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COMPARATIVE STUDY

A Comparative Study Between Bupivacaine with Adrenaline and Carbonated Bupivacaine with Adrenaline for Surgical Removal of Impacted Mandibular Third Molar

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Abstract
Objectives To compare the effectiveness of bupivacaine with adrenaline with that of carbonated bupivacaine with adrenaline on pain, onset of anesthesia and duration of anesthesia following surgical removal of impacted mandibular third molar.
Study design All the patients who underwent surgical removal of impacted mandibular third molar and who fulfilled our inclusion and exclusion criteria from 1st June 2013 to 30th June 2014 were included in our study. Patients who were diagnosed as having impacted mandibular third molar were randomly allocated to two groups namely group A (bupivacaine with adrenaline), group B (carbonated bupivacaine with adrenaline). Pain during deposition of local anesthetic, onset of anesthesia and duration of anesthesia were compared between the two groups. The collected data were subjected to statistical analysis by Chi Square test, Mann–Whitney U test.
Results and conclusion The efficacy of carbonated bupivacaine with adrenaline is more compared with bupivacaine with adrenaline in decreasing pain on deposition of local anesthetic solution and in rapid onset of anesthesia. The duration of anesthesia for carbonated bupivacaine with adrenaline and bupivacaine with adrenaline had no significant difference. The use of carbonated bupivacaine with adrenaline will reduce the patient discomfort both intra-operatively and post-operatively.

Keywords Impacted third molar · Bupicaine · Alkalinisation

Introduction

Tooth is said to be impacted when it fails to erupt or develop in a proper functional position. Third molar is the last tooth to erupt in the oral cavity and may get impacted or displaced due to inadequate space for eruption. Teeth that fail to erupt in a functional position are said to be abnormal or pathological [1], which might be indicated for removal. Preoperative analgesia for surgical removal of tooth is obtained with local anesthetic solution [2–4].

Local anesthetics act by hindering the generation and conduction of nerve impulses and by blocking the entry of sodium ions into their channels, thereby decreasing the sodium permeability to the nerve membrane, resulting in conduction blockade [5]. Among local anesthetics, 2 % Lidocaine Hydrochloride with 1:200,000 concentration of adrenaline is the most commonly used and is effective from 2 to 3 min following administration and lasts for 45 min to 1.5 h [6]. Period of postsurgical pain is circumscribed [6] and its intensity is maximal at 3–5 h [7] and lasts for 8–12 h [6] following surgical removal of impacted mandibular third molar. For this, the patients require oral analgesic in the early postoperative phase [8].

In order to prevent patient discomfort and postoperative pain after surgical removal of mandibular third molar, a long acting local anesthetic, bupivacaine, which is four times as potent as lidocaine, and has three times the duration of anesthesia of lignocaine is used [9].

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Bupivacaine has a higher percentage of the ionised form of molecule, vasodilating property, and increased lipid solubility [6]. The pKa value for plain bupivacaine is 8.1 and at normal tissue pH a higher percentage of molecules are in ionised form which requires more time to be buffered by the tissue. Local anesthetics must be in a non-ionised form to diffuse through the cell membrane. This difference in availability of non-ionised form will slow the onset of action of bupivacaine [6].

A large number of studies have shown that buffering local anesthetic solution will increase the non-cationic form of the drug, which increases the penetration of solution into soft tissue nerve sheath, thereby decreasing the pain during injection [11] and producing rapid onset of action of local anesthetic solution [10, 11].

Alkalinisation is defined as the process of addition of alkalinizing agent before the time of injection. The pKa value determines the potency of local anesthetics [12], so the addition of an alkalinizing agent produces a pH closer to the physiological pH. Increased potency of local anesthetic molecule also depends upon the increased non-ionic portion of the drug and high protein binding capacity [10].

Local anesthestic solutions are in an aqueous form, and the pH of commercially available local anesthetics is acidic. To increase their shelf life and stability, a vasoconstrictor, adrenaline is added. Efficacy of local anesthetic solution depends upon the stability of vasoconstrictor. Adrenaline degrades by oxidation and it gets deteriorated within several hours [13].

