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Post Intra-Alveolar Extraction Analgesia of Bupivacaine and Lidocaine: A Randomized Controlled Clinical Trial

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Abstract

Background and Aim: Pain is a common complaint following exodontia which usually occurs in the first six to twelve hours post-extraction.

Objective: The aim of this study was to evaluate the post-extraction pain control of 0.5% Bupivacaine compared with 2% Lidocaine following intra-alveolar tooth extraction.

Materials and Methods: This study was a double blind randomized controlled trial on patients who underwent intra-alveolar tooth extraction. There were two groups of 126 subjects per Bupivacaine and Lidocaine group respectively. Pain experience was assessed using Numeric Rating Scale (NRS). Data were analyzed using SPSS and $P<0.05$ was considered statistically significant.

Results: Post-operative pain was recorded in Lidocaine group between 3 to 12 hours post-extraction with significant improvements afterward while in the Bupivacaine group, there was almost pain-free period for the first 8 to 9 hours postoperatively. A significant reduction in the need for post-operative analgesics was noted in the Bupivacaine group. Overall patient satisfaction was significantly higher for the Bupivacaine group.

Conclusion: Bupivacaine appears to offer more effective post-operative pain control following intra-alveolar tooth extraction.

Keywords: Bupivacaine; Lidocaine; Post-operative pain

Introduction

Intra-alveolar tooth extraction like other surgical procedures is usually associated with pain, this pain usually lingers on and reaches maximum intensity in the first 3 to 8 hours after the procedure [1-3]. Thus adequate control of pain in the early post-operative period is essential if the desired uneventful post-operative healing period is to be achieved. Unfortunately, there is no standardized management protocol for the control of post-intra-alveolar tooth extraction pain presently, in our environment. Different regimens of analgesics are often prescribed depending on the clinicians' preference; unfortunately, these analgesics are not without their attending shortcomings including side effects, compliance and additional costs [4-7].

Majority of the Local Anaesthetic agents (LA) that are currently in use for most dental procedures give adequate intraoperative pain control but less post-operative pain control.

The mechanisms of action of local anesthesia are complex and incompletely understood [8] There is an assumption that the readily used local anesthetics act by a combination of membrane expansion and blockade of the sodium channels on the neuron [9]. The first phase is the disturbance of the conduction in the membrane of the neuron caused by the structural change of the lipid bilayer. The structural change is produced by penetration of lipid part of the membrane by the uncharged, lipophilic form of the anesthetic (R3N). This is called membrane expansion and is responsible for approximately 10% of the total activity of most local anesthetics [9].

The second process produces a decrease in sodium conduction and thus a reduction in the rate of depolarization and it is called conduction blockade or membrane stabilization, responsible for 90% of all the activity. The decrease in sodium conduction is caused by an interaction between the charged cationic form of the molecule (R3NH +) and the phospholipid phosphatidyl-L-serine in the neuronal membrane [9].

Although patient reports of allergic reactions to local anesthetics are fairly common, investigation shows that most of these are of psychogenic origin and hyperventilation [9-11]. The patient may appear pale, perspires and lose consciousness [9]. Systemic reactions and side effects due to bupivacaine are rare and occur no more frequently than with other local anesthetics [12,13]. Initial neurologic signs of systemic toxicity may include sedation, lightheadedness, dizziness, slurred speech, mood alteration, diplopia, sensory disturbances, disorientation, and muscle twitching. There may be tremors, respiratory depression, tonic-clonic seizures at higher blood level, and if it is severe may result in coma, respiratory arrest and cardiovascular failure [9,14].

Bupivacaine has an intermediate onset of action [15] and a Pka of 8.1, it exists primarily in the cationic form (80-95%) at a tissue pH of 7.4 and hence is relatively slower in onset compared to lidocaine [16].

