Cardiovascular Effects of Bupivacaine and the Role of This Agent in Preemptive Dental Analgesia

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Inappropriately high blood concentrations of bupivacaine have been reported to cause toxicity and even death. The potential for cardiovascular toxicity and the difficulty with which this may be reversed has made the dental practitioners reluctant to use this agent. Nevertheless, cardiovascular toxicity from its use in and around the mouth is exceedingly rare. This study was undertaken to assess bupivacaine's cardiotoxic potential in the practice of oral and maxillofacial surgery. Results showed a dose-dependent decrease in systolic blood pressure, but no other statistically significant cardiovascular change was noted. Preemptive treatment of postsurgical pain has been the subject of numerous trials. Bupivacaine administered preoperatively has been suggested to prevent central nervous system "conditioning," thus decreasing the perceived postoperative pain. However, there was no statistical support for any reduction in the perceived postoperative pain in the treatment groups in this study.

Key Words: Bupivacaine; Cardiotoxicity; Preemptive analgesia; Local anesthetic; Visual Analog Scale (VAS); High Performance Liquid Chromatography (HPLC); Enantiomer.

Bupivacaine is a long-acting amide type local anesthetic. It may have a more prolonged and intensified action if its systemic absorption could be delayed.[1] Addition of vasoconstrictor agents, in particular adrenaline, has been rationalized on this basis. Adrenaline balances the rate of anesthetic biotransformation with the rate of systemic absorption, thus reducing systemic toxicity, but it can lead to increased sympathetic side effects.[2]

Bupivacaine cardiotoxicity manifests itself as cardiovascular collapse and eventual cardiac arrest as the drug continues to be administered.[3] On rare occasions, even small amounts of bupivacaine used for simple infiltration anesthesia has caused cardiovascular collapse and even death. The exact mechanism of this collapse is unknown, but it may be related to cardiac arrest due to either an action on the pacemaker or the sudden onset of ventricular fibrillation; cardiac collapse is most likely when the agent is given intravascularly.[1]

This study was designed to assess the potential cardiotoxicity of bupivacaine when combined with adrenaline or when delivered separately, particularly in relation to volume and an intraoral site for administration.

Bupivacaine has traditionally been used for control of surgical pain after its onset. However, it has been shown that it might be possible to prevent the development of pain after surgery by adding regional nerve blocks to the general anesthetic regime.[4] Blocking the spinal effects of surgically induced nociceptor stimuli has been suggested as a means to lessen postoperative pain.[5] For the purposes of the current study, bupivacaine was proposed as a means to block pain pathways, thus preempting postsurgical pain.

METHODS

Healthy individuals presenting for surgical removal of 4 third molar teeth under general anesthesia were chosen

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Table 1. The Demographic Makeup of the Patient Population: Bupivacaine-Adrenaline Group

Patient No	*Operation Date*	*Sex*	*Age (y)*	*Weight (kg)*
1	February 8, 1996	Female	25	80
2	March 7, 1996	Female	28	68
3	December 7, 1995	Male	35	77
4	March 21, 1996	Female	33	77
5	February 8, 1996	Female	28	64
6	January 25, 1996	Male	22	85
7	January 25, 1996	Female	17	74
8	January 18, 1996	Female	26	55
9	March 7, 1996	Female	22	60
10	February 29, 1996	Female	21	59
11	June 13, 1996	Female	18	59
12	November 16, 1995	Male	39	86
13	July 18, 1996	Male	31	90
14	July 18, 1996	Female	17	68

for the study. For the purposes of the current research, only patients with ASA I between the ages of 16 and 40 were selected. Attempts were made to select age-, weight-, and sex-matched volunteers. Tables 1 through 3 display the demographic makeup of the patient groups. The research proposal was submitted to the relevant human research ethics committee, and approval was secured.

Patients were randomly divided into 3 groups. Group 1 consisted of patients given 20 mL of bupivacaine 0.5% with 1:200,000 adrenaline (Marcaine 0.5% with adrenaline 1:200,000, Astra Pharmaceuticals, North Ryde, Australia). Group 2 comprised individuals given nerve blocks using 20 mL of a 0.5% bupivacaine (Marcaine 0.5%, Astra Pharmaceuticals) solution. Group 3 was the control group. Members of this group were given 20 mL of sterile injectable 0.9% normal saline in place of local anesthetic blocks preoperatively, and at the end of the operation, they received nerve blockade by 0.5% bupivacaine with 1:200,000 adrenaline (20 mL). The general anesthetic delivered was standardized, comprising induction with propofol (Diprivan, ICI Australia Operations, East Melbourne, Australia) and fentanyl citrate (Fentanyl, Astra Pharmaceuticals) titrated to the desired response. The state of general anesthesia was then maintained by a mixture of nitrous oxide and oxygen in a ratio of 3 to 4 L/min to 1 L/min with 0% to 1% isoflurane (Forthane, Abbott Australasia, Kurnell, Australia) delivered through a nasotracheal cuffed tube. Vecuronium bromide (Norcuron, Organon Teknika, Lane Cove, Australia) was the muscle relaxant we chose.

