Original Article

Comparative Evaluation of Effectiveness of 2% Lignocaine Hydrochloride with Clonidine Hydrochloride versus 2% Lignocaine Hydrochloride with Adrenaline Bitartrate as Local Anesthetic for Adult Patients Undergoing Surgical Extraction of Impacted Mandibular Third Molars: A Randomized Controlled Clinical Study

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Abstract

Background and Objectives: Clonidine is a common additive to local anesthetics for various regional and local nerve blocks. However, its effectiveness in dentistry has not yet been fully explored. Thus, this study was performed to evaluate the quality of anesthesia, vasoconstrictive effects, hemodynamic response, and pain control using a solution of 2% lignocaine hydrochloride with clonidine hydrochloride in comparison with the standard solution of 2% lignocaine hydrochloride and adrenaline bitartrate for pterygomandibular nerve blocks. **Materials and Methods:** A parallel arm, triple-blind randomized controlled study was conducted on 152 patients belonging to ASA-I (American Society of Anesthesiologists) category in the age group of 18-45 years, requiring surgical extraction of impacted mandibular third molars. The patients were divided equally into two groups randomly by computer-generated sequence; Group 1: 2% lignocaine hydrochloride with 1 ml of clonidine hydrochloride (150 μg/ml) and Group 2: 2% lignocaine hydrochloride with adrenaline bitartrate 1: 80,000 (12.5 μg/ml). The variables evaluated were systolic, diastolic, and mean arterial blood pressures, heart rate (HR), blood loss, onset, depth (pain), and duration of anesthesia. **Results:** There was a statistically nonsignificant difference seen between the two groups ($P > 0.05$) for the onset of anesthesia, pain assessed, and blood loss, whereas a statistically highly significant difference was seen for cardiovascular variables (systolic, diastolic and mean arterial blood pressures, and HR) at various intervals with higher values for Group 2 ($P < 0.001$) and for the duration of action of local anesthesia (LA), with higher values for Group 1 ($P < 0.001$). **Conclusions:** Clonidine as an additive to lignocaine has proved to have the onset of action, vasoconstrictive properties, and pain control, equivalent to adrenaline. However, with better stability of hemodynamic variables and prolonged duration of action of LA with clonidine, it can be considered as a better, safer, and more effective additive to lignocaine than adrenaline

Keywords: *Additives, adrenaline, clonidine, hemodynamic variables, local anesthetics*

Introduction

The eternal quest for pain control has stimulated researchers globally for innovation in the field of local anesthesia (LA). The importance of LA cannot be overstated in today's surgical and dental procedures.

The most commonly used local anesthetic agent in dentistry is lignocaine hydrochloride. However, due to its vasodilator properties,[1] a vasoconstrictor needs to be added to prolong duration of anesthetic action, to reduce systemic absorption, thereby reducing the systemic toxicity of lignocaine and to provide hemostasis. Adrenaline, a potent vasoconstrictor, serves to achieve these effects.[1] The commonly available local anesthetic solutions contain adrenaline bitartrate in different concentrations, ranging from 12.5 μg/ml (1:80,000) to 5 μg/ml (1:200,000). Even with small doses of adrenaline, there are significant cardiovascular changes in both healthy and cardiac patients.[2,3] Hence, it is prudent to limit or avoid adrenaline in poorly

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controlled American Society of Anesthesiologists (ASA)-III and all ASA-IV group of patients.[3] The use of various additives other than adrenaline has been tested in the literature for various regional and local nerve blocks.

Clonidine is both centrally and peripherally acting, selective α-2 adrenoceptor agonist.[4] By central activation of presynaptic, α-2 adrenoceptors, it decreases blood pressure and provides central analgesic activity.[4] Through peripheral activation, peripheral blood vessel vasoconstriction is achieved.[4] Clonidine has been safely used as an additive to anesthetics for a number of regional blocks in adults as well as pediatric age group. Its use in dentistry has still not been thoroughly explored.

The aim of the present clinical study was to evaluate the effectiveness of 2% lignocaine with clonidine versus 2% lignocaine with adrenaline for surgical removal of impacted mandibular third molars. The study tested the null hypothesis which stated that there is no difference in the effectiveness of 2% lignocaine with clonidine and 2% lignocaine with adrenaline in surgical removal for impacted mandibular third molars, for the outcome variables – quality of anesthesia, vasoconstriction effects, hemodynamic response, and pain control.

