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A Comparison of Centbucridine and Lidocaine with Adrenaline as Local Anesthetic Agents in Dental Procedures: A Randomized Controlled Trial

Snehal Ingole[1], Dhanashree Jadhav*[2], Deepashree Meshram[1], Anand Mohan Nikunj[3], Rushabh Rameshbhai Makwana[4], Mohan Deshpande[1]

[1]*Department of Oral and Maxillofacial Surgery, Nair Hospital Dental College, Mumbai 400008, Maharashtra, India.*

[2]*Dentistry Department, Bharat Ratna Atal Bihari Vajpayee Medical College, Pune, India.*

3Department of Oral and Maxillofacial Surgery, Government Dental College and Hospital, Raipur, India.

[4]*Consultant Oral and Maxillofacial Surgeon, Anantaay Oral and Maxillofacial Surgery Clinic, Bharuch, Gujarat, India.*

Abstract

Lidocaine with adrenaline is the most commonly used local anesthetic agent under routine clinical settings, However, its use is contra-indicated in certain medically compromised patients. Hence, there is a need to develop safer alternatives to lidocaine that is not much taxing on the cardiovascular system. A total of 50 participants requiring bilateral extraction of molars were injected with lidocaine with adrenaline and Centbucridine on either side respectively. The onset, depth and duration of anesthesia, post-operative bleeding, and pulse rate and blood pressure alterations were recorded at baseline and post-injection. A statistically significant difference was observed in the onset, depth, and duration of anesthesia between the two agents with higher values in the Centbucridine group ($p<0.05$). No significant difference was observed in the postoperative bleeding levels and no patients required additional suturing to control the hemorrhage in either group. The average pulse rate reported before and after injection with lignocaine was 80.52 +_ 6.152 and 82.88 $\pm$ 6.641 respectively while those before and after injection with centbucridine were 80.48 $\pm$6.370 and 84.52+_ 6.152. The alteration in pulse rate was found to be statistically significantly higher in the patients injected with Centbucridine. The onset of the anesthetic effect, its depth, and duration of Centbucridine are higher than lidocaine, indicating that the former is a more potent local anesthetic agent. Further research is recommended before it can actually replace the currently used gold standard anesthetic lidocaine.

Keywords: Anesthesia; Oral Surgery; Dental Extraction; Nerve Block

Full length article **Corresponding Author*, e-mail: jadhavdhanashree88@gmail.com

1. Introduction

Achieving adequate pain control with minimum systemic side effects during oral surgical procedures is of paramount importance for dentists which significantly influences the patient acceptance of treatment, cooperation, and well-being. Lidocaine is the most commonly employed local anesthetic agent for dental procedures because its properties are closest to that of an ideal local anesthetic agent [1]. Its rapid onset of action coupled with the intermediate duration of action makes it suitable for surface, infiltration, and block anesthesia in oral surgical procedures.

While the incidence of allergic reactions is low following the use of lidocaine, its vasodilatory effect can lead to high levels of the drug in the blood[2]. To avoid increased Perfusion of the drug, lidocaine is routinely used with a vasoconstrictor such as epinephrine to decrease its absorption rate at the injection site and subsequently prolong the duration and depth of anesthesia. The use of vasoconstrictors may be contraindicated for a subset of medically compromised patients such as those with hypertension. Furthermore, patients with cardiovascular problems may be sensitive to this concentration of epinephrine in lidocaine [3]. The use of lidocaine with epinephrine may be contraindicated in such patients. Thus, there has been a constant endeavor to develop equally effective but safer alternatives for the so-called 'gold standard anesthetic' lidocaine.

Centbucridine, a quinolone derivative, is one such alternative local anesthetic agent with local anesthetic action. It has the advantage of having an inherent vasoconstrictor property and yet not affecting the cardiovascular system except when administered at very large doses[4]. The Central Drug Research Institute of India concluded that Centbucridine has a longer duration of action, better cardiovascular stability, and antihistaminic activity and is four to five times more potent as an anesthetic as compared to lidocaine[5].