In addition, all patients were given 600 mg of penicillin intravenously; if the patient was sensitive to penicillin, he or she was given 1 g Keflin. At the time of induction, all patients received 8 mg of dexamethasone

Table 2. The Demographic Makeup of the Patient Population: Bupivacaine Group

Patient No	*Operation Date*	*Sex*	*Age (y)*	*Weight (kg)*
1	February 1, 1996	Male	27	63
2	December 14, 1995	Female	22	61
3	February 1, 1996	Female	19	63
4	January 25, 1996	Female	21	55
5	March 14, 1996	Male	26	63
6	May 17, 1996	Male	22	60
7	May 2, 1996	Female	22	62
8	May 17, 1996	Female	20	55
9	May 3, 1996	Female	21	76
10	May 3, 1996	Female	23	56
11	May 17, 1996	Female	17	55
12	April 11, 1996	Female	21	73
13	May 2, 1996	Female	32	54
14	May 2, 1996	Female	20	50
15	March 7, 1996	Female	16	55

Table 3. The Demographic Makeup of the Patient Population: Control (Normal Saline) Group

Patient No	*Operation Date*	*Sex*	*Age (y)*	*Weight (kg)*
1	November 23, 1995	Female	25	60
2	February 8, 1996	Female	18	63
3	February 1, 1996	Female	20	67
4	January 18, 1996	Male	19	86
5	February 8, 1996	Male	17	76
6	May 10, 1996	Female	20	50
7	May 17, 1996	Female	27	114
8	May 10, 1996	Female	27	58
9	November 23, 1995	Female	27	60
10	November 9, 1995	Female	17	76
11	November 23, 1995	Female	27	71
12	November 9, 1995	Female	34	72
13	July 18, 1996	Female	21	63

to prevent postoperative edema. Postoperative pain was managed by acetaminophen (500 mg) and codeine phosphate (30 mg) given every 4 to 6 hours as needed. Postoperatively, 10 mg of metoclopramide HCl was given every 6 hours if the patient suffered from emesis or vomiting. Immediately after satisfactory induction of general anesthesia, approximately 5 mL of blood was drawn and placed into a prelabeled vacuum lithium-heparin coated bottle. This constituted the initial blood sample (t = 0 minutes). Heparinized saline solution (1 mL) was infused following each sampling of blood to keep the venous cannula patent. To assure undiluted blood for subsequent sampling, 2 mL of blood was discarded, and then 5 mL was placed in each subsequent bottle (t = 2 to 60 minutes).

Once the patient was deemed stable under surgical anesthesia, an initial 3-lead rhythm strip, baseline heart rate, and blood pressure measurements were recorded. The choice of solution for neural blockade was transmitted only to the operating room nurse, who then provided the surgeon with an unlabeled syringe containing 1 of the 3 possible solutions. This assured that in addition to the patient, the anesthetist and the surgeon would be blind to the chosen agent. Hard copies of electrocardiogram findings from the moment of local anesthetic delivery and for 2 minutes thereafter were recorded; with this information, we hoped to recognize the outcome of the potential intravascular delivery of the local anesthetic. For the purpose of this study, 2.5 mL of solution was deposited adjacent to the landmark, the lingula, for inferior alveolar nerve blockade on either side. A further 15 mL was given as infiltration of the surgical sites, including the distribution field of the long buccal nerve, in the buccal vestibule. The surgeon would only proceed with the delivery of the solution after obtaining a negative aspirate.

Recordings of the blood pressure and heart rate were made and blood samples procured at 2, 5, 10, 20, 30, 40, and 60 minutes following the delivery of the local anesthetic. A hard copy of the rhythm electrocardiogram strip was additionally obtained at each time for evaluation by a cardiologist.