The vasodilating activity of bupivacaine increases blood flow to the tissue at the site of injection enhancing the rapid diffusion of the LA molecule away from the site of injection resulting in a short duration of action and increased blood concentration of anesthetic agent with overdose reaction and intraoperative bleeding [14]. Addition of a vasoconstrictor, such as adrenaline, decreases the diffusion of local anesthetic molecule and promotes haemostasis by its vasoconstricting property [15] thereby fasten the onset of action (2 min) and helps to attain profound anesthesia within few minutes after injection (4–8 min) [6].

Bupivacaine decreases postoperative pain by blocking the surgically induced nociceptor stimuli. The increased liposolubility and protein binding capacity of bupivacaine increase the local anesthetic potency to pass easily into the nerve membrane and increase the duration of action up to 8–10 h [16].

Materials and Methods

This study was conducted in the Department of Oral and Maxillofacial Surgery, Indira Gandhi Institute of Dental Sciences, Puducherry during the period of 1st May 2013–31st July 2014.

Method of Collection of Data

After obtaining research and ethical committee approval, all patients who reported to the department for removal of impacted mandibular third molar from 1st June 2013 to 30th June 2014 were included in this study. Exclusion criteria included conditions such as pregnancy, lactating females, history of drug allergy, medically compromised patients. Inclusion criteria included 18–55 years of age with mesioangular impacted third molar under ASA 1 category.

Procedure

A complete case history including medical history was filled up in the proforma for each patient by the author.

Subjects were randomly divided into two groups as, group A (control group) and group B (study group)—50 subjects in each group. Sample size was calculated using sample size estimation formula. A clinical comparative study was conducted. The solution was prepared freshly before the surgery. If the time between preparation and injection is more than 5 min, the solution was discarded. Under sterile condition 0.1 ml of 1:1000 dilution of adrenaline was drawn into 1 ml of insulin syringe and was added to 20 ml multidose vial of 0.5 % bupivacaine to yield 1:200,000 adrenaline in 0.5 % bupivacaine.

For buffering the above solution, 2 ml of 7.5 % $NaHCO_3$ was added to 20 ml of the above solution which yielded 1/10 dilution. Using standard pH meter, the pH of both the solutions were tested and recorded. The pH of bupivacaine hydrochloride with adrenaline was 3–4.5 and that of carbonated bupivacaine with adrenaline was 7.2–7.4 (Table 1). The procedure was explained to each patient. Informed consent were obtained from each patient prior to starting the procedure. Local anesthetic allergic testing was carried out by depositing 0.2 ml of freshly prepared solution in the forearm intradermally using 2 ml disposable syringe. After administering the test dose, patient was monitored for 30 min for the signs and symptoms of allergic reaction. One of the two local anesthetic solutions was administered to patient. The control group was administred 0.5 % bupivacaine hydrochloride with 1:200,000 adrenaline solution and the study group was administred carbonated bupivacaine with 1:200,000 adrenaline.

All patients were given inferior alveolar, long buccal, lingual nerve blocks. All injections in both groups were given using 2 ml dispovan single use syringes of length 25 mm with 24 gauge needle. The surgery was performed by using a standard technique. All patients were given Ward's incision using no 15 scalpel and the mucoperiosteal flap was reflected using Howarth elevator. Buccal and distobuccal bone guttering was done with adequate saline irrigation. Tooth splitting was done vertically parallel to

Table 1 Descriptive tabulation of pain on injection (deposition of local anesthetic solution), onset of anesthesia and duration of anesthesia for plain bupivacaine, bupivacaine with adrenaline and carbonated bupivacaine with adrenaline

Local anesthetics	pH	Pain during deposition	Onset of action (min)	Duration of action (inferior alveolar nerve block)	
				Pulpal anesthesia (min)	Soft tissue anesthesia (min)
Bupivacaine HCl	4.5–6	Moderate	3–8	90–180	240–540
Bupivacaine with adrenaline	3–4.5	Severe	5–9	>90	240–720
Carbonated bupivacaine with adrenaline	7.2–7.4	Mild	2–8	>90	240–720

long axis of the tooth using the same bur, and the tooth was elevated out of socket. Sharp bony margins were smoothened and curettage done using bone curette. The extracted socket was irrigated with betadine and saline solution. Hemostasis was achieved and socket closed with two to three simple interrupted suture using 3–0 black braided silk suture leaving behind the releasing incision. A gauze pack was placed and postsurgical instructions were given.