Materials and Methods

The study design was parallel arm, triple-blind randomized control clinical study, carried out in the Department of Oral and Maxillofacial Surgery at our tertiary care center. The sample size was calculated using the formula, $n = 2 (Z\alpha + Z\beta)^2 [s]^2/d^2$, where Zα is the z variate of alpha error, i.e., a constant with value 1.96, Zβ having a value of 0.84, considering the mean and standard deviation (SD) from the literature, that concluded approximately 76 patients per group. Approval from the Institutional Ethics Committee was obtained (no. YMTDCH/IEC/OUT/072/2017).

The inclusion criteria were ASA-I patients, between the age group of 18 and 45 years, requiring surgical extraction of impacted mandibular third molars under LA with no history of allergy to the drugs used in this research. The exclusion criteria included pregnant women, lactating mothers, any previous history of cardiovascular conditions, apprehensive patients, and patients with active orofacial infections. Patients with any other contraindication or on any medication that could possibly interact with clonidine/adrenaline were also excluded from the study. It was made sure that the study participants had not been on any medications preoperatively (1 week). Using the above, participants were randomly selected from patients requiring surgical removal of impacted mandibular third molars under LA and randomly allocated to either group by computer-generated sequence. Informed written consent was obtained from all study participants.

In the test group/Group 1, freshly prepared solution made with 9 ml of plain 2% lignocaine with 1 ml of clonidine (150 μg/ml) was used, whereas in the control group/Group 2, a standard solution of 2% lignocaine with adrenaline 1:80,000 (12.5 μg/ml) was used. The entire study was carried out by single operator and single observer who were standardized and blinded. Pterygomandibular nerve blocks were used in all cases with mandatory negative aspiration preinjection. The difficulty index of the impacted mandibular third molars was standardized as moderate level (5–7) as per Pederson's Difficulty Index[5] for both groups.

The outcome variables measured and studied were (a) cardiovascular variables (systolic blood pressure [SBP], diastolic blood pressure [DBP], mean arterial blood pressure [MABP], and heart rate [HR]) and blood loss and (b) quality of anesthesia assessed by onset, duration, and its depth. The cardiovascular variables were measured using a multiparameter monitor (IntelliVue MX 400, Philips, with more than 95% accuracy), just before LA injection and repeated at intervals of 5 min, 10 min, 15 min, 30 min, and 45 min after injection. The estimated volume of blood loss was calculated by subtracting the total quantity of normal saline used for irrigation from the total volume of fluid collected in the suction jar after the procedure. In addition to this, the difference in preoperative and postoperative weights of the used gauze pieces was also used to determine the volume of blood loss. The onset of anesthesia (in minutes) was assessed by subjective and objective symptoms of LA. The duration (in minutes) was recorded from the completion of the pterygomandibular nerve block till the first oral analgesic used by the patient. The depth of anesthesia was evaluated using the visual analog scale (VAS) to determine degree of pain during the procedure.

Statistical procedures

Data obtained were compiled on a MS Office Excel Sheet (v 2010, Microsoft Redmond Campus, Redmond, Washington, United States) and were subjected to statistical analysis using the Statistical Package for the Social Sciences (SPSS v 21.0, IBM). Descriptive statistics such as frequencies and percentage for categorical data and mean and SD for numerical data have been depicted. The normality of numerical data was checked using the Shapiro–Wilk test and was found that the data followed a normal curve; hence, parametric tests have been used for comparisons. Intergroup comparison was done using *t*-test, whereas intragroup comparison up to two observations was done using paired *t*-test. Intragroup comparison was done using repeated measures ANOVA (for >2 observations), followed by *post hoc* test. The comparison of frequencies of categories of variables with groups was done using Chi-square test. For all the statistical tests, $P < 0.05$ was considered to be statistically significant, keeping α error at 5% and β error at 20%, thus giving a power to the study as 80%.

Results

The mean age of the patients was 31.71 + 4.602 (minimum 21 and maximum 45). There were 55 (36.2%) females and 97 (63.8%) male patients.

Intergroup comparison of the mean age of the patients showed a statistically nonsignificant difference ($P > 0.05$) which also ruled out age as a confounding factor. Furthermore, the intergroup comparison of frequencies of sex of the patients showed a statistically nonsignificant difference ($P > 0.05$).

