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Quality of analgesia after lower third molar surgery: A randomised, double-blind study of levobupivacaine, bupivacaine and lidocaine with epinephrine

Kvalitet analgezije nakon hirurškog vađenja donjih umnjaka: randomizovana, duplo slepa studija efikasnosti levobupivakaina, bupivakaina i lidokaina sa adrenalinom

Denis Brajković*, Vladimir Biočanin†, Marija Milić‡, Milan Vučetić‡, Renata Petrović§, Božidar Brković‡

***Department of Maxillofacial Surgery, †Department of Oral Surgery, Faculty of Medicine, University of Kragujevac, Kragujevac, Serbia; ‡Clinic of Oral Surgery, §Department of Restorative Dentistry and Endodontics, Faculty of Dental Medicine University of Belgrade, Belgrade, Serbia**

Abstract

Background/Aim. Surgical extraction of lower third molars is followed by mild or severe postoperative pain which peaks at maximal intensity in the first 12 hours and has a significant impact on a patient's postoperative quality of life. The use of long-acting local anaesthetics is a promising strategy to improve postoperative analgesia. The aim of the present study was to investigate analgesic parameters and patient satisfaction after using 0.5% levobupivacaine (Lbup), 0.5% bupivacaine (Bup) and 2% lidocaine with epinephrine 1:80,000 (Lid + Epi) for an inferior alveolar nerve block following lower third molar surgery. **Methods.** A total of 102 patients (ASA I) were divided into three groups, each of which received either 3 mL of Lbup, Bup or Lid + Epi. The intensity of postoperative analgesia was measured using a verbal rating scale (VRS). The total amounts of rescue analgesics were recorded on the first and during seven postoperative days. Patients satisfaction was noted using a modified verbal scales. **Results.** A significantly higher level of postoperative pain was recorded in Lid + Epi group compared to Bup and Lbup groups. No significant differences were seen between Bup and Lbup, but a significant reduction in the need for rescue analgesics was seen postoperatively in both Lbup and Bup (50%) in comparison with Lid + Epi (80%) in the first 24 hours. The same significant trend in rescue analgesic consumption was recorded for seven postoperative days. Patients' overall satisfaction was significantly lower for Lid + Epi (10%) than for Lbup (56%) and Bup (52%). **Conclusion.** The use of a new and long-acting local anaesthetic 0.5% levobupivacaine is clinically relevant and effective for an inferior alveolar nerve block and postoperative pain control after third molar surgery. In our study Lbup and Bup controled postoperative pain more efficiently after lower third molar surgery compared to Lid + Epi.

Key words:
tooth extraction; molar, third; bupivacaine; lidocaine; anesthesia, dental; pain, postoperative; questionaires.

Apstrakt

Uvod/Cilj. Hirurško vađenje donjih impaktiranih umnjaka praćeno je bolom umerenog do jakog intenziteta, sa maksimalnim intenzitetom tokom prvih 12 sati, koji ima značajan uticaj na kvalitet života pacijenata u postoperativnom periodu. Upotreba dugodelujućih lokalnih anestetika predstavlja obećavajuću strategiju za poboljšanje postoperativne analgezije. Cilj ove studije bio je da se ispitaju analgetički parametri i zadovoljstvo pacijenata postignutom analgezijom u postoperativnom periodu nakon primene 0,5% levobupivakaina (Lbup), 0,5% bupivakaina (Bup) i 2% lidokaina sa epinefrinom (1: 80,000) (Lid + Epi) za sprovodnu anesteziju donjeg alveolarnog nerva prilikom hirurškog vađenja donjih umnjaka. **Metode.** Ukupno 102 pacijenta (ASA I) bila su podeljena u tri grupe u zavisnosti od primljenog anestetika: 3 mL Lbup, 3 mL Bup ili 3 mL Lid + Epi. Intenzitet postoperativne analgezije registrovan je primenom verbalne rangirajuće skale (VRS). Zabeležena je ukupna količina primenjenih analgetika nakon prvog i sedmog postoperativnog dana. Zadovoljstvo pacijenata ocenjivano je na osnovu modifikovanih verbalnih skala. **Rezultati.** Značajno jači intenzitet postoperativnog bola zabeležen je u grupi Lid + Epi, u poređenju sa grupama Lbup i Bup. Značajno smanjenje potrebe za analgeticima u postoperativnom periodu zabeleženo u grupama Lbup i Bup (50%) u poređenju sa grupom Lid +

Correspondence to: Denis Brajković, Department for Maxillofacial Surgery, Faculty of Medicine, Svetozara Markovića 69, 34 000 Kragujevac, University of Kragujevac, Serbia. E-mail: denis.brajkovic@gmail.com

Epi (80%) nakon 24 časa. Značajno smanjenje potrebe za postoperativnim analgeticima u grupama Lbup i Bup zabeleženo je i nakon 7 dana. Potpuno zadovoljstvo pacijenata postignutom analgezijom bilo je značajno slabije u grupi Lid + Epi (10%) u poređenju sa grupama Lbup (56%) i Bup (52%). **Zaključak.** Upotreba novog dugodelujućeg lokalnog anestetika 0,5% levobupivakaina klinički je relevantna i efikasna za sprovodnu anesteziju donjeg alveolarnog nerva i kontrolu postoperativnog bola nakon hirurškog vađenja donjih umnjaka. U našoj studiji Lbup i Bup bili su efikasniji u kontroli postoperativnog bola nakon hirurškog vađenja donjih umnjaka u poređenju sa Lid + Epi.

