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A Perspective Double-Blind Randomized Multifactorial Clinical Study Comparing 2% Lidocaine and Adernaline With 4% Prilocaine and Felypressin

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Abstract: ***Introduction: Lidocaine with Adrenaline and Prilocaine with Felypressin are both available from the Ministry of Health Saudi Arabia. However, both formulations are well documented and found to be clinically safe in numerous clinical studies. This study focused on determining the efficacy of 2% lidocaine and adrenaline in comparison with 4% prelocaine and felypressin local anesthetic agents for dental Extractions in completely healthy ASA class1 patients. Material and Methods: A total of 460 Patients (all ASA type 1) between age group 18 to 60 were divided into two main groups as group 1(lidocaine 2%) and group 2 (prilocaine 4%). These Two main groups were further divided into two subgroups Mg1 (Maxillary group) and Mg2 (mandibular group). The patients were randomized and equally distributed by an assisting nurse whereas the administrating physician and the patients were blind regarding the choice of anesthetic agent. In the Mg1 group the local anesthesia technique used was buccal and palatal infiltration, whereas in Mg2 group inferior alveolar nerve block and buccal infiltration were used. The comparison criteria were: 1) Latency or Onset of anesthesia, 2) The amount of anesthetic agent used, were 3) Need to re-anaesthetize the surgical zone (number of times), 4) Pain perception during procedure on a visual scale of 1 to 10, The results of each group were collected tabulated and subjected to statistical analysis. Results: The results showed that the onset of local anesthesia in buccal infiltration was better with Prilocaine 4% at 0.95 minutes, but time (anesthesia) required for achieving the full effect of local anesthesia was almost similar in both groups. Significant difference was found in the amount of anesthetic solution required to achieve full anesthesia. Prilocaine 4%was required in much higher quantity compared to Lidocaine 2%. Conclusion: In our study, we wanted to compare the success of anesthesia (absence of pain) in both groups. We found that Lidocaine with adrenaline was found to be more superior to prilocaine with felypressin for dental extractions. The amount of Anesthetic solution required to achieve full anesthesia was significantly higher in Prilocaine 4%. The higher number of injections causes discomfort to the patient so we recommend using Lidocaine 2% in healthy ASA class 1 patients.***

Keywords: adrenaline, felypressin, lidocaine, local anesthesia, prilocaine

1. Introduction

The discovery of local anesthesia was a boon to dental practitioners. The administration of local anesthesia in the determined area rather than the whole body fends off the person from feeling pain. Even though the pain during dental treatment can be successfully controlled, it remains a great fear among patients.

There are many local anesthetics available to dentists, as well as a variety of ways to deliver them, to prevent pain.[1] Many factors influence the successful outcome of local anesthetics, include increased difficulty in anaesthetizing teeth in the presence of inflammation, variable susceptibility of different teeth to local anaesthesia and anatomical variations, different operative procedures performed on the tooth (for example, it appears easier to achieve successful anaesthesia for dental extractions than for root canal treatment), and various techniques and solutions used to give the local anaesthetic.

In dental treatment, the commonly used local anesthetics preparations are lidocaine to which the vasoconstrictor adrenaline is added and prilocaine to which the vasoconstrictor felypressin is added.[2] Dental surgeons often use adrenaline-containing local anaesthetic solutions to reduce bleeding during surgery, and to lengthen the duration of action of the local anaesthetic.[3]

Lidocaine 2% with Adrenaline 1:100,000 (Xylocaine) is considered the standard for comparison with all other local anesthetics.[4] Lidocaine is the prototypical amide anesthetic agent and is similar to prilocaine in its clinical profile. prilocaine is an amide-type LA and is slightly less potent and considerably less toxic than lidocaine as an LA agent. Prilocaine produces less tissue vasodilation than lidocaine and can be used reliably in plain solution form for short-duration procedures.[5]

Felypressin consequently achieves a longer duration of action. However, felypressin is a synthetic hormone with properties similar to vasopressin. Unlike adrenaline, felypressin does not cause ischemia at the distal or site of injection. It is especially suitable for patients with contraindications to the use of sympathomimetic solutions. The superiority of lidocaine and epinephrine over buccal injection of prilocaine and felypressin in maxillary extraction is still not 100% clear.[6]

Hence this study is conducted to compare 2% lidocaine and adernaline with 4% prilocaine and felypressin for preventing pain during dental treatment or during an experimental study, and whether this effect occurred quickly or lasted a sufficient length of time, if any unwanted effects occurred, and people's experience of the dental procedures. Local adverse events might include pain during or after injection, or long-lasting anaesthesia.