Lidocaine diffuses readily through the interstitial tissues and into the lipid-rich nerve fibers giving a rapid onset of anesthesia [17]. It has a pka of 7.85, hence possesses a rapid onset of action. Bupivacaine appears to be four times as potent as lidocaine at equivalent doses [12] and has another major advantage of slow return of normal sensation and gradual onset of pain or discomfort [18,19]. With lidocaine, however, severe post-operative pain often abruptly occurs with the cessation of anesthesia, or even before the anesthetic effect has completely worn off [18]. Bupivacaine, a long-acting local anesthetic agent is said to have residual analgesic effect with postoperative pain control potentials [19-21]. Vijay et al. reported that a single injection of 0.5% Bupivacaine can provide anesthesia that lasts for several hours with a persistent long period of analgesia after the return of sensation (residual analgesia) [17]. They also found that Bupivacaine is more effective than centrally acting narcotic analgesics for post-extraction pain control, with avoidance of the side effects of centrally acting analgesic agents [17]. Some authors also found that bupivacaine and other long-acting local anesthetics agent prevented post-operative endodontic pain compared with Lidocaine [20,22]. In the study of Crout et al. there was more post-operative analgesic use in subjects that had Lidocaine compared to those that had Bupivacaine [23]. Brajkovic et al. in a randomized controlled trial concluded that Bupivacaine controlled post-operative pain more efficiently than Lidocaine after lower third molar surgery [2], similar findings have also been reported from other studies following third molar extraction [21,24,25]. Bupivacaine has been shown to be clinically effective for 8-12 hours [26-28], which is much beyond the time period when post-operative pain is most felt, this is theorized to be responsible for its documented success in the management of post-operative pain.

Majority of previous studies that have researched into effective ways of managing postoperative pain following extraction seems to have focused on third molar surgeries [19,29]. This is said to be due to the reproducibility of the pain model of third molar extraction [30]. Another possible reason could be from the assumption that intra-alveolar extraction supposedly is not expected to inflict much postoperative pain unlike surgical extraction with more tissue damage. However, there is evidence that early post-intra-alveolar extraction period like trans-alveolar extraction is often associated with varying degrees of pain [31] and that majority of the patients having extraction under Lidocaine anesthesia often experience varying degrees of post-operative pain [29].

A number of authors have studied the effectiveness of Bupivacaine in controlling post-operative pain after various types of surgeries using different study designs and methodologies, with most of the results affirming its efficacy and superior post-operative analgesic effect in comparison with short-acting LA like Lidocaine [2,20,21,24,25]. However, there is a dearth of knowledge in this environment to show whether Bupivacaine has a role as LA in routine extraction, especially when compared with Lidocaine, the current choice of LA in our environment.

The aim of this clinical trial was to assess the post-extraction analgesic efficacy of Bupivacaine and patient satisfaction with its use and to compare it with Lidocaine.

Material and Methods

The study was approved as a randomized, double-blind, clinical trial by the University of Ibadan UI/UCH Ethical Review Committee.

The study was carried out between September 2015 and August 2016 at the Maxillofacial surgery department, University College Hospital Ibadan. Eligible subjects were consecutive adult patients who presented for intra-alveolar tooth extraction. Patient willingness and no history suggestive of adverse reaction to LA were the inclusion criteria.

Exclusion criteria included pregnancy, use of analgesics within 24 hours before extraction procedure, uncontrolled underlying systemic disease like; cardiovascular disease, liver or renal disease, hyperthyroidism, diabetes mellitus, immunosuppression, and also pre-existing pain other than those related to the offending tooth, mental retardation, and any other psychiatric disorders as well as inability to understand the demands of the study and the instrument that was used for measurement of the pain.

The sample size was calculated using the formula $n=(Z\alpha/2 +Z\beta)2[P1(1-P1)+P2(1-P2)]/(P1-P2)2$

According to this, the sample size was calculated as 120 patients per group (i.e. a total of 240 subjects).