Discussion

Clonidine hydrochloride has been used in different concentrations for improvement of epidural anesthesia, brachial plexus anesthesia, and anesthesia for peripheral nerves. These studies proved and gave effective concentrations at which no significant side effects were observed.[6-8] Our study investigated the effectiveness of clonidine hydrochloride in concentration of 150 μg/ml when used with 2% lignocaine hydrochloride for pterygomandibular nerve blocks for surgical extractions of impacted mandibular third molars.

The time from completion of nerve block to postoperative consumption of the first analgesic was considered duration of action of LA. It was observed that the average value in the test group was 4 h 42 min (282.53 min), whereas it was 3 h 5 (185.42) min in the control group, both statistically and clinically highly significant [Table 1], thereby proving that clonidine was more effective in prolonging the duration of action of LA, in comparison with adrenaline. Multiple research papers by Patil *et al*.,[9] Rajkumar *et al*.,[10] and Brkovic *et al*.[3] showed findings consistent with our study.

The onset of anesthesia is a property that mainly depends on the local anesthetic rather than vasoconstrictor.[3,9,11] In our study, 2% lignocaine was used as a local anesthetic in both the groups, thus the onset of anesthesia was similar and both clinically and statistically nonsignificant. These findings of onset of anesthesia were consistent with the study done by Brkovic *et al*.,[3] Pavan Patil *et al*.,[9] and Chowdhury *et al*.[11]

The cardiovascular variables, SBP, DBP, MABP, and HR, showed a higher statistical significance between the two groups at all time intervals [Table 2]. This suggested that clonidine as compared to adrenaline provides hemodynamic stability after LA injection. The values recorded for HR were significantly stable in the test group. Unlike adrenaline, which is a nonselective alpha and beta agonist, clonidine exhibits a selective α-2 agonist activity without beta side effects on the myocardium, thus leading to no significant fluctuations in HR.[3] Dandriyal *et al*.[2] demonstrated a statistically significant difference between SBP and HR within the two groups, whereas DBP did not show any statistical significance.

The assessment of intragroup cardiovascular variables in each group at different time intervals was done using Scheffe *post hoc* test. In the study group, no statistical significance was seen, indicating stability in blood pressure and HR at various time intervals. In the control group, a statistically significant difference was seen at different time intervals, indicating the recordings to be highly fluctuant. This supports the view that clonidine is a safer and better alternative to adrenaline in terms of maintaining cardiovascular variables.

Table 1: Intergroup comparison of onset, duration, depth, and vasoconstrictive effects of local anesthesia

	Group	*n*	Mean	SD	SEM	*t*	*P* of *t*-test
Onset of local anesthesia (min)	1	76	4.80	0.401	0.046	1.142	0.255#
	2	76	4.72	0.450	0.052		
Completion of nerve block to first analgesic (min)	1	76	282.53	25.219	2.893	26.087	0.000**
	2	76	185.42	20.422	2.343		
VAS score (intraoperative)	1	76	2.506	0.6976	0.0800	−0.731	0.466#
	2	76	2.588	0.6772	0.0776		
Weight of gauze preoperative (g)	1	76	10.51	2.176	0.250	−0.240	0.811#
	2	76	10.58	0.997	0.114		
Weight of gauze postoperative (g)	1	76	12.45	2.294	0.263	−0.137	0.892#
	2	76	12.49	1.039	0.119		
Difference in weight of gauze pre- and postoperative (g)	1	76	1.93	0.957	0.110	0.187	0.852#
	2	76	1.91	0.769	0.088		
Total volume in the jar at the end of the procedure in ml (a)	1	76	441.82	101.949	11.694	7.157	0.000**
	2	76	346.58	55.367	6.351		
Quantity of normal saline used for irrigation in ml (b)	1	76	364.71	107.913	12.379	6.241	0.000**
	2	76	278.16	54.521	6.254		
Volume of blood loss (a-b=c)	1	76	75.79	32.351	3.711	1.489	0.139#
	2	76	68.95	23.641	2.712		

SD: Standard deviation, SEM: Standard error of mean, VAS: Visual Analog Scale, **Means highly significant, #Means non-significant

