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Hemodynamic changes associated with a novel concentration of lidocaine HCl for impacted lower third molar surgery

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Background: The authors studied the hemodynamic effect influent by using the novel high concentration of lidocaine HCl for surgical removal impacted lower third molar. The objective of this study was to evaluate the hemodynamic change when using different concentrations of lidocaine in impacted lower third molar surgery.
Methods: Split mouth single blind study comprising 31 healthy patients with a mean age of 23 years (range 19-33 years). Subjects had symmetrically impacted lower third molars as observed on panoramic radiograph. Each participant required 2 surgical interventions by the same surgeon with a 3-week washout period washout period. The participants were alternately assigned one of two types of local anesthetic (left or right) for the first surgery, then the other type of anesthetic for the second surgery. One solution was 4% lidocaine with 1:100,000 epinephrine and the other was 2% lidocaine with 1:100,000 epinephrine. A standard IANB with 1.8 ml volume was used. Any requirement for additional anesthetic and patient pain intra-operation was recorded. Post-operatively, patient was instructed to fill in the patient report form for any adverse effect and local anesthetic preference in terms of intra-operative pain. This form was collected at the seven day follow up appointment.
Results: In the 4% lidocaine group, the heart rate increased during the first minute post-injection ($P < 0.05$). However, there was no significant change in arterial blood pressure during the operation. In the 2% lidocaine group, there was a significant increase in arterial blood pressure and heart rate in the first minute following injection for every procedure. When the hemodynamic changes in each group were compared, the 4% lidocaine group had significantly lower arterial blood pressure compared to the 2% lidocaine group following injection. Post-operatively, no adverse effects were observed by the operator and patient in either local anesthetic group. Patients reported less pain intra-operation in the 4% lidocaine group compared with the 2% lidocaine group ($P < .05$).
Conclusions: Our results suggest that a 4% concentration of lidocaine HCl with 1:100,000 epinephrine has better clinical efficacy than 2% lidocaine HCl with 1:100,000 epinephrine when used for surgical extraction of lower third molars. Neither drug had any clinical adverse effects.

Key Words: Adverse effects; Concentration of lidocaine hydrochloride; Efficacy local anesthetic; Hemodynamic changes; Inferior alveolar nerve block (IANB); Lower impacted third molar.

INTRODUCTION

Since Swedish chemists, Nils Löfgren and Lundqvist, first found lidocaine in 1943, local anesthetics have been used routinely in dentistry [1]. Lidocaine has been stated to have low toxicity and is considered as a gold standard in local anesthetics [2-3]. However, excessive dosage of

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lidocaine with epinephrine can lead to high blood levels, which can subsequently increase cardiac output (CO), total peripheral resistance (PR), and mean arterial pressure (MAP) [2,4-5]. These side effects may be due to the presence of epinephrine in the local anesthetics, which acts as direct depressant in cardiovascular system and beta-adrenergic receptors. Significant increase in systolic blood pressure (5-12 mmHg) was observed in a patient who underwent scaling and root planning under lidocaine with 1:100,000 epinephrine [6]. Dionne et al (1984) [7] reported that 5.4 ml of 2% lidocaine with 1:100,000 epinephrine increased heart rate in 19% of the cases and cardiac output in as much as 30% of the cases. However, de Morais (2012) [5] administered 2.7 ml of local anesthetic with epinephrine 1:100,000 or 1:200,000 in surgical removal of impacted third molar. The study showed absence of hemodynamic changes that was comparable to a previous study by Santos et al (2007) [8]. There have been very limited reports regarding the influent effects in hemodynamics when using 4% lidocaine HCl for surgical removal of impacted lower third molars. Therefore, more evidence-based studies are required to Shed light on this aspect.

MATERIALS AND METHODS

The protocol for this study was approved by the Institutional Review Board on Ethics of Research in Human Beings of the Faculties of Dentistry and Pharmacy, Mahidol University (Protocol No. MU-DT/PY-IRB 2014/036.0509). Participants were provided with a verbal explanation of the study procedures, informed written consent was obtained prior to the first operation.

This was a split mouth single blind clinical trial to compare the hemodynamic effects of two different dental local anesthetic agents. Inclusion criteria were good health, aged between 18 and 35 years, no smoking habit, no high alcohol consumption, and two symmetrical impacted lower third molars requiring surgical removal (as assessed on a panoramic radiograph). Exclusion criteria were the opposite of the inclusion criteria, as well as systolic blood pressure < 90 or > 140 mmHg, diastolic blood pressure < 60 or > 90 mmHg, resting heart rate < 60 or > 100 bpm, pregnancy, lactating mother, and allergy to local anesthetics.