Not many studies have compared this relatively novel local anesthetic agent to the gold standard in dentistry. In this context, the present study aimed to compare the efficacy of 0.5% Centbucridine HCL to 2% lidocaine HCl with adrenaline as a local anesthetic agent for dental extraction. The study has the objectives to analyze the various parameters associated with the local anesthetic effect of Centbucridine such as the time required for the onset, depth, and duration of the anesthetic effect, and its vasoconstriction ability, and compare it with those of lidocaine. The study also has an objective to address the safety concerns regarding the use of Centbucridine by analyzing its systemic effects, particularly on the cardiovascular system, toxicity, allergic reaction, and any other adverse effects produced by the use of the drug.

2. Materials and methods

The present randomized clinical trial was conducted from March 2014 to August 2015after due approval from the institutional ethical committee. The study population comprised a total of 50 patients (26 females and 24 males) requiring bilateral extraction of erupted mandibular molars. Only healthy subjects (according to ASA –I classification) of ages ranging from 18 to 60 years were included. Patients with systemic or mental conditions and pregnant females were excluded from the study. Those having a history of recent acute infection, radiotherapy to the jaws or hypersensitivity reaction were also excluded.

Informed consent was obtained from the patients considered eligible for inclusion in the study following which their baseline systolic and diastolic blood pressures and heart rates were recorded. For each patient, one quadrant was used as the control side where 2% Lidocaine Hydrochloride with 1: 200000 adrenaline (Makcur laboratories limited) was injected by pterygomandibular block type local anesthesia. The other was used as the experimental side which was injected by the same technique using 0.5% Centbucridine HCl (Anablock, Themis Medicare) each ml of which contained 5mg Centbucridine HCl. There was a minimum interval of one week between the two procedures. The selection process of the participants in both study groups is depicted in Figure 1. The effect of anesthesia was subjectively and objectively assessed over all three branches of the mandibular nerve including the inferior alveolar nerve, lingual nerve, and the long buccal nerve. Objective confirmation of the effect was confirmed by a pin-prick test using a 20-gauge sterile needle which was applied over the attached gingiva of the molar tooth to be extracted and probing buccal and lingual gingival and mental foramen region. The onset of anesthesia was also confirmed subjectively when the patient first described numbness or a tingling sensation over the lower lip and lateral margin of the tongue. The time of onset of anesthesia and subsequent systolic and diastolic blood pressure and heart rate after achieving the anesthetic effect was noted.

The depth of anesthesia was recorded using a visual analog scale. Minimal mucoperiosteum reflection was done and the extraction was carried out using appropriate dental extraction forceps under standard aseptic precautions. An appropriately sized pre-weighed cotton to serve as a pressure pack was placed over the socket for 45 minutes and then weighed to measure blood loss. The blood pressure and heart rate were recorded again at this point in time.

In both groups, the duration of the anesthetic effect was marked by the return of pain sensation since the time of onset of the anesthetic effect was noted. Discomfort, adverse effects, and any signs of an allergic reaction including itching, redness, and localized edema during the procedure were recorded. Additional doses of LA, if required, were also noted.

All patients were discharged after ascertaining hemostasis 45 minutes post-extraction. They were instructed to avoid rinsing for the next 24 hours, maintain good oral hygiene, and take adequate rest. Mild analgesics and antibiotics were prescribed over a 3-day course and the patients were asked to report back in case of bleeding, pain, or discomfort. A review was performed during the follow-up visit on the third-day post-surgery to check for the healing of the socket.