Patient 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 a call to the patient hourly from the first postoperative hour till the requirement of analgesics. The patient were instructed to call when he/she feels the first sensation of mild pain in order to know the duration of action of anesthetic agent. Patients were prescribed amoxicillin 500 mg thrice a day and Hifenac P and Rantac 150 mg twice a day for 5 days and were advised to take medications only after getting instructions from the author.

The following data were recorded and collected by the author:

1. Time of deposition of local anesthetic solution
2. Pain during deposition of local anesthetic solution

Pain during injection is defined as pain that is described by the patient on the visual analogue scale (VAS) during injection of solution and not the needle-prick itself. Pain on injection was determined by using VAS.

Immediately after deposition of the local anesthetic solution, the patient was asked to indicate the level of pain on a 10-point VAS (no pain, 0; light pain, 1–3, i.e. pain reported only in response to questioning and without any behavioural signs; moderate pain, 4–6, i.e. pain reported in response to questioning and accompanied by signs, or pain reported spontaneously without questioning; strong pain or unbearable pain, 7–10, i.e. strong vocal response or response accompanied by withdrawal of arms or tears).

3. Time of onset of anesthesia

Time period between administration of local anesthetic solution and the onset of anesthesia. The time of onset of anesthesia is defined as the first sensation of numbness or tingling in the anesthetised region and is assessed using two point discrimination method. The patient's ability to discriminate between two points was measured with a sliding calliper. The two pointed, tips of the calliper touched the skin simultaneously with light pressure while the patient's eyes were closed. The separation of the two points was gradually reduced from 20 mm at the chin and 10 mm at the lips to the moment where the patient could feel one point only. The minimum separation at which two points could be reported was recorded.

4. Duration of procedure

After administration of local anesthetic solution (in minutes), the time period between first incision until placement of the last suture.

5. Duration of postoperative anesthesia

Represented by the lack of sensibility of the lower lip and tongue. Patient recorded the moment when they noticed the initial recovery of lip and tongue sensibility and the time at which the lip and tongue sensibility had totally returned to normality and they required analgesics. Duration of action of local anesthesia was calculated from the onset of action of anesthesia till the need for postoperative analgesia.

Patients were asked to report after 5 days for suture removal. The patients were also encouraged to comment on their experience of postoperative period, including comments on side effects attributed to drugs used at the time of suture removal.

Mann–Whitney U test and Chi square test were used for comparison of the two groups. A value of $P < 0.001$ was considered statistically significant.

Results

One hundred patients with impacted mandibular third molar (mesioangular impaction) were enrolled in both groups, with 50 patients in each group. Patients between 18 and 55 years of age were selected. The control group was

administered 0.5 % bupivacaine hydrochloride with 1:200,000 adrenaline solution and the study group was administered carbonated bupivacaine with 1:200,000 adrenaline. In the present study, pain on deposition of local anesthetic solution (VAS) for group A—0 to 1 was (6.90 %), 2–3 was (60.80 %), 4–5 was (85.00 %) for group B—0–1 was (93.10 %), 2–3 was (39.20 %), 4–5 was (15.00 %), the difference was statistically significant using Chi square test (Table 2). Mean onset of anesthesia for group A was 3.70 ± 0.953 and for group B was 2.66 ± 0.872, the difference was statistically significant Mann–Whitney U test (Table 3). Mean duration of anesthesia for group A was 7.97 ± 1.375 and for group B was 8.41 ± 1.299 which was found to be not statistically significant using Mann–Whitney U test (Table 4).

Discussion

Bupivacaine is one of the commonly used long acting amide type of local anesthetics. Large number of studies were done to compare the efficacy of bupivacaine with other amide local anesthetics such as lidocaine. The anesthetic efficacy of bupivacaine hydrochloride was more compared to lidocaine hydrochloride and was effective in postoperative pain management [17]. Many studies reported that the combination of lidocaine hydrochloride with long acting local anesthetic will increase the duration of action and decrease patient discomfort [18]. Bupivacaine hydrochloride along with lidocaine hydrochloride is widely used for ophthalmic surgery as it has long duration of action [19] and there was no significant difference in cardiovascular response between the two groups [20]. Only few studies were conducted to compare the efficacy of carbonated bupivacaine with adrenaline with that of bupivacaine hydrochloride with adrenaline for surgical removal of impacted tooth.