Aims
This study aims to compare the efficacy of 2% Lidocaine with Epinephrine versus 4% Prilocaine with felypressin as a local anesthetic in dental extraction.

2. Materials and Methods

Ethical approval:
The study was registered with the Department of public health, ministry of Health, Hafar al Batin. Ethical Approval of the Ministry of Health's Ethics Committee was taken before starting the study. Informed written consent of the patients who were willing to participate in the study was taken.

Method
The present study is a perspective double-blind randomized multifactorial clinical study. It involves 460 patients reporting Department of Public Health, Ministry of Health, Hafar al Batin.

The case selection of the study is done based on the following criteria: 1) patients requiring extractions either in maxilla or mandible. 2) Patients without any systemic diseases. 3) Non-smokers and non-alcoholics. 4) Both males and females are included and females should not be pregnant.4) No history of allergy to any anesthetic agents.

Exclusive criteria: 1) patients with a history of smoking. 2) Subjects not willing to participate in the study. 3) Patients who have been on any long-term medication.

A total of 460 Patients (all ASA type 1) between the age group 18 to 60 who satisfied the above criteria, and who were willing to participate in the study were divided into two main groups as group 1 and group 2. The patients selected in the study were randomized and equally distributed by assisting nurses.

The instructions were explained to each patient before the procedure, indicating the aims of the study. The patients were explained to tell the pain caused by actual injection not the transdermal insertion of the needle. The injection was performed by single surgeon. The administrating physician and the patients were blind regarding the choice of anesthetic agent. The anaesthetic solutions used in this study are 2% lignocaine with adrenaline and 4% prilocaine with felypressin. Group 1 was injected with 2% lidocaine and the group 2 was injected with 4 % prilocaine.

These Two main groups were further divided into two subgroups as M1 (Maxillary group) and M2 (mandibular group). In the M1 group the local anesthesia technique used was buccal and palatal infiltration, whereas in M2 group inferior alveolar nerve block and buccal infiltration were used. After the injection the patient was asked to record the level of pain perceived on a visual analog scale, where 1 = no pain and 10 = worst pain experienced. After the procedure was done, the nurse disclosed which anaesthetic agent was used and a data was entered in the sheet and the following criteria were compared among the groups

The comparison criteria's were:
1) Latency or Onset of anesthesia,
2) The amount of anesthetic agent used,
3) Need to re-anaesthetize the surgical zone (number of times),
4) Pain perception during a procedure on a visual scale of 1 to 10,

The results of each group were collected tabulated and subjected to statistical analysis.

3. Results

A total of 460 patients were participated in the study and a comparison of 4 criteria was done among the two groups.

Statistical analysis:
SPSS 23 version has been used for statistical analysis. Descriptive statistics was done to assess the mean and standard deviation. Frequency and percentage distribution were also used in descriptive statistics. Intergroup comparison has been done by independent sample t-test to determine the mean difference between the groups. Statistical significance has been kept at $p < 0.05$. A total sample of 460 patients in which 230 sathe mples were present in each group. Both the groups were compared based on filtration techniques at maxilla and mandible. The assessment methods were observed and evaluated.