3. Results and Discussions

The age of the participants in the present study ranged from 21 to 40 years with a mean age of 29.92 $\pm$ 6.49 years. The values for the onset and duration of the two respective local anesthetic agents are summarized in Table 1. A statistically significant difference ($p<0.05$) was noted for the onset and duration of anesthesia of the two agents. p-value for the t-test between the mean onset of anesthesia of the two agents was found to be less than 0.05 indicating that the onset of anesthesia is significantly higher in 0.5% Centbucridine than that in 2% Lidocaine. The p-value for the t-test is less than that of 0.05 for the duration of anesthesia as indicated by the time after which analgesia is required indicating that the duration of anesthesia is significantly more in Centbucridine than that of 2% Lidocaine. The depth of anesthesia of lidocaine was 2.48$\pm$ 0.544 and that of Centbucridine is 3.10$\pm$ 0.647.The depth of anesthesia achieved was found to be statistically significantly more ($p<0.05$)by Centbucridine as compared to Lignocaine. The mean values for depth of anesthesia and post-extraction bleeding are tabularized in Table 2. A statistically non-significant difference was noted in the post-operative bleeding levels achieved by the two anesthetic agents while none of the cases in either group required additional management of post-surgical hemorrhage by sutures. The values for systolic and diastolic blood pressure before and after injection of the respective anesthetic agents are comprehensively summarized in Table 3. A statistically significant increase in systolic and diastolic blood pressure after the use of lidocaine with adrenaline ($p<0.05$).

