

## **A comparative study between 0.5% centbucridine and 2% lignocaine with adrenaline (1:200,000) for bilateral extraction of mandibular premolar using nerve block anesthesia: a double blind randomized controlled clinical study**

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**Received:** 06 July 2017

**Accepted:** 29 July 2017

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### **ABSTRACT**

**Background:** The purpose of the study was to compare the efficacy of 0.5% centbucridine and 2% lignocaine with adrenaline (1:200,000).

**Methods:** A clinical prospective, controlled, randomized, double blind group study was conducted on 22 patients referred for extraction of mandibular premolars, who were randomly assigned to 2 groups by the split mouth method. Before extraction of mandibular premolar, either 0.5% centbucridine or 2% lignocaine with 1:200,000 adrenaline were used for anesthesia. All the patients were given inferior alveolar, lingual, and long buccal nerve blocks. Pain on injection, onset of anesthesia, duration of anesthesia and changes in blood pressure and pulse rate were monitored and recorded.

**Results:** In our study, statistically significant difference was found between the efficacy of agents as for time for onset of anesthesia, duration of action, and changes in blood pressure and pulse rate, but no statistically significant difference was found for pain on injection between two groups.

**Conclusions:** The efficacy of centbucridine was found to be more as compared to lignocaine with adrenaline, in rapid onset of anesthesia, longer duration of action, and cardiovascular stability. There was no significant difference in the pain on injection for both centbucridine and lignocaine with adrenaline. Centbucridine can be used in medically compromised condition where adrenaline is contraindicated.

**Keywords:** Centbucridine, Lignocaine, Local anaesthetic

### **INTRODUCTION**

In dental procedures, the ability to provide adequate pain control with minimal side effects remains a major concern all over the world, even after using synthetic local anaesthetic agents in dental oral surgeries for well over a century. Lignocaine (diethyl-2, 6-acentanilol) is one of the most popular and first amide local 48 anesthetic agent. Because of its potency, safety, and effectiveness, lignocaine has become the standard for comparison among the newer agents.<sup>1</sup>

Centbucridine, a new quinolone derivative with local anesthetic action, chemically known as 4-N-butyl-amino-1,2,3,4-tetrahydroacridine hydrochloride, was developed in India and introduced by Patnaik et al at Central Drug Research Institute of India. After a multicentric trial in more than 2700 patients of various age groups, Central Drug Research institute of India, concluded that It has an inherent vasoconstrictor property and longer duration of action, better cardiovascular stability, and possesses antihistamine activity. Its potency is four to five times more than lignocaine.<sup>2-5</sup> Centbucridine produced less side effects and showed better cardiovascular stability and

hardly any sensitivity reactions. It has proven to have the same efficacy as other local anesthetic agents in ophthalmology and when used for subarachnoid blocks.<sup>6-10</sup> There has been conflicting reports regarding the onset of action and duration of action of centbucridine. Potential reasons for these contradictory results include differences in method of use, the complex and multifactorial nature of pain and its perception in human patients. The aim of this study was to compare the efficacy of 0.5% centbucridine HCl and 2% lignocaine HCl with adrenaline (1:200,000) in extraction of mandibular premolars. The study was planned to find out suitability of Centbucridine in patients, where Lignocaine with adrenaline is contraindicated due to systemic conditions.<sup>11,12</sup>

## METHODS

### *Patients*

Subjects were selected from a pool of patients admitted for regular dental treatment. The population studied was composed of patients seeking treatment for bilateral mandibular pre - molar removal. Inclusion criteria included absence of any pathologic clinical conditions related to mandibular pre - molars, physically fit (ASA 1) adult patients of either sex. All potential participants were explained the need and design of study and the new drug; and about its advantages and disadvantages. All patients gave written evidence of informed consent. Orthopantomograms were taken to ensure similarity of the tooth inclination.

### *Study design*

The protocol of this was randomized, double - blind clinical trial. A split - mouth design was employed: the right and left quadrants of the mouth constituted the experimental units and were randomly assigned to treatments groups.

