Postoperative Pain Relief After Surgical Removal of Impacted Third Molars: A Single-Blind, Randomized, Controlled Study to Compare Levobupivacaine and Mepivacaine

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Aim: *To compare the efficacy of 0.75% levobupivacaine with that of 3% mepivacaine for pain control after surgical removal of impacted mandibular third molars.* ***Methods:*** *Forty-two subjects (23 females and 19 males, mean age 23.5 ± 4) underwent surgical removal of third molars in two separate sessions. Within each patient, levobupivacaine was used to anesthetize one extraction side and for the other side, mepivacaine. Onset of anesthesia, duration of surgery, lip numbness, timing of pain appearance and analgesic consumption were evaluated.* ***Results:*** *There were no significant differences in onset of anesthesia, duration of surgical procedure, and lower lip numbness between the two groups (*$P > .05$*). Timing of pain appearance and of first drug consumption was significantly lower in the mepivacaine group (*$P < .05$*). Patients with levobupivacaine anesthesia had significantly lower visual analog (VAS) pain scores at 1 and 2 hours postoperatively than those with mepivacaine anesthesia.* ***Conclusion:*** *Levobupivacaine is a valid alternative to traditional local anesthetics for surgical removal of lower third molars. It presents better pain relief when compared to mepivacaine in the immediate postoperative period as evidenced by lower VAS scores.* J OROFAC PAIN 2009;23:325–329

Key words: anesthesia, levobupivacaine, oral surgery, postoperative pain, third molar

The continuous improvement in local anesthetic agents has contributed more than any other factor to the control of pain during and especially after dental surgery. The surgical removal of the lower third molars is a common oral surgical procedure which causes severe postoperative pain. Among the several commercially available anesthetic solutions, lidocaine is the one most frequently used in dentistry, and is the benchmark for any comparison.[1] Mepivacaine, an amide anesthetic, is as effective as lidocaine at the same concentration and with the same vasoconstrictor agent.[2] However, none of these agents has been proved to be effective for prolonged procedures.[3]

On the other hand, bupivacaine hydrochloride (HCL) provides an extended anesthetic effect, as well as a period of prolonged postoperative analgesia.[4,5] The potency of bupivacaine is approximately 4 times greater than that of mepivacaine and lidocaine. Thus it has the advantage of a 4 times lower dosage for anesthetic effects and a lower acute toxicity (LD_{50}) than mepivacaine.[6]

Bupivacaine is a racemic local anesthetic, resulting from an equal mixture of its component enantiomers, R(+) and S(–) bupivacaine.[7–9] After injection, the two enantiomers behave pharmacokinetically as independent drugs. Levobupivacaine is the S(–) enantiomer of bupivacaine and produces a longer nerve block duration and has a lower toxicity to both the central nervous and cardiovascular systems than R(+) bupivacaine.[10,11]

The aim of the present study was to compare the efficacy of 0.75% levobupivacaine with that of 3% mepivacaine for pain control after surgical removal of impacted mandibular third molars.

Materials and Methods

This study was performed from January 2006 to June 2007 in the Department of Dentistry and Surgery of the University of Bari, Italy. The study was conducted in accordance with the provisions of the Declaration of Helsinki, and the Internal Ethical Committee gave its approval. Each patient gave his or her written, informed consent to participate and had the right to withdraw from the trial at any time.

All patients requiring bilateral surgical removal of impacted mandibular third molars were enrolled. Over 18 years of age and good health were inclusion criteria. For the patients, exclusion criteria were: age < 18 years, the presence of systemic diseases such as thyrotoxicosis, immunosuppression, diabetes mellitus, cardiovascular or liver diseases, allergy to local anesthetics, pregnancy, and presence of anxiety requiring the use of a sedative or anxiolytic drug. An inflammatory state around the third molar was considered an exclusion criteria.

A split-mouth design was chosen. Random sampling by means of opaque, sealed envelopes was used to determine which of the two mandibular molars would be extracted first. All extractions were performed under local anesthesia, without any premedication, by the same surgeon using a standard technique. A mucoperiosteal flap was reflected to gain access to the impacted third molar. Thereafter, bone was removed by a water-cooled bur in a surgical drill. All wounds were closed with 3/0 polyglactin (Vicryl) interrupted sutures. The duration of each operation from incision to wound closure was recorded.