Table 2: Intergroup comparison of cardiovascular variables

	Group	*n*	Mean	SD	SEM	*t*	*P* of *t*-test
SBP preoperative	1	76	122.49	6.807	0.781	−5.493	0.000**
	2	76	127.30	3.476	0.399		
SBP 5 min	1	76	118.36	5.085	0.583	−32.685	0.000**
	2	76	140.89	3.207	0.368		
SBP 10 min	1	76	118.32	5.076	0.582	−39.324	0.000**
	2	76	144.38	2.761	0.317		
SBP 15 min	1	76	119.86	3.966	0.455	−40.137	0.000**
	2	76	146.03	4.073	0.467		
SBP 30 min	1	76	117.22	6.090	0.699	−27.141	0.000**
	2	76	139.59	3.813	0.437		
SBP 45 min	1	76	121.05	5.356	0.614	−17.966	0.000**
	2	76	133.24	2.503	0.287		
DBP preoperative	1	76	80.70	7.135	0.818	−1.942	0.054#
	2	76	82.53	4.061	0.466		
DBP 5 min	1	76	76.24	8.472	0.972	−15.091	0.000**
	2	76	92.66	4.266	0.489		
DBP 10 min	1	76	77.42	6.587	0.756	−18.908	0.000**
	2	76	96.79	6.030	0.692		
DBP 15 min	1	76	78.53	5.934	0.681	−27.066	0.000**
	2	76	102.32	4.848	0.556		
DBP 30 min	1	76	77.37	4.841	0.555	−21.229	0.000**
	2	76	95.76	5.799	0.665		
DBP 45 min	1	76	78.41	5.335	0.612	−14.441	0.000**
	2	76	88.59	3.056	0.351		
MABP preoperative	1	76	41.79	3.645	0.418	−5.515	0.000**
	2	76	44.78	3.000	0.344		
MABP 5 min	1	76	42.20	5.007	0.574	−6.933	0.000**
	2	76	48.24	5.711	0.655		
MABP 10 min	1	76	40.89	4.165	0.478	−8.509	0.000**
	2	76	47.59	5.453	0.626		
MABP 15 min	1	76	41.33	5.749	0.659	−2.369	0.019*
	2	76	43.43	5.193	0.596		
MABP 30 min	1	76	39.96	4.916	0.564	−4.019	0.000**
	2	76	43.83	6.801	0.780		
MABP 45 min	1	76	42.64	3.999	0.459	−2.899	0.004**
	2	76	44.64	4.492	0.515		
HR preoperative	1	76	82.75	10.172	1.167	2.607	0.010*
	2	76	79.28	5.613	0.644		
HR 5 min	1	76	75.33	9.266	1.063	−10.050	0.000**
	2	76	88.46	6.626	0.760		
HR 10 min	1	76	75.37	9.941	1.140	−12.210	0.000**
	2	76	92.72	7.398	0.849		
HR 15 min	1	76	76.51	7.387	0.847	−23.248	0.000**
	2	76	99.00	4.066	0.466		
HR 30 min	1	76	74.61	5.317	0.610		
	2	76	92.50	8.495	0.974	−15.566	0.000**
HR 45 min	1	76	77.36	4.598	0.527	−6.114	0.000**
	2	76	83.43	7.347	0.843		

*Statistically significant difference ($P<0.05$), **Statistically highly significant difference ($P<0.01$), #Nonsignificant difference ($P>0.05$) … for both tables. SD: Standard deviation, SEM: Standard error of mean, SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MABP: Mean arterial blood pressure; HR: Heart rate

Two indirect methods, namely suction jar and gauze method were used to compute and assess the vasoconstrictive property of clonidine and adrenaline. With both methods, the calculated amount of blood loss was marginally higher

for the clonidine group. However, there was no statistically significant difference between the two groups. Thus, the vasoconstrictive property of clonidine is equivalent to adrenaline. Patil *et al.* in their study concluded that clonidine could be used as a safer alternative to adrenaline considering the vasoconstrictive property.[9]

The VAS scale was used intraoperatively to evaluate the depth and intensity of LA. Although VAS scores in the clonidine group presented lower values, there was no statistical significance between the two groups. Eisenach *et al*.[12] showed a similar finding on the intensity of anesthesia when evaluated with the VAS scale.

Limitations and future scope

We had to restrict this study to ASA-I category patients based on approval from the Institutional Ethics Committee. However, more studies may be designed with larger sample sizes and including patients in ASA-II, III, and IV categories. Effects of addition of clonidine to LA may be tested with other anesthetic agents and for other orofacial nerve blocks.

Conclusions

Based on the aforementioned results of the current study, it can be concluded that clonidine as an additive to lignocaine is a better, safer, and more effective alternative to adrenaline as it maintains hemodynamic variables stable and prolongs the duration of LA effect without affecting the onset and depth of anesthesia.

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Conflicts of interest

There are no conflicts of interest.

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