Individuals who met the inclusion criteria were randomly assigned to receive one cartridge (1.8 ml) of either 0.5% Bupivacaine with 1:200,000 epinephrine or 2% Lidocaine with 1:100,000 epinephrine as the LA for the extraction (groups A and B), using Computer generated randomization method (Winpepi 235, version 11.4). The details of the study including how and when the pain measurements would be done were explained to the patients pre-operatively and informed consent was obtained.

The labels on LA cartridges were removed and the cartridges were then re-labeled A or B under aseptic condition, only the nurse who had been trained on the handling of the labeling knew which local anesthetic agent was A or B. Both the patients and the surgeon (researcher) performing the extraction were blinded. The tooth extraction was carried out between the hours of 8:00 am and 11:00 am to give allowance for pain experience recording, as subjects may not wake up at night to do the recording and all extractions were carried out by the same surgeon. Cases in which additional anesthesia was administered due to intolerable intraoperative pain, anesthesia was considered unsuccessful and the patients were excluded from the study.

Both groups had dispensed to them oral tablets of Paracetamol 1000 mg 8 hourly for 3 days which they were instructed to commence when they started experiencing pain. They were also instructed to record the time of the first rescue analgesia, the intensity of pain experienced and the total amount of analgesic used.

The Numerical Rating Scale (NRS) pain score was recorded before the administration of the local anesthetic agent, at 10 minutes after administration of LA and post-operatively at 1, 3, 6, 9, 12, 24, 36 and 48 hours respectively. The NRS measures subjective pain by the respondent selecting a number (0-10 integers) that best reflects the intensity of his or her pain, 0 representing no pain and 10 representing the worst imaginable pain [32].

Patient satisfaction with the local anesthetic used as well as overall satisfaction with treatment was also evaluated with the use of a modified 2-point verbal scale; 1- satisfied, 2- dissatisfied.

Result

The flow diagram demonstrates the randomization of patients enrolled in the study (Figure 1).

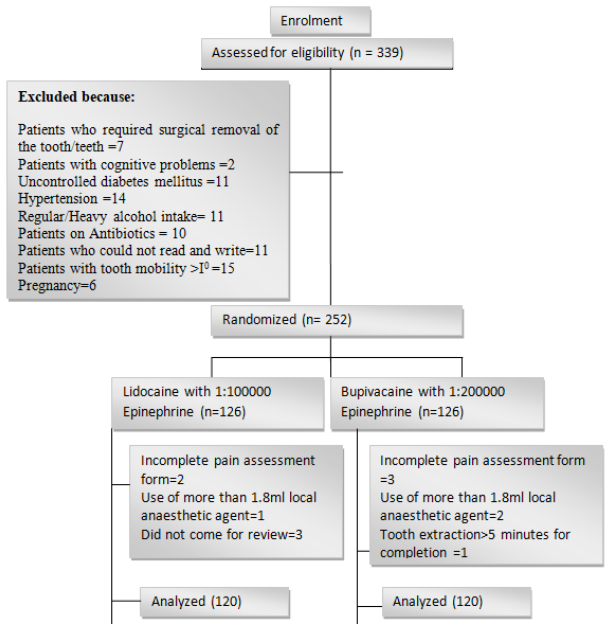

Figure 1: Flow chart of the study design.

Out of the 240 subjects, 204 (85%) subjects did not experience any degree of pain, while 36 recorded different degrees of pain before administration of LA (Table 1).

The onset of action of Lidocaine ranged between 2 and 4 minutes with the mean onset of 2.7 ± 0.5 minutes and that of Bupivacaine ranged between 3 and 6 minutes with the mean onset of 4.7 ± 1.1 minutes (Table 2). None of the subjects in the two groups experienced any form of pain after the onset of anesthesia until after 2 hours post-extraction when 12 (10%) experienced varying degrees of pain in the Lidocaine group. At 3 hours post-extraction, 57 (47.5%) subjects in the Lidocaine group and none in the Bupivacaine group experience varying degrees of pain.