Throughout the operation, the anesthetist closely scrutinized his monitors in an effort to detect outward features of any unusual cardiovascular phenomena. At the conclusion of the operation, the investigator alerted the surgeon to deliver local anesthetic blockade in the control group, and the state of general anesthesia reversed promptly thereafter. The procured blood samples were then frozen at −70°C. On discharge, patients were asked to complete a questionnaire utilizing a visual analog scale (VAS). They were also asked to record the type, dose, and frequency of their analgesic consumption.

Pain experience information was sought preoperatively, immediately postoperatively, and then at 4, 8, 16, 24, 48, 72, and 96 hours following surgery. Each patient was then interviewed at 4 and 11 days after the operation, and the questionnaires were collected.

Standard series were prepared with a concentration range of 0.01 μg to 20 μg by adding known concentrations of bupivacaine to banked blood. Once thawed at around 20°C, 0.6 mL of whole blood was accurately pipetted using disposable tips fitted to a micropipette and the contents carefully deposited into a capped tube of 1.5-mL capacity. Diphenhydramine 0.003 mg/mL was added at 50 μL to serve as the internal standard. Hexane (0.8 mL) and 4 M sodium hydroxide (20 μL) were added next. The mixture was then vortex-mixed for 2 minutes and then frozen in a bed of dry ice for at least 30 minutes. Each tube was then rethawed in a water bath at a temperature of approximately 45°C for 3 to 4 minutes. The solution was then centrifuged at 3000 rpm for 3 to 5 minutes and then refrozen for 15

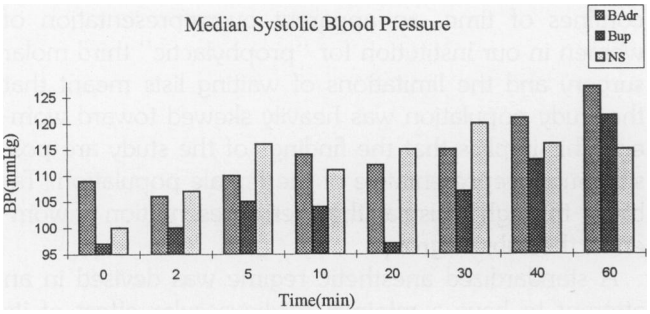

Figure 1. Median systolic blood pressure.

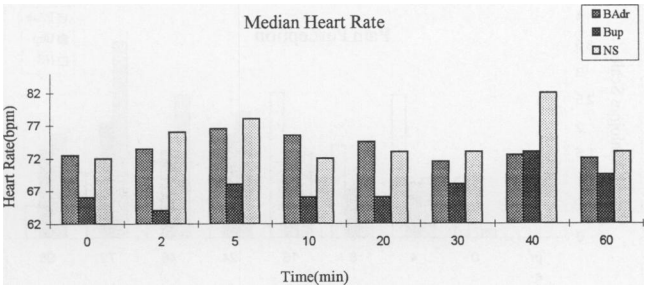

Figure 3. Median heart rate.

minutes. The organic supernatant was then decanted into another 1.5-mL tube and evaporated under vacuum. Reconstitution was with 70 μL of pH-adjusted (pH 3) water. Volumes of the order of 10 to 20 μL were then subjected to high-performance liquid chromatography using a Shimadzu set up (Shimadzu Corporation, Tokyo, Japan). An α_1 acid glycoprotein chromatography column (CHIRAL-AGP columns, ChromTech AB, Hagersten, Sweden) was chosen because of its ability to directly resolve enantiomers without derivatization, allowing separation over an extremely broad range of chemical makeup.[6]

The selected mobile phase was prepared by addition of a 0.15 M sodium phosphate buffer (pH 6.8) solution to a 4.5% isopropanol aqueous phase. The flow rate was set to 0.9 mL/min, and the ultraviolet detection range was adjusted to 220 nm.

RESULTS

Forty-two volunteers were recruited for the study: 9 men and 33 women ranging in age from 16 to 39 years. Volunteers varied in body mass, weighing between 50 kg and 114 kg (Tables 1 through 3).

The subjects were assigned to 1 of 3 groups. Group 1 consisted of 14 patients, 10 women and 4 men. Group 2 comprised 15 individuals, 12 women and 3 men. Group 3, the control group, was made up of 13 people, 11 women and 2 men. No subject demonstrated clinically obvious signs or symptoms of bupivacaine toxicity, either intraoperatively or during the recovery phase. The median data for systolic and diastolic blood pressure and heart rate are presented in Figures 1, 2, and 3, respectively.