Following informed consent, the participants were alternately assigned to Group A or Group B. One solution was 4% lidocaine with 1:100,000 epinephrine (Jayson Pharmaceuticals Ltd.) and the other was 2% lidocaine with 1:100,000epinephrine (Novocol Pharmaceutical of Canada Inc.). Each participant required 2 surgical interventions by the same surgeon with a 3-week washout period. Each group receive a standard IAN block with 1.8 ml volume. After anesthesia was achieved another 0.5 ml volume of the same local anesthetic was injected for buccal nerve block. Then, the operation was started.

Evaluation parameters included:

A. Hemodynamic parameters (heart rate and blood pressure): measured at baseline, 1 minute post-injection, during soft tissue incision, during bone removal, and during suturing. BP cuff (Terumo cooperation Tokyo, Japen) was used to monitor cardiac and hemodynamic changes before and after delivery of local anesthetic.

B. Requirement of additional anesthetic

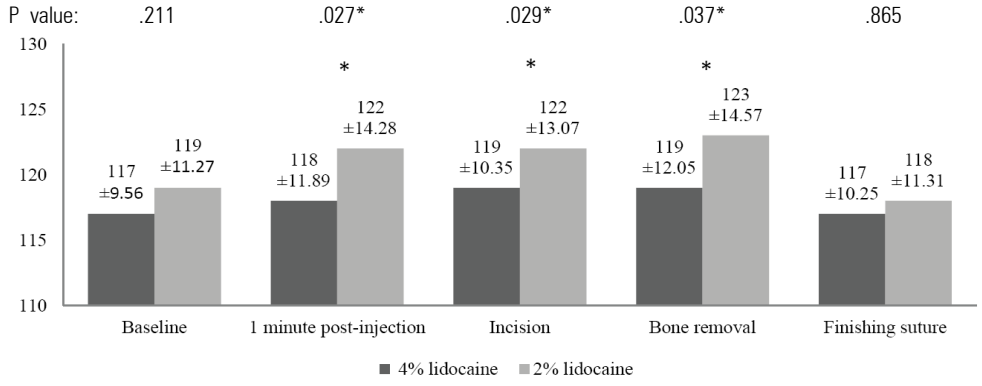
C. Adverse effects and patient preference for the type of local anesthetic, in terms of less pain intra- and post-operation (recorded on a patient report form). This form was collected at follow-up on day seven. Post-operatively, the volunteer was observed in a comfortable room for one hour, and any immediate side effects of the drug were recorded.

The Paired t-Test or Wilcoxon's signed rank test were used to compare hemodynamic changes and intensity of pain between the two groups.

Mc-Nemar's Test was used to calculate case distribution according to the type of anesthetic used and necessity for re-anesthesia with an IAN Block, and also for the number of additional anesthetic injections given.

The study sample comprised 31 healthy patients with a mean age of 23 years (range 19-33 years) with

symmetrically impacted lower third molars requiring surgical removal, as observed on panoramic radiograph. Figures 1, 2 and 3 show the hemodynamic changes occurring at different stages of the surgical intervention in each of the two groups (2% and 4% lidocaine). Systolic blood pressure was significantly higher in the 2% lidocaine group 1 minute post-injection, during the incision period, and during the bone removal period ($P < 0.05$). Diastolic arterial blood pressure was significantly higher in the 2% lidocaine group ($P < 0.05$) during the



*: significant difference

Fig. 1. Distribution of systolic arterial blood pressure (mmHg) by type of local anesthetic for different stages of the surgical procedure.