At 6 hours post extraction, 105 (87.5%) subjects in the Lidocaine group and none in the Bupivacaine group experienced post-extraction pain (Table 1) while at 9 hours post extraction, 110 (91.7%) subjects in the Lidocaine group and 6 (5.0%) subjects in the Bupivacaine group experienced post-extraction pain (Table 1). At 12 hours post extraction, 90 (75.0%) subjects in the Lidocaine group and 13 (10.8%) in the Bupivacaine group experienced post-extraction pain (Table 1).

At 24 hours post extraction 116 (96.7%) in the Bupivacaine and 115 (95.8%) subjects in the Lidocaine group did not experience post-extraction pain (Table 1), likewise, there was no statistically significant difference between the level of pain observed at 36 hours (X2=2.017, p=0.157) and at 48 hours (X2=2.017, p=0.156) post-extraction in Lidocaine and Bupivacaine groups.

Time	Pain experienced	Local Anaesthetics		Total n (%)	X^2	p-value
Hours	No pain	Lidocaine n (%)	Bupivacaine n (%)			
Pre anaesthetic	0	103 (85.8)	104 (84.2)	207 (85.0)	1.528	0.676
10 minutes post anaesthetic	0	120 (100)	120 (100)	240 (100)		
1	0	120 (100.0)	120 (100.0)	240 (100.0)		
2	0	108 (100.0)	120 (100.0)	240 (100.0)		
3	0	63 (52.5)	120 (100.0)	183 (76.3)	97.072**	0.0001*
6	0	15(12.5	120 (100.0)	135 (56.3)	219.120**	0.0001*
9	0	10 (8.3%)	114 (95.0)	124 (51.7)	180.47	0.0001
12	0	30 (25.0%)	107 (89.2)	137 (57.1)	100.84	0.0001
24	0	115 (95.8)	116 (96.7)	221 (96.3)	0.12	1
36	0	118 (98.3)	118 (98.3)	236 (98.3)	0. 0000	1
48	0	120 (100.0)	118 (98.3)	238 (99.2)	0.14	1
*Likelihood Ratio						
**Fisher's exact test						

Table 1: Effectiveness of Lidocaine and Bupivacaine in controlling post-extraction pain.

Quadrant	The onset of action of LA (Minutes)	Local Anaesthetics		Total N (%)	X^2	P-value
		Lidocaine n (%)	Bupivacaine n (%)			
Upper Left Quadrant	2	12 (10.0)	0 (0.0)	12 (5.0)		
	3	19 (15.8)	13 (10.8)	32 (13.3)		
	4	0 (0.0)	10 (8.3)	10 (4.2)		
	5	0 (0.0)	6 (5.0)	6 (2.5)	25.39	0.0001
Lower Left Quadrant	3	44 (36.7)	1 (0.8)	45 (18.8)		
	4	0 (0.0)	10 (8.4)	10 (4.2)		
	5	0 (0.0)	10 (8.4)	10 (4.2)		
	6	0 (0.0)	20 (16.7)	20 (8.3)	77.27	0.0001
Lower Right Quadrant	2	2 (1.7)	0 (0.0)	2 (0.8)		
	3	19 (15.8)	1 (0.8)	20 (8.3)		
	5	0 (0.0)	7 (5.8)	7 (2.9)		
	6	0 (0.0)	15 (12.5)	15 (6.3)	40.19	0.0001
Upper Right Quadrant	2	18 (15.0)	0 (0.0)	18 (7.5)		
	3	5 (4.2)	9 (7.5)	14 (5.8)		
	4	1 (0.8)	11 (9.2)	12 (5.0)		
	5	0 (0.0)	7 (5.8)	7 (2.9)	27.91	0.0001
	Total	120 (100.0)	120 (100.0)	120 (100.0)		
Overall X^2 =148.92; P=0.0001						

Table 2: Onset of action of LA.

me	Local Anaesthetic agents		Total N (%)	X^2	p-value
	Lidocaine n (%)	Bupivacaine n (%)			
3	63 (52.5)	0 (0.0)	63 (26.3)		
4	26 (21.7)	0 (0.0)	26 (10.8)		
5	5 (4.2)	0 (0.0)	5 (2.1)		
6	2 (1.7)	0 (0.0)	2 (0.8)		
9	0 (0.0)	1 (0.8)	1 (0.4)		
12	1 (0.8)	0 (0.0)	1 (0.4)		
24	1 (0.8)	2 (1.7)	3 (1.3)		
Total	98 (81.7)	3 (2.5)	101 (42.1)	23.190*	0.02*
*Likelihood ratio					

Table 3: Commencement of post-operative analgesics.