There was a strong statistically significant alteration in the systolic blood pressure of all 3 volunteer groups between 0 minutes and 60 minutes ($P = .016$ Bupivacaine with adrenaline (BAdr); $P = .038$ Bupivacaine (plain) (Bup); $P = .034$ Normal Saline (NS). No statistically significant difference could be detected between the various groups at 60 minutes, this time being the selected endpoint of the data collection.

The findings pertaining to diastolic blood pressure were less clear. In the bupivacaine group, a significant difference ($P = .034$) between the findings at time 0 and those at 60 minutes was detected. There was still no significant difference between the 3 groups at 60 minutes. Both systolic and diastolic blood pressures showed an overall tendency to increase. In the 2 treatment groups, the increase was steady from about 20 minutes to 60 minutes. No statistically significant change in heart rate was observed in any of the 3 groups at any time. The median blood concentration for each enantiomer of both treatment groups is shown in Figure 4. After the initial measurement ($t = 0$ minutes), a statistically significant change was consistently noted between the concentration of each of the enantiomers of the bupivacaine group and that of the bupivacaine-adrenaline group. At 2 minutes, the P value was .02 (P

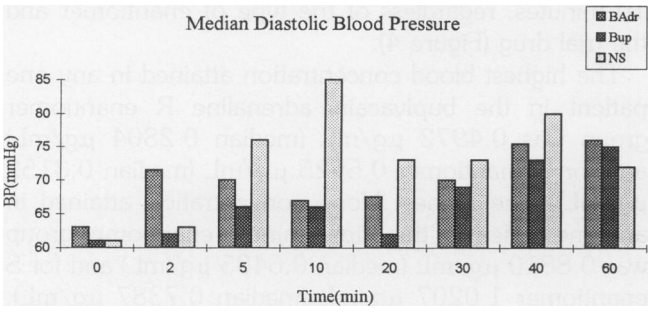

Figure 2. Median diastolic blood pressure.

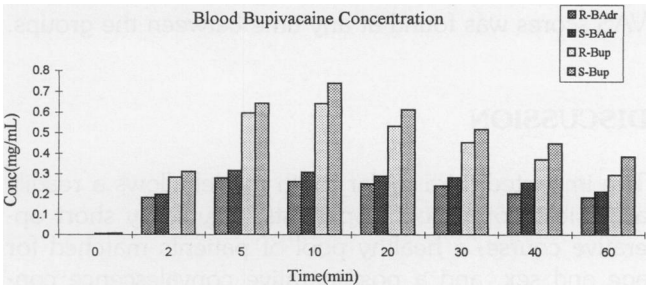

Figure 4. Blood bupivacaine concentration.

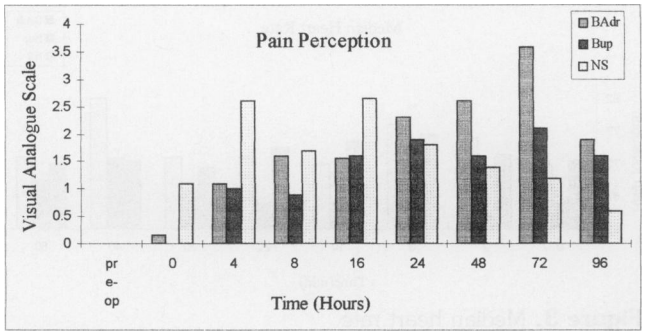

Figure 5. Pain perception.

< .05) and remained statistically significant for all measured times. The peak in the difference in the blood bupivacaine concentration between the 2 treatment groups occurred at 10 minutes (Figure 4).

An attempt was made to assess the effect of each enantiomer separately on systolic blood pressure. The enantiomer concentration was correlated with the change in the systolic blood pressure between 2 consecutive times. In the bupivacaine group, a significant (P = .044) Spearman rank correlation (−0.539) for R enantiomer concentration was noted for the change in the systolic blood pressure between 2 minutes and 5 minutes. A similar effect (P = .047; Spearman correlation −0.53) was observed for the S enantiomer within this group. The negative significant correlation strongly suggests that increased blood concentration of either enantiomer is associated with a fall in systolic blood pressure for the bupivacaine group. The ordinary (Pearson) correlation values were −0.77 and −0.76 respectively. Corresponding results for the diastolic blood pressure were not significant for either group.