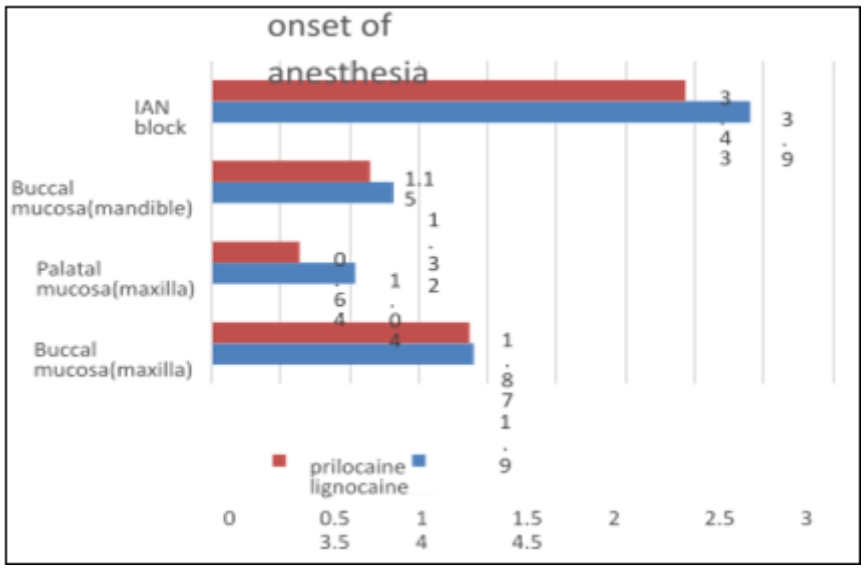
On evaluating the pain perception during a procedure on the visual scale of 1 to 10 between the groups of lignocaine and prilocaine. A statistical significance was observed at visual scale ranges from 1 to 4 ($p<0.05$) and no significant difference was observed at 5 to 10 range ($p>0.05$). (Table 1)

Table 1: Pain perception during a procedure on a visual scale of 1 to 10

Pain Scales	Buccal infiltration	Palatal infiltrataion	Buccal infiltrate ion	IAN block	Buccal infiltratation	Palat al infiltrataion	Buccal infiltration	IAN block	P value
	Lidocaine				Prilocaine				
	Ma xill a		Mandible		Maxilla		Mandible		
	N (%)				N (%)				
1	9 (3.91)	10 (4.34)	9 (3.91)	7 (3.04)	8 (3.47)	10 (4.34)	8 (3.47)	9(3.91)	0.032*
2	8 (3.47)	9(3.91)	7 (3.04)	8(3.47)	3 (1.30)	8 (3.47)	4 (1.73)	7 (3.04)	0.021*
3	9(3.91)	7 (3.04)	8 (3.47)	7 (3.04)	9 (3.91)	6 (2.60)	9(3.91)	2 (0.86)	0.045*
4	5 (2.17)	8 (3.47)	10 (4.34)	10 (4.34)	8 (3.47)	7 (3.04)	5 (2.17)	10 (4.34)	0.039*
5	3 (1.30)	7 (3.04)	6 (2.60)	3 (1.30)	8 (3.47)	9(3.91)	8 (3.47)	7 (3.04)	0.271
6	3 (1.30)	6 (2.60)	4 (1.73)	4 (1.73)	6 (2.60)	5 (2.17)	4 (1.73)	3 (1.30)	0.310
7	7 (3.04)	4 (1.73)	7 (3.04)	2 (0.86)	7 (3.04)	5 (2.17)	7 (3.04)	4 (1.73)	0.299
8	4 (1.73)	5 (2.17)	6 (2.60)	5 (2.17)	5 (2.17)	6 (2.60)	7 (3.04)	4 (1.73)	0.304