Number of Tablets	Local Anaesthetic agents		Total N (%)	X^2	P-Value
	Lidocaine n (%)	Bupivacaine n (%)			
2	2 (1.7)	1 (0.8)	3 (1.3)		
4	8 (6.7)	0 (0.0)	8 (3.3)		
6	59 (49.2)	2 (1.7)	61 (25.4)		
10	10 (8.3)	0 (0.0)	10 (4.2)		
12	14 (11.7)	0 (0.0)	14 (5.8)		
18	5 (4.1)	0 (0.0)	5 (2.1)		
Total	98 (81.7)	3 (2.5)	101 (42.1)	5.585*	0.349*
*Likelihood ratio					

Table 4: Total number of analgesics tablets taken by the subjects.

Majority of the subjects in the Lidocaine group used the prescribed analgesics and the use of the analgesics commenced as early as 3 hours post extraction, unlike Bupivacaine which did not commence until 9

hours postoperatively (Table 3). The total analgesic consumption was significantly less in the Bupivacaine group compared to Lidocaine group. Out of a total of 762 analgesic tablets used, 748 tablets were consumed by 98 subjects in the Lidocaine group while only 14 tablets were consumed by 3 subjects in the Bupivacaine group (Table 4).

Regarding the overall satisfaction with anesthesia and treatment, almost all subjects (113) in the Bupivacaine group were satisfied with the overall treatment while only 12 subjects in the Lidocaine group were satisfied with overall treatment.

Discussion

Trauma and subsequent inflammation from surgical sites sensitize the nociceptors, and the impulses from the site of trauma reach the maximum intensity in about 8 to 12 hours post-operatively after which the nociceptive input from the trauma site begins to drop [33]. This is responsible for the pattern of pain often reported after surgical procedures including intra-9 experienced by the subjects which however started to reduce in intensity at about 12 hours postoperatively. Bupivacaine, a long-acting LA that is clinically effective for 8 to 12 hours (coinciding with the time post-operative pain is most felt) has been shown to have the capability to control the pain that accompanies several surgical procedures. Consistent evidence from the literature has shown that short-acting LA is not clinically effective in the control of post-operative pain because the duration of action falls short of the early post-operative period when the maximum pain intensity is reached [2,20,24,34]. This study also compared Bupivacaine with Lidocaine because there is a dearth of knowledge to show whether it will be advantageous to use Bupivacaine rather than Lidocaine for routine intra-alveolar extraction.

Contrary to previous findings [2,20], we did not find any association between the presence of pre-operative pain and post-operative pain experience. The reason for the observed difference could be that the studies that reported a correlation were in endodontic treatment in which the site of 'surgical trauma' and possible inflammatory response was in a confined space. Trauma resulting from the intervention to an area of pre-existing inflammation in a confined space (e.g. periapical region or pulpal chamber) may lead to tissue hyperalgesia and aggravate the pain experience unlike what happens following extraction where there is open socket that allows for immediate relief of pressure from any inflammatory response.