VAS readings at each time recorded by the patients are presented in Figure 5. Most patients were pain-free preoperatively (n = 31; 75.6%). For up to 16 hours, the VAS median score for the control group was consistently higher than the bupivacaine or bupivacaine-adrenaline groups. The findings for 24 hours onward, on the whole, favored an increased pain in the treatment groups compared with the control. The statistical comparison between the groups necessitated the use of Wilcoxon 2-sample tests. No significant difference in VAS scores was found at any time between the groups.

DISCUSSION

The impacted third molar tooth model allows a readily accessible population of patients, a typically short operative course, a healthy pool of patients matched for age and sex, and a postoperative convalescence conducive to analysis of pain.[7-9] Unfortunately, given the confines of time, an apparent overrepresentation of women in our institution for "prophylactic" third molar surgery and the limitations of waiting lists meant that the study population was heavily skewed toward women. This implies that the findings of the study are possibly more representative of the female population. Tables 1 through 3 display the overrepresentation of women in the subject groups.

A standardized anesthetic regime was devised in an attempt to have a minimal cardiovascular effect of its own and for this effect, if it occurred, to be universal. Thus, any observed CVS effects could be attributed to bupivacaine.

A separation of R and S enantiomers of bupivacaine was considered appropriate in that these enantiomers differ in their toxic properties.[10] Isolated rabbit heart preparations subjected to the racemic mixture or to the R enantiomer demonstrated a more pronounced QRS widening and severe arrhythmia than those subjected to a solution of S enantiomer bupivacaine. Analysis of findings presented in the literature seems to support the premise that the S enantiomer of bupivacaine in all study models carries a smaller risk of cardiotoxicity.[10] Sudden cardiovascular collapse in nonhypoxic patients given inadvertent intravascular injections of usual doses of bupivacaine is documented.[11] Current technique and appropriate dosage administration should lead to minimal risk of any undue sequelae.

In this study, continuous electrocardiogram monitoring of all 3 groups of trial patients did not demonstrate any change in the electrical activity of the heart in presence of deep (surgical) anesthesia and blood bupivacaine concentrations likely to arise from intraoral dosing with 20 mL of bupivacaine.

Bupivacaine toxicity has been associated with a high plasma concentration either due to high doses or accidental intravascular administration. Intravascular route bypasses the natural drug buffering provided by tissues and the extracellular fluid, which alters its disposition kinetics.[12] The mean peak venous plasma toxic concentration of bupivacaine has been reported to be between 1 and 2.24 μg/mL.[13,14] The peak blood concentration of bupivacaine in the present study occurred at around 10 minutes, regardless of the type of enantiomer and the trial drug (Figure 4).

The highest blood concentration attained in any one patient in the bupivacaine-adrenaline R enantiomer group was 0.4972 μg/mL (median 0.2804 μg/mL) and for S enantiomer 0.5925 μg/mL (median 0.3152 μg/mL). The highest blood concentration attained in any one patient in the bupivacaine R enantiomer group was 0.8810 μg/mL (median 0.6405 μg/mL) and for S enantiomer 1.0207 μg/mL (median 0.7387 μg/mL). Figure 4 is a graph of the results. The implications

Table 4. Difference in Blood R Enantiomer Concentration Between the 2 Trial Groups

Time (min)	*Lower Quartile*	*Median Difference*	*Upper Quartile*	*P Value*
0	0.000	0.002	0.006	.427
2	0.014	0.113	0.295	.022
5	0.210	0.327	0.420	.001
10	0.261	0.334	0.404	.001
20	0.211	0.251	0.369	.002
30	0.108	0.221	0.242	.004
40	0.050	0.162	0.204	.008
60	−0.028	0.133	0.177	.011

Table 5. Difference in Blood S Enantiomer Concentration Between the 2 Trial Groups

Time (min)	*Lower Quartile*	*Median Difference*	*Upper Quartile*	*P Value*
0	−0.004	0.000	0.016	.480
2	−0.032	0.105	0.297	.031
5	0.243	0.328	0.414	.001
10	0.274	0.388	0.441	.001
20	0.176	0.286	0.424	.002
30	0.127	0.257	0.322	.004
40	0.034	0.183	0.250	.006
60	−0.010	0.157	0.242	.019

would therefore be that when administered correctly, avoiding an intravascular delivery, in healthy, young, nonpregnant, nonhypoxic individuals, administration of 20 mL of either bupivacaine (0.5%) or 0.5% bupivacaine-adrenaline (1:200,000) in and around the mouth would fail to achieve a blood concentration that may be potentially toxic. This change in blood bupivacaine concentration following intraoral dosing was found to be statistically significant.