Both local anesthetics, levobupivacaine and mepivacaine, were tested on the same patient. For the first extraction, the choice of the anesthetic was randomized and performed in blocks of four patients by means of opaque, sealed envelopes. Therefore, each patient served as his or her own control. The second extraction was performed 1 month later using the anesthetic not used for the first extraction. Each patient was blind to the anesthetic type.

For the molar extraction with levobupivacaine, the alveolar nerve block was performed by means of a 2.0 mL solution (7.5 mg/mL Chirocaine). In addition, the buccal soft tissues were infiltrated with 1.0 ml. Since levobupivacaine is not available in dental cartridges, it was drawn from a 10 mL vial. Levobupivacaine was admistered without vasoconstrictor according to Rood and coworkers.[12] In the case of mepivacaine, the alveolar nerve block was obtained by means of a 1.8 mL solution (30 mg/mL) without epinephrine. In addition, the buccal soft tissues were anesthetized with 1.8 ml solution (20 mg/ml) with 1:80.000 epinephrine, using cartridges inserted into carpule syringes (Carbosen). Therefore, the total dose of injected levobupivacaine was about one fourth of the total dose of mepivacaine (22.5 mg versus 90 mg).

Third molar surgery is usually considered a clean-contaminated surgery, ie, a surgery with a higher risk of infection, therefore routine antibiotic administration is a controversial topic. However, in surgical removal of impacted third molars, dental depth and angulation, the need of ostectomy and of crown sectioning are risk factors for postoperative infection and inflammatory complications. Therefore, postsurgery antibiotic therapy is recommended by some authors.[13,14] The choice of antibiotic therapy by intramuscular route (1 g im cefazoline twice a day for 5 days) derived from the need to administer antibiotics as soon as possible after surgery, when potential difficulties in consuming tablets and drinking due to prolonged lip numbness could be hypothesized. In case of pain, ibuprofen 600 mg was suggested.

The following parameters were evaluated: *(1)* onset of anesthesia, defined as the period between the end of the local anesthetic administration and the onset of lower lip anesthesia; *(2)* duration of surgery, from incision to wound closure; *(3)* duration of lower lip numbness; *(4)* pain intensity at 1, 2, 12, and 24 hours after surgery; *(5)* time lapse to postoperative pain; *(6)* time lapse to first analgesic intake; and *(7)* any adverse event.

All patients were asked by a single person blind to the anesthetic used to complete a diary reporting on the last four parameters for 24 hours after surgery. Patients were trained to assess lip numbness by lightly tapping the lower lip with index or middle finger. Subjects had to rate whether they felt the lip normal or numb and to record the time of

Table 1 Onset of Anesthesia, Duration of Surgery, Duration of Lip Numbness, Delay to Pain Onset, Delay to Rescue Analgesic Intake

	Mepivacaine anesthesia (n = 42)	Levobupivacaine anesthesia (n = 42)	Onset of anesthesia *P* value
Onset of anesthesia (s)	80.0 (44–130)	112.00 (55–170)	.15
Surgery duration (min)	26.4 ± 8.75	29.55 ± 8.01	.11
Lip numbness duration (min)	161.5 (89–216)	225.00 (85–504)	.053
Time lapse to pain onset (min)*	170.0 (100–240)	302.50 (125–566)	.004
Time lapse to rescue analgesic (min)**	216.0 (140–400)	418.50 (214–597)	.004

* 41 patients and 40 patients.
** 39 patients for mepivacaine and 32 patients for levobupivacaine.
All values but surgery duration are provided as median (25–75 quartile). Surgery duration time is shown as mean ± SD.

reversal of lip numbness. In addition, patients were asked to record the pain intensity on a visual analog scale (VAS) with the anchor points "0 = no pain" and "10 = the worst pain imaginable."[15] The VAS is a sensitive and reliable method for recording pain intensity, and is considered to be better than the verbal, digital, numerical, and descriptive scales.[15] These data were recorded after administration of both levobupivacaine and mepivacaine. Primary outcome was to assess intensity of postoperative pain as evaluated by VAS, whereas secondary outcomes were onset of pain and timing of first analgesic consumption.