Statistical efficiency was enhanced by the cross-over design of the study (i.e., each patient served as his or her own control).<sup>13</sup> The main purpose of the split - mouth design was to remove all components related to inter subject differences. By making comparison within patients, rather than between them, the error variance of the experiment was reduced, thereby allowing a more powerful statistical test.<sup>14,15</sup>

Randomization was performed based on items 8e10 of the 2001 checklist of CONSORT for randomized, controlled, clinical trials (Cochrane Collaboration, Manchester, UK).<sup>16</sup> Allocation to the 2 groups was performed by selecting from a set of sequentially numbered, opaque, sealed envelopes containing either of 2 interventions (centbucridine or lignocaine with adrenaline). Each mandibular pre - molar (right or left side) had an equal chance of being assigned to either group. The randomization process also determined which

side would undergo the first surgery. All patients received both interventions, with one for each side.

During the entire double-blind study, randomization was maintained by the same researcher (who had previous research experience).

### *Sample size calculation*

The sample size needed for sufficient statistical power was estimated with the SPSS 19. Standard deviation (SD) was 22 mm with an alpha value of 5% and study power of 90%. It was calculated that  $n = 17.1$  mandibular pre molars (approximately in each group). Considering 30% drop out, it was calculated that  $n = 44$  mandibular pre molars were needed for the study ( $n = 22$  for each treatment group).

### *Clinical parameters*

A single examiner performed all clinical measurements prior to surgery and post operatively. Pain during injection was assessed using a VAS, which consisted of a horizontal line running from 0mm (no pain) to 100mm (worse pain).<sup>17</sup> Patient were instructed to place a vertical mark on the scale that best represented the degree of pain intensity. Onset of anesthesia was recorded from the time of administration of local anesthesia to the time of appearance of numbness of soft tissues, using two point discrimination method. Duration of anesthesia was measured from onset of anesthesia to complete disappearance of numbness. Change in systolic and diastolic blood pressure were recorded by measuring blood pressure preoperatively and after 10 minutes and 30 minutes post anesthesia. Change in pulse rate was recorded by measuring pulse rate preoperatively and after 10 minutes and 30 minutes post anesthesia.<sup>1</sup>

### *Surgery procedure*

A complete case history including medical history was obtained and filled up in the preformed for each patient by the author. Centbucridine (0.5%) or lignocaine (2%) with epinephrine (1:200000) were administered after giving test dose, using nerve block anesthesia (Inferior alveolar, lingual, and buccal nerve). To minimize discrepancies in the handling of oral tissues, the same surgeon operated on each patient, using the same technique on both sides. Extraoral antisepsis was performed with 2.0% chlorhexidine. Intraoral antisepsis was performed with a 0.12% chlorhexidine rinse.

Preoperative blood pressure and pulse rate were recorded before administration of the local anesthetic.

Pain on injection, onset of action, were recorded. The blood pressure and pulse rate 10 minutes and 30 minutes after injection were recorded. After attaining adequate anesthesia extraction procedure was carried out under aseptic condition. During the extraction procedure, the patients were periodically questioned about pain. The pain

experienced by each patient was evaluated using the visual analogue scale, during and after extraction.

The teeth were extracted with the help of forceps. A pressure pack was given to achieve hemostasis.

Postoperatively, the patients were asked to record the time of complete disappearance of numbness. Appropriate postoperative instructions were given to the patients. The patients remained at the clinic for the first postoperative hour and were discharged only if there were no complications. Every patient received a leaflet where the medications were prescribed. Pain assessment was carried out by the author by making calls to the patients every hour from the first postoperative hour till the requirement of analgesics. The patients were instructed to call when they felt the first sensation of mild pain in order to know the duration of action of the anesthetic agent. The patients were prescribed amoxicillin 500mg thrice a day and Aceclofenac 100mg and Ranitidine 150mg twice a day for 3 days and were advised to take medications only after getting instructions from the author. The contralateral mandibular pre - molar was removed on the second surgical visit, which was scheduled for 2 weeks later. Patients were instructed to eat soft foods and to abstain from mouth washing for the first 24 hours post operatively. Patients were instructed to abstain from brushing and flossing around the extracted socket area until healing is satisfactory. For plaque control, patients used a 0.12% chlorhexidine mouth rinse for 1 min twice a day for 1 week. patients were seen as per the protocol for follow up at 48 post operatively. To avoid observer bias, all data

were recorded by the same independent investigator, following the blind control.