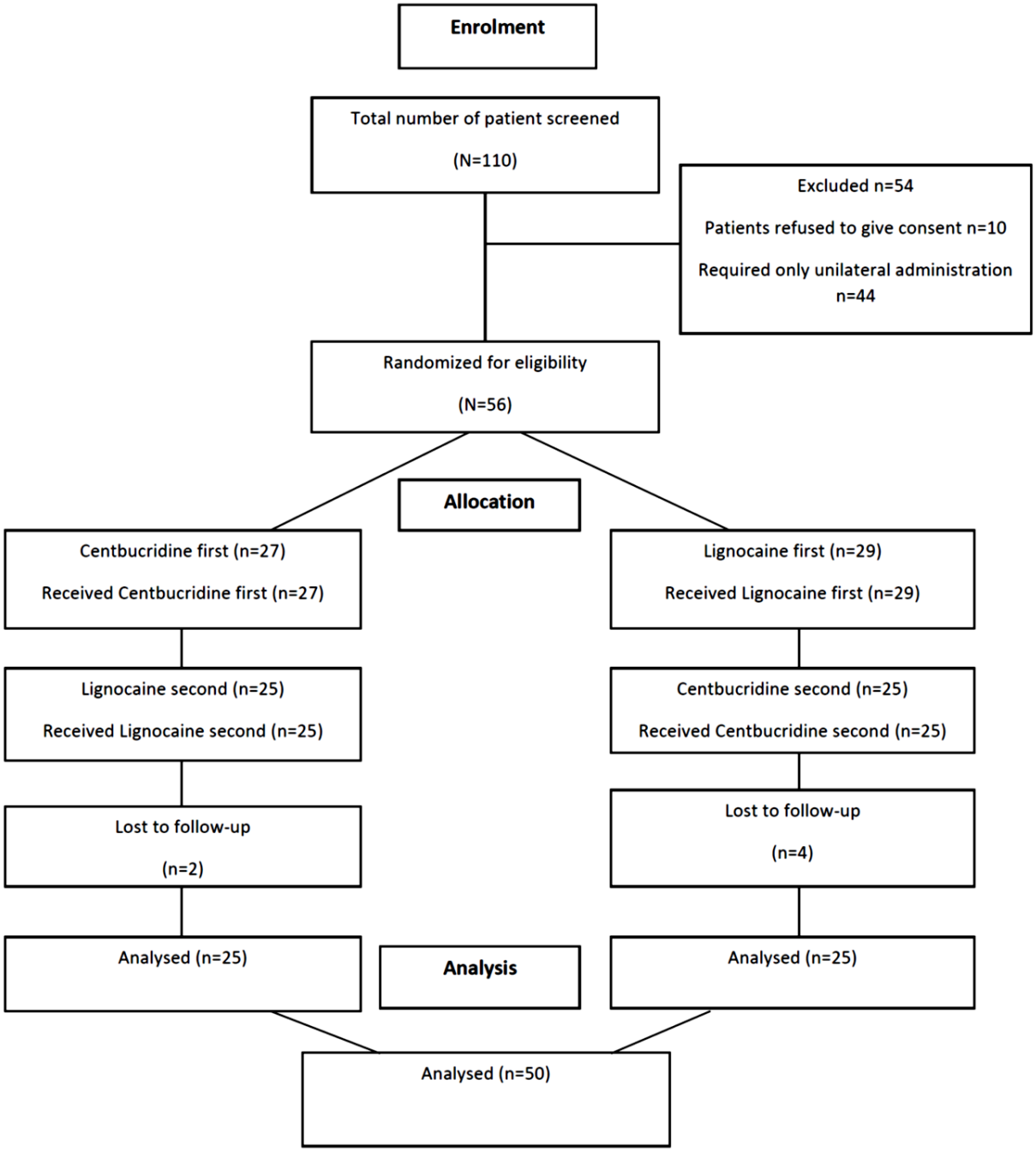

Figure 1: Flow diagram indicating the selection process of the participants in both groups in the present randomized controlled trial

There was a statistically non-significant difference between the systolic as well as diastolic blood pressure of the participants before injection indicating that the baseline characteristics of the participants in the two respective groups

were identical. The increase in blood pressure after injection was found to be statistically significantly higher ($p<0.05$) in the Centbucridine group. The average pulse rate reported before injection with lidocaine plus adrenaline was 80.52 ±6.152 and that before extraction was 82.88± 6.641. Also, the average pulse rate before injection with Centbucridine reported was 80.48 ±6.370, and that before extraction was 84.52+_ 6.152. The change in pulse rate was found to be significantly higher ($p<0.05$) in patients injected with Centbucridine as compared to those administered with lignocaine. No side effects were observed in patients in the lidocaine group while only two patients in the Centbucridine group experienced vomiting and dizziness after injection; however, the difference was statistically non-significant.