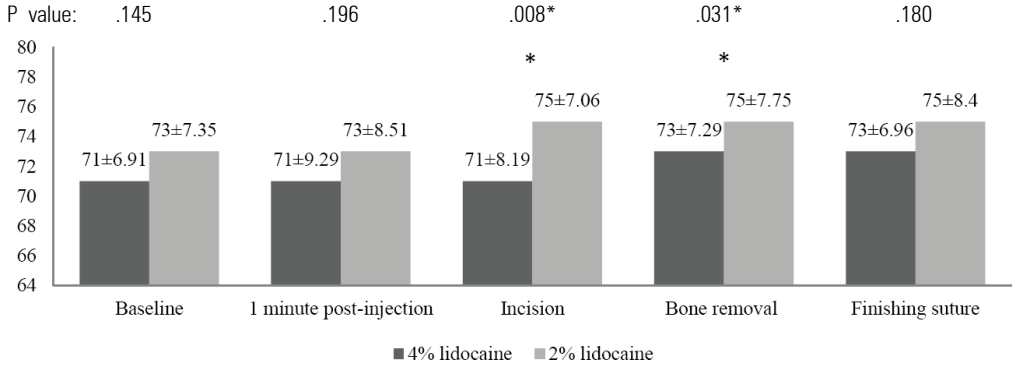


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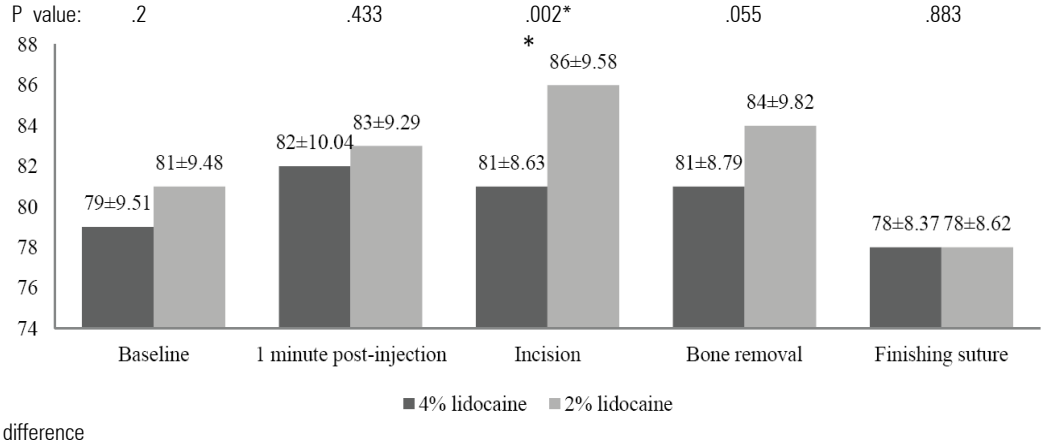
Fig. 2. Distribution of diastolic arterial blood pressure (mmHg) by type of local anesthetic for different stages of the surgical procedure.



*: significant difference

Fig. 3. Distribution of heart rate (beat/min) by type of local anesthetic for different stages of the surgical procedure.

incision and bone removal periods. Heart rate was significantly higher in the 2% lidocaine group, but only during the incision period ($P < 0.05$).

RESULTS

Tables 1 and 2 show the significance of differences in hemodynamic change at various times of the surgery, compared with the baseline. The mean heart rate in the 4% lidocaine group 1 minute post-injection (82.00 ± 10.04) was significantly higher than at baseline (79.00 ± 9.51) ($P = 0.008$).

The 2% lidocaine group had four variables with significant differences from the baseline. Systolic arterial blood pressure during soft tissue incision and during bone removal were significantly higher ($P < 0.05$). Heart rate was significantly higher during soft tissue incision and significantly reduced after suturing compared to baseline ($P < 0.05$) (Table 2) (Fig. 3).

Tables 3, 4 and 5 showed that the 2% lidocaine group required additional anesthesia significantly more often than the 4% lidocaine group (83.9%, and 51.6% of cases, respectively) ($P < 0.05$). Intra-operation, 1.8ml for the

Table 1. Comparing p-values for hemodynamic changes at each surgical stage with baseline (4% lidocaine group)

4%lidocaine	Post-injection				
	1 minute	Incision	Bone removal	Finishing suture	
Baseline	.828	.175	.132	.952	Systolic
	.950	.914	.114	.096	Diastolic
	.008*	.217	.647	.318	Heart rate

Heart rate: 1 min = 82 ± 10.04 > Baseline = 79 ± 9.51, P = .008

Table 2. Comparing p-values for hemodynamic changes at each surgical stage with baseline (2% lidocaine group)

2%lidocaine	Post-injection				
	1 minute	Incision	Bone removal	Finishing suture	
Baseline	.164	.024*	.032*	.328	Systolic
	.838	.238	.188	.297	Diastolic
	.273	.005*	.219	.023*	Heart rate