Lidocaine has a shorter onset of action than Bupivacaine in this study, this is different from the findings of Moore and Dunsky who reported no significant difference in onset of action between Lidocaine and Bupivacaine and numbing depth in endodontic treatment [22], but it is in agreement with a number of other studies [26,35]. The reason for the shorter duration of onset of action has been attributed to the smaller pka (7.7) of Lidocaine which allows it to be able to diffuse faster than Bupivacaine with a larger pka (8.1) resulting in shorter latency time for Lidocaine [21]. There was adequate intra-operative pain control in this study for both groups and this was maintained until about 2 hours post-operation after which the pain experience was seen to differ significantly between the groups. Evidence from previously documented studies have shown that most available LA agents are comparable in terms of intra-operative anesthetic efficacy but differ mainly in post-operative pain control [20,34,36,37]. The significant difference was also observed between Lidocaine and Bupivacaine in terms of pain control in the early post-operative period. Subjects in the Lidocaine group started to experience pain as early as about 2 hours post-operation which increased in intensity to about 12 hours post-operation after which progressive reduction was noticed. This is in concordance with findings in the literature of which 3.3 hours duration of action was reported for Lidocaine [23,38]. Similarly, Nespeca observed severe postoperative pain which abruptly occurred with the cessation of anesthesia using 2% Lidocaine with adrenaline even before the anesthetic effect had completely worn off [18]. In comparison, no subject in the Bupivacaine group experienced any pain in the first 8 hours post-operation in agreement with earlier studies that shows bupivacaine to be clinically effective for 8-12 hours [18,21]. Superior protein binding characteristics of Bupivacaine has been reported to be responsible for the long duration of action [39,40]. By 12 hours the intensity in the pain in the Lidocaine group dropped and by 24 hours and 36 hours, there was no significant difference in pain experience between Lidocaine and Bupivacaine groups in agreement with previous studies that show the time period of maximum post-operative pain intensity to be 6 to 12 hours post-operation. Al-Kahtani also reported no significant difference in pain experience between Lidocaine and Bupivacaine group by 24 or 46 hours post-operation, other authors have also reported similar findings [34,37].

Our study shows a significant difference between Lidocaine and Bupivacaine regarding the time of commencement of rescue analgesic and the total dose of rescue analgesic required post-extraction. The Lidocaine group rescue analgesic was commenced as early as 3 hours post-extraction whereas none in the Bupivacaine group required additional analgesia in the first 8 hours post-extraction, the total dose of rescue analgesic in the Bupivacaine group was significantly less than that in the Lidocaine group ($p=0.0001$). Similar findings have also been reported in previous studies [23,38] Nespeca et al. in a comparative study reported less use of analgesic in Bupivacaine group than Lidocaine group similar to findings from other studies following third molar extraction [18,25,41]. In another comparative study by Chapman and Ganendran, all patients who received Lidocaine reported pain and required oral analgesics by the fourth hour compared to subjects in Bupivacaine group that had a reduction in total postoperative analgesics intake [35]. In another similar study, Brajkovic et al. also reported a significantly lower total amount of rescue analgesic in the Bupivacaine group compared to the Lidocaine group and suggested suppression of central sensitization by Bupivacaine as the possible reason [2].

In terms of patient satisfaction with overall treatment, a significantly higher percentage of the subjects in the Bupivacaine group were satisfied with the overall treatment in comparison with Lidocaine that showed more dissatisfaction. This could be linked with the better patient experience resulting from satisfaction about pain control.

Although the findings from the present study shows Bupivacaine as an attractive choice in routine extraction to attain better patient experience, however there is need for caution in lieu of the fact that long-acting local anesthetics are associated with some possible drawbacks including prolonged numbness which could be unpleasant to patients and risk of soft tissue injury [42-45]. There is also the need for assessing the cost-effectiveness of using Bupivacaine. There is a need for further studies that will allow the risks and benefits of using Bupivacaine for routine extraction to be properly weighed. If the benefit outweighs the risks recommending it as the local anesthetic agent of choice in routine extraction will likely lead to better patient experience following routine extraction.

Conclusion

In conclusion, this study has been able to show that Bupivacaine appears effective in controlling post-operative pain following intra-alveolar extraction with a significant reduction in the need for post-extraction analgesics compared with Lidocaine. Further studies to weigh risks and benefit are recommended before Bupivacaine can be recommended as the LA of choice for intra-alveolar extraction.

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