### Statistical analysis

The statistical software namely SPSS 19 were used for the analysis of the data, considering a type 1  $\alpha$  error of 0.05 and 90% power. The Kolmogorov - Smirnov test was used, parametric (paired sample t-test) or Mann whitney U test and chi square test were employed.

## RESULTS

A total of 22 individuals participated in the selection process (n=44 mandibular pre - molars were 16 needed for the study). Age range: 19-45 years; mean age 23.6±6.03 years scheduled for removal of bilateral mandibular pre molars were enrolled in the study. Twenty two mandibular pre molars were allocated to the centbucridine group, and the twenty two contralateral mandibular pre molars were allocated to the lignocaine with adrenaline group. All participants followed the instructions contained in the protocol and completed the study period. Use of the split-mouth design allowed standardization of the extraction technique, because each patient acted as his or her own control.

### Efficacy of local anesthesia

Among the 44 procedures, onset of action of two drugs was statistically significant with lignocaine group slower by 45seconds (Table 1).

**Table 1: Summary of outcome variables: comparison of efficacy of lignocaine with adrenaline and centbucridine.**

Variable	Time of measurement	Lignocaine mean±SD (n=22)	Centbucridine mean±SD (n=22)
Time of onset of anaesthesia	-	4.23±1.8	3.45±1.3*
Duration of Anaesthesia	-	117.5±4.8	142.2±7.1**
DBP	Pre-Anaes	76.23±11.86	81.09±11.99
	After 10mins	72.0±10.99	80.55±11.38
	After 30mins	76.82±14.11	80.77±11.37
P -value		P <0.05	P >0.05
SBP	Pre-Anaes	123.4±10.8	125.09±9.62
	After 10mins	119.9±7.67	123.82±8.8
	After 30mins	123.2±7.28	124.00±8.77
P -value		P <0.05	P >0.05
Pulse rate	Pre-Anaes	73.09±3.4	74.55±12.4
	After 10mins	69.95±5.1	72.82±9.7
	After 30mins	69.09±9.3	72.55±14.2
P -value		P <0.05	P >0.05

\* Not significant at 5% level. \*\* Significant at 5% level

Abbreviations: DBP - Diastolic blood pressure, SBP- Systolic blood pressure, mins - minutes

The difference in mean duration of action was statistically significant. The mean values for centbucridine and lignocaine groups were found to be 142.2 minutes and

117.5 minutes, respectively, with a mean difference of 24.7 minutes, which was statistically and clinically

significant. The difference in pain on injection was not statistically significant.

#### **Cardiovascular stability (blood pressure and pulse rate)**

Systolic and diastolic blood pressure were analysed separately and compared within the group. The mean diastolic blood pressure of centbucridine group pre anesthesia was 81.09 and 10 minutes post anesthesia was 80.55 minutes and 30 minutes post anesthesia was 80.77mmHg. The change in the diastolic blood pressure was not significant.

The mean systolic blood pressure of centbucridine group pre anesthesia was 125.09mmHg and 10 minutes post anesthesia and 30 minutes post anesthesia were 123.82mmHg and 124mmHg, respectively. The change in systolic blood pressure was not significant.

The mean diastolic blood pressures of lignocaine HCl group pre anesthesia, 10 minutes post anesthesia, and 30 minutes post anesthesia were 76.2mmHg, 72mmHg, and 76.8mmHg, respectively. The change in mean diastolic pressure 10 min post anesthesia was significant.