Small doses of lidocaine have a mild bronchodilating effect. Centbucridine is a novel anesthetic agent that has tetrahydroacridine as its basic chemical moiety instead of amides or esters that are generally present in other local anesthetic agents [4,5]. Owing to this difference in the basic chemical structures, it does not exhibit any danger of cross-sensitivity with available local anesthetic agents and also, no specific contraindications have been identified for its use. While most of the properties of lidocaine match that of an ideal local anesthetic agent, it can have certain toxic effects on the cardiovascular system which are not recorded in the short-term duration of most of the studies including the present one. Furthermore, the chemical possesses inherent vasodilating properties which reduce the depth as well as the duration of the anesthesia. Consequently, a vasoconstrictor is used in conjunction with lidocaine which is most commonly adrenaline in a concentration of 1:80000 to 1:200000. While the addition of a vasoconstrictor prolongs the duration of the anesthesia it has prominent adverse effects in certain sensitive individuals or those suffering from systemic illnesses and its use may, thus, be contraindicated [3]. Centbucridine, on the other hand, has been reported to elicit a pressor response endowing it with a vasoconstrictor ability[6]. This property of Centbucridine fulfilled the existing need to develop a local anesthetic agent that possessed inherent vasoconstrictive ability without affecting the stability of the cardiovascular system. While varied concentrations of Centbucridine starting from as low as 0.0125% could be used for the purpose of achieving local anesthesia, its effect is dose-dependent and the optimal infiltration anesthetic effect has been reported with the use of a concentration of 0.5% [7]. Further support of the statement was provided by a study conducted by Gupta et al. in 1989 which found that the depth and efficacy of Centbucridine as a local anesthetic agent was significantly better in a concentration of 0.5% as compared to 0.25%[8].Therefore, a concentration of 0.5% Centbucridine was used in the present study. The solution is stable in the solid form for more than 40 months at room temperature while the aqueous solution of 0.5% concentration remains viable for about 18 months. The onset of anesthesia was measured on the ipsilateral mental foramen region and the contralateral labial mucosa similar to the methodology followed by an earlier study by Gune and Katre with similar settings [9]. While in the present study, we observed an average time of onset of the anesthetic effect to be 3.7 minutes (223 seconds), earlier studies have reported the time to be less than two minutes. [Mansuri et al.[10] - 162 seconds, Dugal et al.[11] - 116.54 seconds, Gune and Katre [9] - 61.77 seconds]. The lower duration of onsets reported could be due to differences in the populations and techniques of anesthesia across the various studies. While the onset of action was slower for Centbucridine, a matter of a few seconds for the onset of a local anesthetic agent does not make much of a difference in the real clinical situation. Earlier studies have reported the duration of the anesthetic effect of Centbucridine to range from 91 to 151 minutes [9-11]. In the present study we found this value to be slightly higher with the average duration of the effect being about 163 minutes. This duration was found to be significantly higher than that of lidocaine. Since unlike lidocaine, there is no adjunctive vasoconstrictor used along with Centbucridine, the prolonged duration can be solely attributed to the chemical compound. The depth of anesthesia was gauged by the use of a visual analog scale in the present study which is a widely accepted scale for the subjective assessment of pain. In the present study, it was found that Centbucridine achieved a significantly greater depth of anesthesia as compared to lidocaine. This finding was in contrast to that from earlier studies that did not find any significant difference between the two chemicals in terms of depth of anesthesia [9-11]. While there were some issues concerning the depth of anesthesia in patients in the lidocaine group, the surgeon did not have any particular trouble in performing the surgical procedures in general. There was a mean rise in pulse rate by 2.36 after injection with lidocaine while the rise was 4.04 after injection with Centbucridine. Previous studies have shown an increase in the pulse rate 10 minutes after administration of both drugs, however, the levels returned to normal after 20 minutes and no significant difference was seen between both the drugs during the following assessment intervals. At the end of one hour, both the drugs elicited a fall in the pulse rate without much significant difference between the two. The initial increase in the pulse rate after administration of lidocaine can be attributed to the sympathomimetic effect of the adrenaline added to lidocaine [12]. On the other hand, a dose-dependent negative ionotropic effect has been demonstrated following the administration of Centbucridine[6,13]. In the present study, systolic and diastolic blood pressure was measured before injection of anesthesia and before extraction. Also in the present study, it was found that there was a statistically significant increase in systolic and diastolic blood pressure with Centbucridine. The results further showed that the change in systolic and diastolic BP is more with Centbucridine as compared to lidocaine. Meiller et al[18]. in a study on normotensive and hypertensive patients, determined that during local anesthesia and tooth extraction, the blood pressure increased continually, though without statistical significance.[18] Ezmek et al.[19] performed a study comparing the hemodynamic effects of lidocaine, prilocaine, and mepivacaine in hypertensive patients and concluded that the systolic BP did not show statistically significant differences among the groups, but significant changes were observed in the lidocaine and prilocaine groups in diastolic BP and mean arterial pressure, though not in an increasing fashion.

Table 1: Onset and duration of anesthetic effect of Lidocaine and Centbucridine

	Group	Mean	Std. Deviation	P value
Onset (in seconds)	**Lidocaine**	207.2	57.81	.001
	Centbucridine	223.4	52.97	
Duration (in Minutes)	**Lidocaine**	138.2	19.97	0.00
	Centbucridine	163.8	19.55	

Table 2: Comparison of the depth of anesthesia and post-extraction bleeding between Lidocaine and Centbucridine

		Mean	Std. Deviation	P value
Depth of anesthesia	**Lidocaine**	2.48	.544	0.001
	Centbucridine	3.10	.647	
Post-extraction bleeding	**Lidocaine**	7.41	.81891	.687
	Centbucridine	7.47	.67091	