Few studies have compared the efficacy of bupivacaine hydrochloride and alkalinized bupivacaine in brachial plexus anesthesia; the results show less pain on injection and rapid onset of anesthesia for alkalinized bupivacaine than bupivacaine hydrochloride [21]. We agree with them in terms of less pain on injection and rapid onset of anesthesia for carbonated bupivacaine with adrenaline than bupivacaine with adrenaline. Niklasson in 2012 administered bupivacaine hydrochloride intraoperatively to control postoperative pain in his study [22]. Preoperative administration of NSAIDs was not effective in controlling pain postoperatively [23]. Bupivacaine hydrochloride was also used with the combination of sustained release analgesic for preventing postoperative pain following surgical removal of impacted tooth [7].

William E. Ackerman et al. in 1992 reported that pH and pCO_2 of local anesthetic solutions was increased following alkalinisation and it gets decreased gradually. 0.5 % of bupivacaine hydrochloride was buffered with 8.4 % of sodium bicarbonate, the initial pH of the solution was 5.86 ± 0.13 and the final pH was 6.75 ± 0.14; 2.0 % lidocaine hydrochloride was buffered with 8.4 % of sodium bicarbonate, the initial pH of the solution was 6.18 ± 0.10 and the final pH was 7.01 ± 0.05; 2.0 % chloroprocaine was buffered with 8.4 % of sodium bicarbonate, the initial pH of the solution was 4.23 ± 0.14 and the final pH was 7.56 ± 0.03. We agree with this fact on pH of the alkalinised solution. In the present study, pH of the carbonated bupivacaine with adrenaline was 7.2–7.4.

Bupivacaine acts by stimulating COX-2 gene expression which is associated with the release of higher PGE_2 as a result of tissue injury [24]. Maximum single dose of bupivacaine hydrochloride with epinephrine is 175 mg

Table 2 Distribution of subjects according to pain on visual analogue scores for bupivacaine with adrenaline and carbonated bupivacaine with adrenaline

Pain score	Bupivacaine with adrenaline	Carbonated bupivacaine with adrenaline	Total	Chi square	*P* value
0–1	2	27	29	33.724	<0.001*
	6.90 %	93.10 %	100.00 %		
2–3	31	20	51		
	60.80 %	39.20 %	100.00 %		
4–5	17	3	20		
	85.00 %	15.00 %	100.00 %		
Total	50	50	100		
	50.00 %	50.00 %	100.00 %		

This shows the pain on injection (deposition of local anesthetic solution) for carbonated bupivacaine with adrenaline was significantly less than bupivacaine with adrenaline. This was found to be statistically significant using Chi square test

* Statistically significant

Table 3 Comparison of onset of anesthesia between carbonated bupivacaine with adrenaline and bupivacaine with adrenaline using Mann–Whitney U test

	Group	N	Mean	SD	U value	*P* value
Onset of anesthesia in minutes	Bupivacaine with adrenaline	50	3.70	0.953	0547	<0.001*
	Carbonated Bupivacaine with adrenaline	50	2.66	0.872		

The mean time for onset of anesthesia for bupivacaine with adrenaline was 3.70 ± 0.953 and carbonated bupivacaine with adrenaline was 2.66 ± 0.872. This was found to be statistically significant using Mann–Whitney U test. This means carbonated bupivacaine has least time of onset and this is proved statistically

* Statistically significant

Table 4 Comparison of duration of anesthesia between carbonated bupivacaine with adrenaline and bupivacaine with adrenaline using Mann–Whitney U test

	Group	N	Mean	SD	U value	*P* value
Duration of anesthesia in hours	Bupivacaine with adrenaline	50	7.973	1.375	1054	0.176^{NS}
	Carbonated bupivacaine with adrenaline	50	8.413	1.299		

The mean duration of anesthesia for Bupivacaine with adrenaline was 7.97 ± 1.375 and Carbonated Bupivacaine with adrenaline was 8.413 ± 1.299. This was found to be not statistically significant using Mann–Whitney U test. (This means carbonated bupivacaine and normal bupivacaine has almost the same duration of action)

NS Not significant

(Finland), 150 mg (Germany), 100 mg (Japan), 150 mg (Sweden), 175 mg (US) [25], that is maximum of 400 mg in 24 h. Incidence of pain in first 24 h after surgical removal of impacted tooth was 21 % [9]. Period of postsurgical pain was circumscribed [6] and its intensity was maximal at 3–5 h [7] and lasted for 8–12 h [6] following surgical removal of impacted mandibular third molar. Patient requires oral analgesics in the early postoperative phase [8]. The time of onset of bupivacaine hydrochloride was 4–8 min for profound anesthesia and lower lip numbness begins after 2 min [6].