The mean systolic blood pressures of lignocaine with adrenaline group pre anesthesia, 10 minutes post 21 anesthesia, and 30 minutes post anesthesia were 123.3mmHg, 119.9mmHg, and 123.2mmHg, respectively.

The change in mean systolic blood pressure 10 min post anesthesia and 30 minutes post anesthesia were 24 significant.

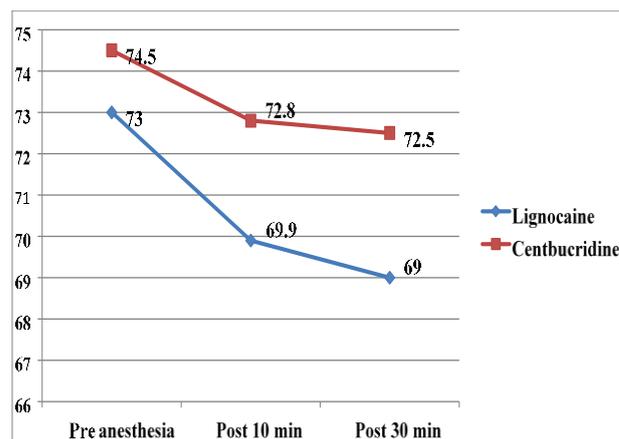
The mean pulse rates of centbucridine group pre anesthesia, 10 min post anesthesia, and 30 minutes 28 post anesthesia were 74.55, 72.82, and 72.55 per minute, respectively. The change in pulse rate for centbucridine group was not significant (Figure 1).

The mean pulse rate of lignocaine group pre anesthesia and 30 minutes post anesthesia were 73.09, 69.95, and 69.09 per minute, respectively. The change in pulse rate of lignocaine group 10 minutes post anesthesia was found to be significant ( $P < 0.05$ ). The change in pulse rates of lignocaine group 10 minutes post anesthesia and 30 minutes post anesthesia were nonsignificant ((Figure 1).

The mean difference in pulse rate between pre and post anesthesia for centbucridine was found to be less than the lignocaine group, which was statistically significant.

#### **Side effects**

Side effects like headache, dizziness and nausea seen after administration of centbucridine, which gradually resolved within 10 minutes without any medication.



**Figure 1: Distribution of mean pulse rate pre and post 10 min and 30 min local anesthesia for lignocaine with adrenaline and centbucridine.**

#### **DISCUSSION**

Certainly pain is difficult, if not impossible, to quantify. The management of pain is of utmost importance and interest in the field of dentistry. Today there are potent local anesthetic solutions available which make satisfactory pain control possible during different dental and surgical procedures. The conventional local anesthetic agents though adequate has short comings due to adrenaline, in some medically compromised patients. A local anesthetic with inherent vasoconstriction ability with prolonged duration of analgesia would be desirable. The present study compared the clinical properties of 2% lignocaine with 1:200,000 adrenaline and 0.5% centbucridine with respect to onset of anesthesia, the duration of anesthesia, pain on injection, and cardiovascular stability, measured in terms of change in systolic and diastolic blood pressures and pulse rate, and also any signs of systemic toxicity, clinically. The action of local anesthetics is dependent on the anesthetic potency, which indicates the minimal anesthetic concentration required; lipid solubility is the single most important determinant of local anesthetic potency. Highly lipid soluble local anesthetics are very potent. All clinically effective injectable local anesthetics are vasodilators resulting in increased rate of absorption of local anesthetic and decrease in depth duration of anesthesia. Vasoconstrictors (adrenaline) are added to local anesthetic solution to oppose the inherent vasodilation actions of local anesthetics.<sup>18,19</sup>