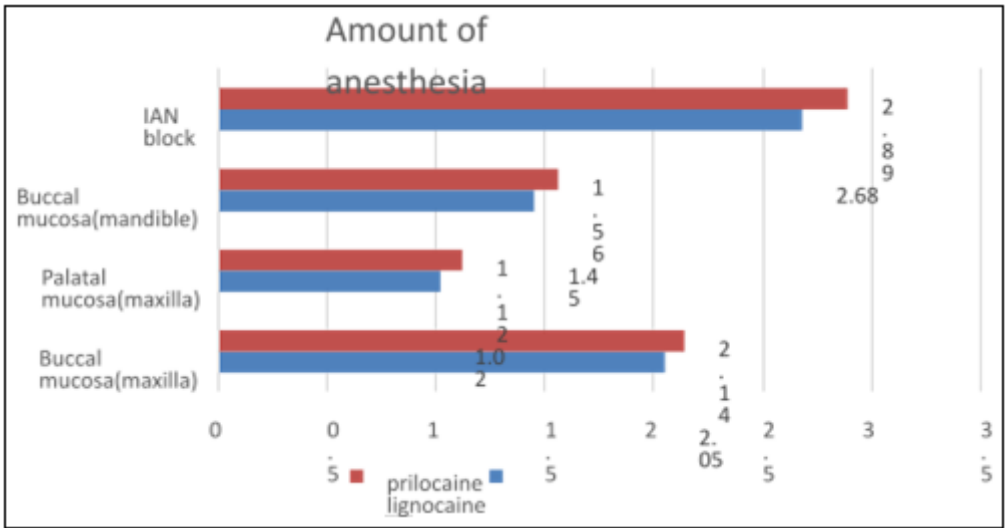
9	3 (1.30)	3 (1.30)	5 (2.17)	4 (1.73)	2 (0.86)	4 (1.73)	5 (2.17)	2 (0.86)	0.419
10	2 (0.86)	2 (0.86)	2 (0.86)	2 (0.86)	2 (0.86)	2 (0.86)	3 (1.30)	2 (0.86)	0.211
Total	230				230				

A Comparison was done between the mean time of first numbness observed by the patients in lidocaine and Prilocaine infiltration groups. In the lignocaine group, on comparison between buccal mucosa and palatal mucosa in the maxilla, the mean observed is 1.90 (0.21) and 1.04 (0.13) respectively. On comparison between buccal mucosa and IAN block in the mandible in the lignocaine group, the mean of onset of anesthesia observed is 1.32 (0.42) and 3.90 (0.32) respectively. In prilocaine group, On comparison between buccal mucosa and palatal mucosa in the maxilla, the mean observed is 1.87 (0.30) and 0.64 (0.24) respectively. On comparison between buccal mucosa and IAN block in the mandible in the prilocaine group, the mean of onset of anesthesia observed is 1.15 (0.38) and 3.43 (0.29) respectively. On intergroup comparison, there was a statistically significant difference was observed between lignocaine and Prilocaine groups of p =0.041*. (Graph 1)



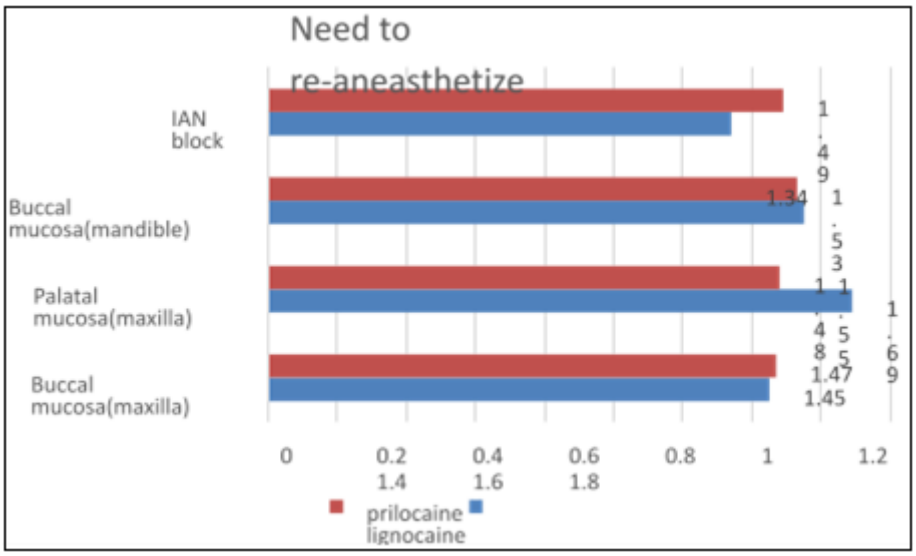
Graph 1: A comparison of onset of anesthesia between two groups