Table 4 displays the median, upper, and lower quartiles for the difference in R enantiomer concentration at each time between the bupivacaine and bupivacaine-adrenaline groups. The same data for S enantiomer is presented in Table 5. Note that the *P* value for the change in median value of both R and S enantiomer blood concentration (in both subject groups) over each interval is significant ($P < .05$). At each time, the median value of the blood concentration was chosen given the small sample size and the presence of outlying values (readings outside the results cluster). The statistically significant difference in the systolic blood pressure over the entire time period in all 3 patient groups ($P = .016$ BAdr, $P = .038$ Bup, $P = .034$ NS) would imply that general anesthesia alone causes a decrease in systolic blood pressure (as seen in the NS group). The change in diastolic blood pressure was clear. However, the heart rate did not show any statistically significant change.

Blood pressure and heart rate measurements of the control group tended to consistently increase from the baseline. It may be reasonable to suggest, as this group of patients was not given any preoperative local anesthesia, that surgical trauma may have led to pain perception, which in turn sympathetically up-regulated these cardiovascular parameters.

Increase in concentration of both R and S enantiomers correlated with a fall in systolic blood pressure in both drug trial groups. Regarding the R enantiomer subgroup of the bupivacaine series, the fall in systolic blood pressure was strongly statistically significant at 2 minutes ($P = .044$) with a Spearman correlation of −0.539. Although not as statistically significant, the same trend was seen at other times also. Similar findings in the S enantiomer subgroup was detected ($P = .047$ and Spearman correlation of −0.53).

The negative Spearman correlation implies strongly that with increased bupivacaine concentration (regardless of the particular enantiomer), a decreased systolic blood pressure may be expected. This is in keeping with our current view on the cardiovascular effects of bupivacaine.[15] For the bupivacaine-adrenaline group, the Spearman correlation (−0.351) was not significant at the time interval between 10 and 20 minutes ($P = .206$).

Several authors have successfully shown that the patient groups given preoperative local anesthetic blocks suffer less pain postoperatively than those receiving the same operation under general anesthesia alone.[16] Wall[17] suggested that under regional anesthesia, the spinal cord is denied the "barrage" of afferent surgical stimuli. The unprevented signals not only lead to prolonged spinal cord hyperexcitability, but could also cause morphological cord change.

In the current investigation, it was postulated that the 2 trial groups given either bupivacaine or bupivacaine-adrenaline would present with less pain than those individuals given a local anesthetic block at the end of the operation. For the current study, a 10-cm-long horizontal line was chosen with no divisional markings for the VAS pain scale. Divisional markings on the scale can "prompt" patients and were avoided. The lack of immediate postoperative pain was taken as the measure of success of the local anesthetic blockade.

Up to 16 hours postoperatively, the VAS score for the control group was consistently higher than that for either test groups. However, after 24 hours, the pain experience in the treated groups was consistently higher than that of the control group. The control group had local anesthetic blockade at the end of the procedure—that is, about 60 minutes later than the trial groups. This alone cannot explain the decreased pain perception in the control group compared to the trial groups, since by 24 hours after surgery, any advantage from the delay

in local anesthetic delivery that the control group may have benefited from would have been removed. There is need for a larger patient population and better and more quantitative measures of pain to assess the significance of this finding.

The VAS is at best semiquantitative. Given its subjectivity, the low number of samples and the missing values attributable to measurements lost during sleep, statistical analysis of the results by Wilcoxon rank correlation appeared to us to be the most meaningful analysis. Nevertheless, there was no significant difference between perceived pain in the 2 trial groups compared with one another and compared with the normal saline control group.

Recent opinion points to optimal pain management by interference with pain pre-, intra-, and postoperatively to preempt the establishment of pain hypersensitivity. The outcome of the current study appears to support these suggestions—that is, to maintain preemptive analgesia, the local anesthesia needs to be extended over a prolonged period; otherwise, stimulation of the affected area would reestablish pain. Although the volume of bupivacaine administered in this study (20 mL) is in the upper range applicable to the practice of oral surgery, the dosage delivered adjacent to the inferior alveolar neurovascular bundle was only 2.5 mL (either side). This means that the volume most at risk of being administered intravascularly would have been indeed small.

We hope that based on the findings of this trial, bupivacaine will continue to enjoy popularity in the practice of dentistry; the practitioner needs to exercise caution in minimizing the potential risk of intravascular dosing.

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