Table 3: Comparison of Blood Pressure between Lidocaine and Centbucridine

Parameter	Group	Mean	Std. Deviation	P value
Systolic BP	Before Injection Lidocaine	122.28	11.794	0.212
	Before Injection Centbucridine	122.00	11.321	
Diastolic BP	Before Injection Lidocaine	80.44	7.002	0.212
	Before Injection Centbucridine	80.16	7.112	
Systolic BP	After Injection Lidocaine	126.36	11.254	0.003
	After Injection Centbucridine	129.40	10.022	
Diastolic BP	After Injection Lidocaine	82.64	6.533	0.001
	After Injection Centbucridine	84.90	6.228	

They concluded that this may be due to the agents themselves or to the dental anxiety felt by the patients. In the present study, postoperative hemostasis was evaluated 45 minutes after the procedure in both groups and it was found that suturing of the extraction wound was never required to control the hemorrhage. No case of reactionary or secondary hemorrhage was reported in both groups. Furthermore, no significant difference was observed between the post-extraction bleeding of the two drugs. Lidocaine with adrenaline has been the gold standard local anesthetic agent for the extraction of teeth and minor oral surgical procedures. The use of Adrenaline along with lidocaine increases the duration and provides a bloodless field of surgery due to its vasoconstrictor action[14]. Centbucridine has an inherent vasoconstrictive property and hence, can be used in patients in whom adrenaline is contraindicated. It is only in those patients in which the use of adrenaline is contraindicated that the inherent vasoconstrictor property of Centbucridine becomes prominently advantageous.

No signs of local irritation were noted after subcutaneous injection of Centbucridine at 0.25% and 0.5% concentrations by Patnaik et al. This property can prove to be beneficial as there is a possibility of accidental intramuscular injection of the local anesthetic agent into medial pterygoid muscle, during the administration of pterygomandibular nerve block and the patient can develop post-injection trismus as seen routinely in many patients [15]. However, in the present study, the development of trismus was not observed in any patient in either of the groups. The development of trismus *per se* is the effect of the technique of injection rather than the agent. Even after the entry of a large amount of the compound into the systemic circulation, no toxic symptoms except for bradycardia were observed [16]. Therefore, Centbucridine can be considered a safe local anesthetic agent in the recommended dose for use in dentistry. In the present study we found that none of the patients injected with lidocaine experienced any side effects, however, two administered with Centbucridine experienced nausea, vomiting, and dizziness. Although the difference was statistically non-significant, findings reported by earlier researchers are also in support of the fact that Centbucridine evokes more adverse reactions as compared to lidocaine. Vachharajani et al.[17] reported that two patients in the Centbucridine group complained of giddiness. However, they did not have any alterations in blood pressure. The lack of data concerning the biotransformation of Centbucridine constitutes one of its shortcomings. Nevertheless, the drug was discerned as safe by the Central Drug Research Institute wherein the vital parameters and hematological and urine tests were found to be unaffected 24 hours after the administration of Centbucridine as a local anesthetic agent [5,11] .The present study demonstrates the potential of Centbucridine as a safe and effective local anesthetic agent. Further research regarding the drug is recommended before the novel chemical can replace the existing anesthetics used in routine clinical settings.

4. Conclusions

Centbucridine is not only as effective as lignocaine with adrenaline as an anesthetic agent but is also advantageous in medically compromised patients in which the latter is contraindicated. The onset of the anesthetic effect, its depth, and duration of Centbucridine were higher as compared to lidocaine owing to its inherent vasoconstrictor ability. While the safety concerns for the use of Centbucridine could not be completely addressed within the scope of the present study, the drug can be safely used in regular dental clinical settings without any adverse effects. Further research is recommended before it can actually replace the currently used gold standard anesthetic lidocaine.

References

[1] C. Ball, & R.Westhorpe. (2004). Local anaesthetics—the origins of lignocaine. Anaesthesia and intensive care. 32(5):611.

[2] L. Weinberg, B. Peake, C. Tan, M. Nikfarjam. (2015). Pharmacokinetics and pharmacodynamics of lignocaine: A review. World Journal of Anesthesiology. 4(2):17-29.

[3] R. Balakrishnan, & V.Ebenezer. (2013). Contraindications of vasoconstrictors in dentistry. Biomedical and Pharmacological Journal. 6(2):409-14.

