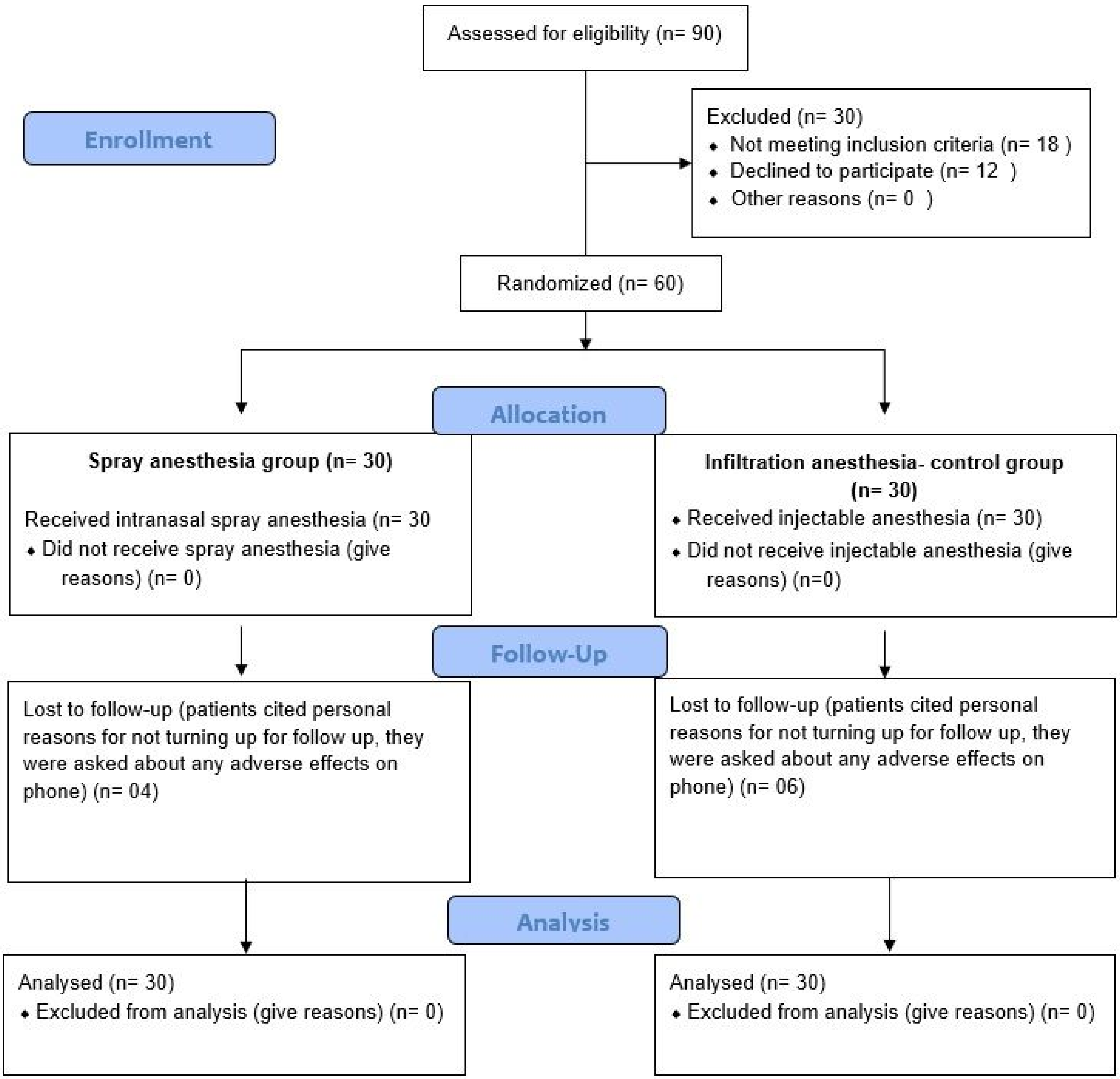

Figure 1

CONSORT Patient Flow Chart

Figure 2

(i & ii): Alcohol sniff test

Figure 3

Administration of first dose of spray anesthesia

Figure 4

Administration of second dose of spray anesthesia

Figure 5

Assessment of spray anesthesia

Figure 6

Infiltration local anesthesia

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AppendixFiles.pdf