A Comparison was done between mean time of amount of anesthesia observed by the patients in lidocaine and Prilocaine infiltration groups. In lignocaine group, on comparison between buccal mucosa and palatal mucosa in maxilla, the mean observed is 2.05 (1.66) and 1.02(0.47) respectively. On comparison between buccal mucosa and IAN block in mandible in lignocaine group, the mean of onset of anesthesia observed is 1.45(0.48) and 2.68(1.75) respectively. In prilocaine group, on comparison between buccal mucosa and palatal mucosa in maxilla, a mean observed is 2.14 (1.78) and 1.12(0.58) respectively. On comparison between buccal mucosa and IAN block in mandible in prilocaine group, the mean of onset of anesthesia observed is 1.56(0.69) and 2.89(1.89) respectively. On intergroup comparison, there was a statistically significant difference was observed between lignocaine and Prilocaine groups of p =0.002*. (Graph 2)



Graph 2: Comparison of the amount of anesthesia used to get the effect of anesthesia in two groups

A Comparison was done between mean time of re-anesthetize observed by the patients in lidocaine and Prilocaine infiltration groups. In lignocaine group, on comparison between buccal mucosa and palatal mucosa in maxilla, a mean observed is 1.45 (0.32) and 1.69 (0.47) respectively. On comparison between buccal mucosa and IAN block in mandible in lignocaine group, the mean of onset of anaesthesia observed is 1.55(0.34) and 1.34(0.29) respectively. In prilocaine group, on comparison between buccal mucosa and palatal mucosa in maxilla, a mean observed is 1.47(0.29) and 1.48(0.30) respectively. On comparison between buccal mucosa and IAN block in mandible in prilocaine group, the mean of onset of anesthesia observed is 1.53(0.34) and 1.49(0.32) respectively. On intergroup comparison, there was no statistically significant difference was observed between lignocaine and Prilocaine groups of p =0.129*. (Graph 3)



Graph 3: Comparison of the amount of anesthesia used to re-anesthetize the area to achieve the effect between the two groups.

Both the groups have shown significant differences at the onset of anesthesia and the amount of anesthesia used for infiltration whereas evaluating the need of re -anesthesia has shown similar results in the lignocaine and prilocaine groups. The pain perception was maximum in 1 to 4 ranges of pain scale in both the groups and few participants have observed pain 5 to 10 pain scale range

Our study showed the success of anesthesia was better with 2% lidocaine in all groups compared to 3%prilocainegroup. The onset of anesthesia was quicker in 3%prilocaine in buccal infiltration compared to 2% lidocaine. In the 3% prilocaine group, the amount of anesthetic agent and the need to reanesthetize the area required was significantly higher than 2% lidocaine.

4. Discussion

There are sustained efforts in the field of dental local anesthetic research to find the optimal local anesthetic that can be used safely for normal and medically compromised patients. Local anesthetics are agents that cause a localized, reversible loss of sensation, upon the area of administration and the technique used. Local anesthesia causes, and reduces pain, and provides safe and comfortable dental treatment for patients. The success of a dental procedure depends on the success of the local anesthesia induced. Local anesthetics are normally associated with loss of pain in bone and soft tissue during surgical intervention.

Lidocaine and prilocaine are amide local anesthetic agents but prilocaine is less toxic and vasodilator than lidocaine.[7] Lignocaine is the gold standard and the most commonly used local anesthetic solution worldwide

The present double-blind randomized multifactorial clinical study aimed to compare the effectiveness of 2% lidocaine with adrenaline and 4% prilocaine with felypressin in dental anesthesia procedures. We assessed various outcome measures, including the latency of anesthesia onset, the amount of anesthetic agent used, the need for re-anesthetization, and patients' pain perception during the procedure on a visual scale of 1 to 10.

Pain Perception:
The assessment of pain perception on a visual scale of 1 to 10 revealed an interesting pattern. Both lidocaine and prilocaine demonstrated significant differences in pain perception within the 1 to 4 range, with lidocaine generally outperforming prilocaine. This result corroborates existing literature suggesting that lidocaine is a potent and reliable local anesthetic. However, no significant differences were observed in the 5 to 10 pain scale range.

Our findings align with several studies comparing lidocaine and prilocaine for dental anesthesia. Lidocaine is considered the gold standard for many dental procedures due to its established efficacy and safety profile. Clinically, palatal injections were more painful than buccal infiltrations in the maxilla and IAN is more painful than buccal infiltrations in the mandible.