Systolic: Incision = 122 ± 14.28 > Baseline = 119 ± 11.27, P = .024
Systolic: Bone removal = 123 ± 14.57 > Baseline =119 ± 11.27, P = .032
Heart rate: Incision = 86 ± 9.58 > Baseline = 81 ± 9.48, P = .005
Heart rate: Finishing = 78 ± 8.62 < Baseline = 81 ± 9.48, P = .023

Table 3. Distribution of cases requiring additional anesthetic

	Type of anesthetic						
Additional anesthetic	4% lidocaine		2% lidocaine		Total		P value
Needed	N	%	N	%	N	%	.006*
Yes	16	51.6	26	83.9	42	67.7	
No	15	48.4	5	16.1	20	32.3	
Total	31	100	31	100	62	100	

Table 4. Number of patients needed additional anesthetic injections

Surgical procedure	4% lidocaine	2% lidocaine	P value
Repeated IANB	0	4	.046*
Incision	0	0	
Flap elevation	0	0	
Bone removal	1	3	.317
Tooth sectioning	12	24	.001*
Tooth elevation	6	12	.157
Suture	0	0	

Table 5. Total volume of local anesthetic used

Type of anesthetic	Mean ± SD (ml)	Minimum	Maximum	P value
4% lidocaine	2.49 ± 0.21	2.3	2.9	.001*
2% lidocaine	2.91 ± 0.58	2.3	4.7	

Table 6. Patient local anesthetic preference

Type of anesthetic	Less pain/more preferable		P value
	N	%	.004*
4% lidocaine	24	77.4	
2% lidocaine	7	22.6	
Total	31	100	

inferior alveolar nerve block plus 0.5 ml for the buccal nerve block of 2% lidocaine were often not sufficient to control pain. The total volume of local anesthetic used was significantly higher in the 2% lidocaine group ($P < 0.05$) (Table 5).

Table 6 shows the results of patient preference for the type of local anesthetic they were given. Significantly more participants preferred the 4% lidocaine over the 2% lidocaine for this surgical procedure ($P < 0.05$).

DISCUSSION

Participants with symmetrically impacted third molars were invited to participate in a single blind split mouth clinical trial, with a single clinical variable. All those approached agreed to participate.

Since all participants had surgery at separate times under both local anesthetics (split mouth design), this removed any possibility of selection bias. Variables such as difficulty of surgery, gender, age, anxiety and reaction to pain were all equally spread between the comparison groups. However, other similar studies investigating the effects of different anesthetic solutions in third molar surgery have not used the split mouth design, hindering comparison of the results [16,17]. Also, although there are many studies which have measured hemodynamic changes following administration of a range of local anesthetic agents, using 2% lidocaine as the gold standard, there have been a few studies comparing different concentrations of lidocaine [18-22].

1. Factors associated with increasing the hemodynamic

1.1. Anxiety

Hemodynamic variations can be affected emotional stress respond in types of dental treatment or types of anesthetic used [4,6,9,23]. There was a case report of a dental patient increasing their heart rate by 12 beats/min and systolic blood pressure by 5 or 6 mmHg while simply discussing treatment with their dentist [4].

In the present study, during the 1 minute post-injection period, a standard amount of local anesthetic solution (1.8 ml) was injected in both groups. [Therefore each group had the same concentration of epinephrine (10 μg/ml)]. However, the study found a significantly higher systolic blood pressure in the control (2% lidocaine) group. Whereas in the 4% lidocaine group the hemodynamic parameters were slightly increased, but not significantly when compared with baseline.

1.2. Pain during operation and blood level of epinephrine

Studies show hemodynamic changes are mainly related to the concentration of epinephrine in the body. This epinephrine can be either exogenous (injected) or endogenous. When a patient experiences pain or stress, epinephrine is secreted from adrenal medullar at rate of 2.5-7.5 ng/kg per minute. This rate is increased 20-40 fold when people have severe stress [5]. Likewise if there is insufficient pain control during a surgical operation, the epinephrine concentration in the body will increase.

In the present study the requirement for additional anesthetic was significantly higher in the control group ($P < 0.05$) (Table 5). Therefore, a higher epinephrine volume was administered to some of the subjects in the control group, resulting in a higher frequency of hemodynamic changes.

Lipp et al (1993) injected 2 ml volumes of local anesthetic with 1:100,000 epinephrine into the blood stream and showed that plasma levels of epinephrine increased 3 foldwithin 7 minutes of administration [6].