Statistical Analysis

A pilot study with mepivacaine indicated that 40 patients were necessary in order for the trial to have an 80% power of detecting a 1-point decrease in VAS with levobupivacaine, at $\alpha = 0.05$.

Continuous normally distributed data were expressed as mean ± standard deviation (SD) and compared using paired Student *t* test. Non-normally distributed data were expressed as median and interquartile ranges and compared using the Mann-Whitney test. The effects over time of the two anesthetics on pain intensity were evaluated by analysis of variance (ANOVA). A Newman-Keuls post-hoc test was performed to detect significant differences if the ANOVA showed a significant difference. Categorical data were expressed as number and percentage and compared using chi-square or the Fisher's exact tests. In all comparisons, a *P* value < .05 was considered statistically significant.

Results

Fifty patients were enrolled in the study. Eight patients did not return for the second extraction and therefore were excluded from the analysis. The final sample consisted of 42 individuals, 23 females and 19 males, mean age 23.5 ± 4 years (median of 24 years, quartile 19–27 years). All subjects were in good health as assessed by health history, physical examination, blood pressure, and pulse rate. No patient was taking any medication that would alter pain perception or antibiotics before the procedure. All extractions were performed without premedications. In all cases anesthesia was satisfactory and there was no need to inject other anesthetic. Table 1 reports data regarding the onset time of anesthesia, duration of surgery, duration of lower lip numbness, onset time of pain, and time of first requirement of medication after levobupivacaine or mepivacaine anesthesia.

There was no statistically significant difference in onset time of anesthesia ($P = .15$), duration of surgery ($P = .11$), and lower lip numbness duration ($P = .053$) between the two groups. Two patients after levobupivacaine anesthesia and one patient after mepivacaine anesthesia did not feel pain during the 24 hours postsurgery. Among all patients with postoperative pain, the timing of pain appearance was significantly longer after levobupivacaine than mepivacaine anesthesia. Ten patients after levobupivacaine and three patients after mepivacaine did not need rescue analgesia for postoperative pain. In patients who required analgesia, the timing of the first drug intake was significantly

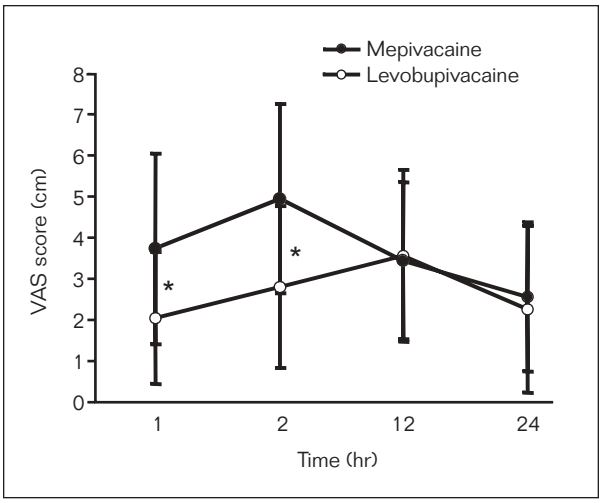

Fig 1 VAS scores at 1, 2, 12, and 24 hours postoperatively in mepivacaine and levobupivacaine groups. * = $P < .05$ between groups.

longer for levobupivacaine than mepivacaine. Pain score at 1 and 2 hours after surgery was different between the two anesthetics; the mean (± SD) VAS scores recorded after injection of levobupivacaine (2.02 + 1.61 and 2.79 + 1.96 at 1 and 2 hours, respectively) were significantly lower than after mepivacaine (3.71 + 2.31 and 4.93 + 2.30 at 1 and 2 hours, respectively; Fig 1). No significant differences in pain score were observed between the two anesthetics at 12 and 24 hours postsurgery. No side effect was reported with either levobupivacaine or mepivacaine.