Onset of Anesthesia:
Our study revealed that prilocaine had a faster onset of

anesthesia in buccal infiltration compared to lidocaine which showed a statistical difference of P=0.002. This is consistent with the pharmacological properties of prilocaine, which is known for its shorter onset time.

The dissociation constant value of prilocaine (pKa 7.7) is slightly lower than lidocaine (pKa 7) It means prilocaine there are more uncharged LA base molecules present to diffuse more through the neural cortex than lidocaine, and therefore, the onset time will be.[8] The quicker onset of prilocaine may be advantageous in situations where a rapid induction of anesthesia is crucial. However, it's important to note that the clinical significance of this difference should be considered in light of the other outcome measures.

Amount of Anesthetic Agent Used:
While prilocaine exhibited a faster onset of anesthesia, our data showed that lidocaine required significantly less anesthetic agent to achieve the desired effect. This result may have important clinical implications, as using a lower volume of anesthetic solution can reduce the risk of systemic toxicity and may also be more cost-effective.

The difference in the amount of anesthetic agent used between lidocaine and prilocaine likely stems from their distinct pharmacokinetic and pharmacodynamic properties. Lidocaine is well-established as an effective and efficient local anesthetic agent, and our findings support its reputation. Reducing the amount of anesthesia used is desirable from both safety and economic perspectives, making lidocaine an attractive choice for dental practitioners.

Need for Re-Anesthesia
Surprisingly, our study did not reveal a statistically significant difference in the need for re-anesthetization between the lidocaine and prilocaine groups. This result suggests that while prilocaine may offer a faster onset of anesthesia, it does not necessarily prolong the duration of anesthesia beyond what lidocaine provides

Brown and Ward, compared 4% prilocaine versus 2% lidocaine with 1: 100,000 epinephrine for maxillary infiltrations and found that 4% prilocaine had a shorter duration of anesthesia, hence there is a need to re-anesthetize the area for long procedures.[9]

The need for re-anesthetization may be influenced by various factors, including patient variability, the type and duration of the procedure, and individual pain thresholds. Further investigation is needed to explore the specific clinical scenarios in which one agent might be favored over the other in terms of re-anesthetization requirements.

This can be because the molecular structures of lidocaine and prilocaine are nearly the same. Both of them have a benzene ring and a similar degree of lipid solubility. The potency of the LA agent is determined by the degree of its lipid solubility. Greater lipid solubility enhances diffusion through the nerve.[10]

On the other hand, Gazal G27 mentioned that prilocaine has a smaller vasodilator effect than lidocaine, thus overcoming the weakness of felypressin as a vasoconstrictor and promoting a long-lasting anesthetic effect. In that sense, he recommended its use as an alternative for cardio-vascular patients in dental treatment.[11]

5. Clinical Implications

The results of this study have several clinical implications. Lidocaine appears to be the preferred choice for achieving effective anesthesia with a lower anesthetic volume, consistent with its established use in many dental procedures. On the other hand, prilocaine and its faster onset of action may make it valuable in situations where rapid induction of anesthesia is critical. When choosing an appropriate local anesthetic, physicians must carefully consider the specific clinical context, procedure and expected duration, and individual patient factors.

6. Limitations

Several constraints of this investigation must be recognized. Initially, the outcomes are derived from a distinct group of patients and a specific range of dental treatments. Variations in individual patient reactions, disparities in dental procedures, and patient attributes could potentially affect the applicability of our discoveries. Furthermore, the examination did not delve into potential negative occurrences or systemic consequences of these localized anesthetics, which is a crucial aspect of their clinical application.

7. Conclusion

The study concludes that 2 lidocaine with adrenaline is more effective than 4 prilocaine with felypressin for dental extractions, offering quicker onset, reduced anesthetic quantity, and improved patient comfort. The selection of these agents should be based on specific clinical requirements and patient needs.

Further studies and clinical studies are needed to validate these results and explore additional factors that may influence the selection of local anesthetics in various dental clinical settings. It is worth noting that the results of this study may help dentists select the most appropriate local anesthetic based on the specific needs of the patient and procedure. However, the final decision should always be made in consultation with the patient, taking into account individual differences and clinical considerations. Further research is needed to examine the efficacy and safety of these anesthetics in a broader range of dental procedures and patient populations.

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