Bupivacaine hydrochloride has duration of action up to 8–10 h following nerve blocks [16, 26, 27]. Bupivacaine hydrochloride produces pulpal anesthesia for 90 min and is effective in controlling postsurgical pain following extraction of teeth than commonly used amide local anesthetic agent such as lidocaine. Altering the pH of bupivacaine hydrochloride by adding sodium bicarbonate increases the non-cationic form of drug which enhances the penetration of local anesthetic molecule into the soft tissue and nerve sheath thereby decreases the onset of action [10].

Addition of adrenaline in local anesthetic solution decreases the peak plasma concentration of local anesthetics by its vasoconstrictor property, and increases the duration and quality of anesthesia [15]; it also decreases the requirement of local anesthetics needed for nerve block. This study confirms that alkalinisation of local anesthetic solution reduces pain on injection during deposition of local anesthetic solution and produces rapid onset of action of local anesthetic [28, 29].

Alkalinisation of local anesthetic solution has significantly low VAS score during first 12 h of postoperative period, change in VAS score is significantly higher for non-alkalinised local anesthetic solution [30]. Alkalinisation of local anesthetic solution produces less stinging pain during deposition of local anesthetic solution, injected solution is absorbed quickly by the normal tissue pH, increases the rate of diffusion and rapid onset of action. When too much solution is added, pH rises too far and uncharged basic form will get precipitated. So alkalinised local anesthetic solutions should be freshly prepared before injection [14]. Plain bupivacaine has slow onset of pulpal anesthesia of 8–10 min [31].

Administration of 0.5 % of bupivacaine hydrochloride with 1:200,000 adrenaline will produce a significant pain relief post operatively for 8–10 h [32]. Less concentration of use of local anesthetic solution will decrease the adverse drug reaction. Minimally effective concentration of adrenaline added to bupivacaine is 1 mg/ml. Addition of adrenaline with bupivacaine hydrochloride produces pain relieving effect, decreases the absorption of local anesthetic agent which prolongs the duration of action thereby decreases blood concentration of drug and its toxicity and adverse drug reaction [33, 34].

To the best of our knowledge, a comparative assessment between bupivacaine hydrochloride with adrenaline and carbonated bupivacaine with adrenaline in surgical

removal of impacted mandibular third molar has not been published thus far. One therefore remains confused with different articles in the literature propounding the merits of individual medicaments alone. A comparative assessment is therefore essential in order to make a rational choice. In the present study efficacy of bupivacaine hydrochloride with adrenaline and carbonated bupivacaine with adrenaline was evaluated on the basis of pain during deposition of local anesthetics, onset of anesthesia and duration of anesthesia for surgical removal of impacted mandibular third molar. Differentiation between pulpal and soft tissue anesthesia was not observed separately which may be considered as a drawback of this study.

Statistically significant differences were observed in decreasing pain during deposition of local anesthetic, rapid onset of anesthesia for carbonated bupivacaine with adrenaline. Results showed less pain during deposition and rapid onset of anesthesia for carbonated bupivacaine with adrenaline as compared to bupivacaine hydrochloride with adrenaline.

The aim of treatment is to decrease patient discomfort intra-operatively and post-operatively during and following surgical removal of impacted mandibular third molar. It is important to evaluate other clinical parameters to provide a more objective comparison of treatment.

Conclusion

This study was undertaken to evaluate and compare the effectiveness between bupivacaine hydrochloride with adrenaline and carbonated bupivacaine with adrenaline in surgical removal of impacted mandibular third molar. From the results obtained and comparing it with other studies conducted universally, it may be concluded that:

1. The efficacy of carbonated bupivacaine with adrenaline is more compared with bupivacaine hydrochloride with adrenaline in decreasing pain on deposition of local anesthetic solution and in rapid onset of anesthesia.
2. The duration of action of anesthesia for both carbonated bupivacaine with adrenaline and bupivacaine hydrochloride with adrenaline had no significant difference.

Conflict of interest None.

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