[4] A. Goyal, G. Jain, A. Jain, T. Ansari, S.S. Bumb. (2013). A new era of local anaesthetic agent: Centbucridine. Archives of CraniOroFacial Sciences.1(3):40-43.

[5] Centbucridine- A novel anesthetic , summary of data CDRI, New drug no. 3 pp7.2009.

[6] A. Arivazhahan. (2021). Local Anesthetics. Introduction to Basics of Pharmacology and Toxicology: Volume 2: Essentials of Systemic Pharmacology: From Principles to Practice, pp. 255-270.

[7] Y. Gülnahar, A.L. Alpan, E. Gülnahar (2023) Articaine versus lidocaine inferior alveolar nerve block in posterior mandible implant surgeries: a randomized controlled trial. Medicina oral, patologia oral y cirugia buccal, 28(2):e108.

[8] P.P. Gupta, Y.C. Mishra, and B.N. Dhawan. Comparision of Centbucridine and Lignocaine in dental surgery. International Journal of Obstetric Anesthesia, 37(3):106-111.

[9] N.S. Gune, and A.N. Katre. (2020). Comparison of 0.5% centbucridine and 2% lignocaine as local anesthetic agents for dental procedures in children: A randomised controlled trial. The Indian Journal of Pediatrics, 87:268-274.

[10] S. Mansuri, A. Bhayat, E. Omar, F. Jarab, MS Ahmed. (2011). A randomized controlled trail comparing the efficacy of 0.5% centbucridine to 2% lignocaine as local anesthetics in dental extractions. International Journal of Dentistry, Article ID 795047.

[11] A. Dugal, R. Khanna, A.Patankar (2009) A comparative study between 0.5% centbucridine HCl and 2% lignocaine HCl with adrenaline (1: 2, 00,000). Journal of maxillofacial and oral surgery. 8: 221-223.

[12] A Eriguchi, N Matsuura, Y Koukita, and T.Ichinohe (2021) Effects of Remifentanil on Cardiovascular Stimulation Caused by Local Anesthetic With

Epinephrine: A Power Spectral Analysis. Anesthesia Progress, 68(1):10-18.

[13] V.M. Whizar-Lugo, K.L. Íñiguez-López, A.C. Cárdenas-Maytorena, C.D. Ramírez-Puerta. (2020). Local Anesthetics. Topics in Local Anesthetics, 30:1.

[14] S. Patel, M.T. Ansari, R. Mathew, P. Aggarwal, L.R .Murmu. (2022). Role of Wide Awake Local Anaesthesia in Soft Tissue Injury of Hand. Mathews Journal of Emergency Medicine. 7(2):1-7.

[15] R. Priyanga, R. Balamurugan, and P.S. Rajan (2022). Comparison of dexamethasone administration through sublingual and intramuscular routes for evaluation of pain, swelling, and trismus after impacted mandibular third molar surgery—a prospective randomized controlled study. Oral and Maxillofacial Surgery, 26(1):155-159.

[16] Y. V.Suri, and Patnaik G. K. (1983). Evaluation of Centbucridine for intravenous regional anesthesia Indian Journal of Medical Research, 77:722 — 727.

[17] G.N. Vacharajani, N. Parikh, .T Paul, R.S. Satoskar. (1983). A comparative study of centbucridine and lidocaine in dental extraction. International Journal of Clinical Pharmacology Research, 3(4):251-255.

[18] B.J. Patel, P. Surana, K.J. Patel, and B. Patel (2023). Recent Advances in Local Anesthesia: A Review of Literature. Cureus, 15(3): e36291.

[19] E.D. Odai, R.I. Ozolua, O.N. Obuekwe (2020). Anaesthetic Effectiveness of Articaine and Lidocaine with Epinephrine and Cardio-respiratory Responses in Hypertensive and Normotensive Minor Surgical Patients. Nigerian Journal of Medical and Dental Education, 2(1):1-2.