Troullos et al (1987) showed that the normal injection of 1 or 2 dental cartridges of local anesthetic containing 1:100,000 epinephrine (18-36 μg) resulted in the same increase in the plasma epinephrine level as the physiological activities of public speaking and moderated exercise [7]. He suggested that the use of approximately 10 cartridges of lidocaine with 1:100,000 epinephrine in healthy young patients for removal four wisdom teeth, resulted in the plasma levels of epinephrine equivalent to those found after excessive exercise, and that these levels were not appropriate for medical compromised patients. Therefore, the limited dose administration of local anesthetic should not be based on the type of local anesthetic alone; epinephrine also must be taken into consideration. However, de Morais et al (2012) [9] showed an absence of hemodynamic change following administration of 2.7ml of lidocaine with epinephrine 1:100,000 for surgical removal impacted third molars.

1.3. Type of local anesthetic

Hemodynamic changes following administration of local anesthesic can be due not only to the vasoconstrictor,but also to the agent itself. However few studies have reported on this [10-12]. Adverse cardiovascular responses to normal therapeutic doses of local anesthetic agents are generally not manifested [12]. However when high doses of lidocaine are given,both hypertensive and hypotensive reactions can occur, representing different interplays of the direct depressant actions of the drug on the myocardium, centrally mediated disturbances in autonomic function, andthe effects of hypoxia and hypercarbia [12]. Eventually convulsions may occur.

Bahadir et al (2010) [11] administered three different anesthetic solutions without vasoconstrictors during tooth extraction in hypertensive patients, and recorded mild increases in heart rate and mean arterial blood pressure. In the present study, the use of 4% lidocaine HCl with 1:100,000 epinephrine slightly elevated the heart rate post-injection but did not influence hemodynamic parameters during the operation. However administration of 2% lidocaine HCl with 1:100,000 epinephrine was associated with elevation of hemodynamic parameters without perceptible clinical adverse effect (nousea, dizziness, and headache etc) in healthy patients undergoing surgical removal impacted lower third molar. However it is not possible to know whether the hemodynamic changes were due to the epinephrine, the agent or a combination of both. This could be an area for future research.

2. Efficacy of high concentration of lidocaine and adverse effect

In the present study four subjects in the control group required repeat IAN blocks even though they reported complete lower lip numbness. Probably the dose of lidocaine was insufficient in these cases. The experimental group did not have this problem, and the subjects had a preference for the 4% lidocaine.

In this study there were no adverse complications reported immediately post-operation and at day seventh. This finding is in agreement with previous studies of lidocaine, confirming its low toxicity and place as the gold standard local anesthetic [2,3]. However, high concentrations of lidocaine can cause neurotoxicity in laboratory studies [25], although there have been no reports of neurotoxicity in humans [24].

Eldridge and Rood (1977) found that using 50 mg/ml lidocaine with 1:80,000 epinephrine for routine dental treatment did not show any clinical adverse events. Later this local anesthetic was used in the pediatric patient clinical trial and was found to be safe with no adverse reactions [21,22]. In 1978, Rood evaluated plasma levels of lidocaine,comparing injection of equal doses of lidocaine (1 ml of 5% lidocaine versus 5 ml of 1% lidocaine). After 2 hours the lidocaine plasma levels were between < 0.1–0.2 μg/ml in the 5% lidocaine group, and 0.1-5 μg/ml in the 1% lidocaine group (approaching toxic levels). The paper concluded that injection of the higher concentration of lidocaine did not produce particularly high levels of lidocaine in the plasma of healthy adults [20]. According to Becker and Reed, lidocaine toxicity may commence at plasma concentrations > 5 μg/ml, but

convulsive seizures generally require concentrations > 10 μg/ml [8]. Clinical adverse reactions were not observed in our study in either groups but the plasma levels of 4% lidocaine HCl could be measured in future research.

CONCLUSIONS

In healthy patients undergoing surgical removal impacted lower third molars, significant differences in arterial blood pressure and heart rate were found between the 2% and 4% lidocaine groups, During operation 2% lidocaine group were found significant higher than 4% lidocaine group. Use of 4% lidocaine HCl with 1:100,000 epinephrine improved the efficacy of the IAN block in the surgical removal of impacted lower third molars, without any measurable adverse effects. The 4% Lidocaine anesthetic could be a good alternative dental local anesthetic for dentists to use during surgical removal of third molars.

2% lidocaine HCl with 1:100,000 epinephrine was associated with more changes in hemodynamic parameters, although without perceptible clinical changes.

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