Patnaik G et al, concluded in his study that centbucridine is 4-5 times more potent as a local anesthetic agent than lignocaine. As centbucridine is four times potent than lignocaine, equal concentrations (the smaller 0.5% concentrators of centbucridine becomes equipotent to 2% lignocaine and their toxicities at these concentrations should be equal so these concentrations were used for comparison in this study).<sup>2</sup> Samir Mansuri et al, compared the efficacy of 0.5% centbucridine to 2% lignocaine and concluded that centbucridine has inherent vasoconstrictor

ability.<sup>1</sup> As centbucridine has inherent vasoconstriction ability it can be used without addition of vasoconstrictor, while lignocaine is used with 1:200,000 adrenaline to nullify its inherent vasodilating property. Dugal et al, did a comparative study between 0.5% centbucridine HCl and 2% lignocaine HCl with adrenaline (1:200,000). He concluded that centbucridine had a slightly slower onset of action, but in our study we found that centbucridine showed faster onset on anesthesia than lignocaine with adrenaline.<sup>20</sup>

Dugal et al, in their comparative study of 0.5% centbucridine and 2% lignocaine with adrenaline concluded that centbucridine has shorter duration of anesthesia than lignocaine with adrenaline but it was not significant. In our study centbucridine showed longer duration of anesthesia than lignocaine. Dugal et al, in the comparative study of 0.5% centbucridine and 2% lignocaine with adrenaline (1:200,000) found that 0.5% centbucridine did not produce significant change in blood pressure while the increase in systolic blood pressure with lignocaine was significant.<sup>20</sup> The present study also showed that centbucridine causes minimal change in intraoperative blood pressure and pulse rate as compared to lignocaine with adrenaline (1:200,000).

The change in mean systolic pressure was significant ( $P < 0.001$ ). This may be attributed to vasoconstrictor ability of adrenaline which has high affinity for receptors present in the smooth muscles of the vessel walls, stimulation of which, leads to vasoconstriction. In the present study it was seen observed that centbucridine has got no chronotropic action on the myocardium whereas with lignocaine may be attributed to the effect of adrenaline on receptors present in myocardium leading to increase in heart rate.

Swran Nithyanand studied prolonged toxicity of centbucridine and concluded that it is devoid of any toxic effects and that it is safe to administer this agent. In the present study, there was no sign or symptoms of central nervous system or any other toxicity clinically in both the centbucridine and lignocaine with adrenaline groups. Lignocaine with adrenaline has been used in every oral and maxillofacial surgery procedure for a very long time and has become the gold standard for comparing efficiency of any new local anesthetic agent.<sup>6,7</sup>

To the best of our knowledge, a comparative study between the use of centbucridine and lignocaine with adrenaline in the removal of bilateral mandibular premolars has not been published so far. Differentiation between pulpal and soft tissue anesthesia was not observed separately which may be considered as a drawback of this study.

## CONCLUSION

After reviewing the results of the study we can conclude onset of action of centbucridine is faster than that of Lignocaine with adrenaline, duration of action of

centbucridine was longer than duration of action of lignocaine. It shows sufficient efficacy as local anesthetic agent. Cardiovascular parameters showed, statistically significant changes in lignocaine with adrenaline cases, which may be attributed to the presence of Adrenaline in lignocaine injection, while patients injected with Centbucridine had good cardiovascular stability. This finding can be significant in known severe cardiac patients. Hence Centbucridine can be effectively used as an ideal substitute in place of lignocaine to patients undergoing minor oral surgical procedures, where Adrenaline is contraindicated due to systemic problems.

Additional study in known cardiac cases needs to be carried out to confirm this. This research hopes to guide the surgeons to adopt such recent advances and available pharmacological agents.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee (IGIDSIEC 2014OMFS02PGLKDP)*

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**Cite this article as:** Shrihari L, Suresh V, Yuvaraj V, Sathyanarayanan R, Shyamala M, Monica S. A comparative study between 0.5% centbucridine and 2% lignocaine with adrenaline (1:200,000) for bilateral extraction of mandibular premolar using nerve block anesthesia: a double blind randomized controlled clinical study. *Int J Basic Clin Pharmacol* 2017;6:2244-9.