Discussion

The present study demonstrated that levobupivacaine is more effective than mepivacaine for pain control in the first hours after dental extractions. Moreover, the delay to pain appearance and to the first analgesic needed was longer in patients receiving levobupivacaine than mepivacaine. On the other hand, no difference in the onset and quality (ie, how the patients responded to the drug) of anesthesia between mepivacaine and levobupivacaine was observed. The absence of significant differences in pain intensity in the following VAS evaluations (12 and 24 hours) may be related to the use of systemic analgesic, although it should be noted that fewer patients needed an analgesic after levobupivacaine than mepivacaine anesthesia. The prolonged duration of action may be attributable to the intrinsic characteristics of levobupivacaine presenting higher lipid solubility and protein-binding properties than mepivacaine.[16] These characteristics likely explain why, although not statistically significant, lip numbness duration was longer in the levobupivacaine group than in the mepivacaine group, although this effect may be considered unpleasant since persistent anesthesia may cause difficulty in eating, drinking, and speaking and inadvertent biting of the lips.[17] Moreover, large differences between minimal and maximal duration of lip numbness in the levobupivacaine group were observed (see Table 1) for which an explanation is lacking.

There are few studies reporting bupivacaine or levobupivacaine application in dentistry. Bupivacaine has been compared to lidocaine and mepivacaine in removal of impacted mandibular third molars,[18] in tori removal, multiple extractions with alveolectomies, facial fractures,[3] and in endodontic therapy.[16] These studies concluded that subjects treated with bupivacaine had prolonged anesthesia following treatment and a significant decrease in postoperative pain. Volpato and coworkers[19] compared the anesthetic efficacy of two bupivacaine solutions for inferior alveolar nerve blocks: 0.5% racemic bupivacaine with 1:200,000 epinephrine and a 0.5% mixture of 75% levobupivacaine and 25% dextrobupivacaine with 1:200,000 epinephrine. The solutions had similar anesthetic efficacy. However, a solution with higher proportion of levobupivacaine could be used due to its lower toxicity than racemic bupivacaine.

As far as the use of levobupivacaine in oral surgery, there is, to the best of our knowledge, only the study by Rood and coworkers.[12] These authors compared the efficacy of 0.75% levobupivacaine (without vasoconstrictor) with 2% lignocaine (with adrenaline 1:80,000) and with placebo for postoperative pain control in 93 patients who underwent removal of mandibular third molars under general anesthesia. Their results are similar to ours regarding the lower number of patients requiring rescue analgesia, the lower pain scores, and the larger time laps to analgesic intake after levobupivacaine than mepivacaine. However, there are basic differences in the design of the two studies. First of all, the present study tested levobupivacaine versus mepivacaine and surgery was performed only by one surgeon while Rood and coworkers compared levobupivacaine versus lignocaine and placebo and surgery was performed by two surgeons. Furthermore, in the study by Rood and coworkers, subjects underwent oral surgery under general anesthesia while in the present study subjects were operated under local anesthesia with no premedication. Lower medical risk and lower

social costs and economic costs for the individual were the main reasons for using local anesthesia instead of general anesthesia. In addition, patients under local anesthesia, being awake, can provide details on the onset of the anesthesia and what they feel immediately after surgery. Also, patients in the present study did not get premedications while in the earlier study two patients in the levobupivacaine, three in the lignocaine, and seven in the placebo groups received fentanyl, a powerful opioid analgesic that could have influenced the results. All patients in the study were discharged the same day of surgery after receiving a supply of analgesics (ibuprofen), while patients of the present study took analgesics only in case of need. Finally, in both studies, pain was evaluated with VAS. However, in the present study a split-mouth design was used, ie, each patient was his or her own control, while Rood and coworkers divided subjects into three groups: placebo, lignocaine, and levobupivacaine. Although the VAS is a sensitive and well-accepted instrument to evaluate pain intensity, it shares the common disadvantages of all subjective measurements. It is likely that testing different local anesthetics on the same patient may eliminate biases deriving from different pain thresholds and emotional perceptions and may give more reliable comparative data.

Conclusions

The data of this study showed that levobupivacaine presents clinical advantages when compared to mepivacaine for postoperative pain control after extraction of impacted mandibular third molars and may therefore be considered a valid and safe alternative to traditional local anesthetics.

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