Ključne reči:
zub, ekstrakcija; umnjaci; bupivakain; lidokain; anestezija, stomatološka; bol, postoperativni; upitnici.

Introduction

Surgical extraction of impacted lower third molars is considered the standard clinical model in pain studies, due to the evidence of moderate to severe postoperative pain which leads to increased pain perception and causes patient dissatisfaction [1]. Postoperative pain levels have also been found to have a significant impact on the quality of life after third molar surgery [2]. Thus, the successful control of postoperative pain is a prerequisite for general patient compliance with oral-surgical procedures.

The standard protocol for pain control in third molar surgery involves the preoperative administration of local anaesthetics along with the intermediate action and postoperative use of analgesics. However, intermediate anaesthetics are not analgesics during the periods of the most intensive postoperative pain experienced (6–8 hours), leading to the faster onset of postoperative pain and increased consumption of postoperative analgesics. Furthermore, any failure in postoperative pain control may contribute to the develoment of central sensitisation [3], a state of hyperexcitability in the central nervous system that may even persist for 30 days after third molar surgery [4]. It has been demonstrated that the use of long-acting local anaesthetics for the prolonged blockage of nociceptive impulses arising from the site of surgery may be a promising strategy for improving postoperative analgesia [5].

Bupivacaine (Bup) was a widely used, long-acting local anaesthetic which provided relatively fast relief and prolonged block anaesthesia and delayed onset of postoperative pain [6]. However, due to clinical reports citing life-threatening cardiac issues and its neurotoxic effects, it became evident that bupivacaine had a narrow safety margin, especially after an unwanted intravascular injection [7–10]. On the other hand, levobupivacaine (Lbup) is a long-acting local anaesthetic with chemical and physical properties identical to bupivacaine but with lower toxicity seen in *in vitro*, *in vivo* and human volunteer studies [11–14]. Comparative clinical studies evaluating equivalent doses of 0.5% Lbup and Bup for peripheral nerve blocks have suggested that clinical parameters were similar or even better with 0.5% levobupivacaine [15–18]. In dentistry, one human volunteer study compared the anaesthetic properties of 0.5% Bup and 0.5% Lbup, both associated with epinephrine (1 : 200,000), and found no significant differences between the two anaesthetics in achieving onset time and duration of soft tissue and pulpal anaesthesia for an inferior alveolar nerve block [19].

The aim of the study was to investigate analgesic parameters and patient satisfaction after using 0.5% Lbup, 0.5% Bup and 2% lidocaine with epinephrine (1 : 80,000) (Lid + Epi) for inferior alveolar nerve block in patients undergoing lower third molar surgery.

Methods

The study was performed at the Clinic for Oral Surgery, Faculty of Dental Medicine, University of Belgrade, with institutional approval from the Ethical Commitee (No. 36/32). The patients were classified as having physical status 1 according to the American Society of Anesthesiologists (ASA) classification. Exclusion criteria were: age under 18, pregnant women, nursing mothers, smokers, patients with any signs of acute or chronic pain in the orofacial region and any antibiotic or analgesic intake within seven days preoperatively. Specific inclusion criteria were patients with fully impacted lower third molars (more than two-thirds of the crown covered with alveolar bone, confirmed by radiographic analysis) with no signs of acute pericoronitis or any acute infection. The patients were studied using a double-blind, controlled design and were randomly allocated to three groups receiving either 3 mL of 2% lidocaine with 1 : 80,000 epinephrine (Lidokain-Adrenalin 2%®, Galenika, Serbia) – Lid + Epi; 3 mL of 0.5% bupivacaine (Marcaine®, AstraZeneca, United Kingdom) – Bup; 3 mL of 0.5% levobupivacaine (Chirocaine®, Abbott, USA) – Lbup.

Random assignments were carried out by an independent investigator according to a computer-generated randomisation list with sealed numbered envelopes. The patients received a total of 3.0 mL of local anaesthetic in the following manner: 2.0 mL for the inferior alveolar nerve block, 0.5 mL for the lingual nerve block and 0.5 mL for the buccal nerve block. No premedication was given. Since 0.5% Bup and 0.5% Lbup were not available in dental cartridges, they were drawn from 10 and 20 mL vials by a clinical pharmacist not involved in the study. The same surgeon performed all the blocks. The time from the application of anaesthetic to the beginning of surgery was limited to 15 minutes. If additional anaesthesia was given due to a prolonged onset time or the presence of intolerable intraoperative pain, anaesthesia was considered unsuccessful and the patients were excluded from the study. Additional anaesthesia was achieved by administering 2% lidocaine with epinephrine (1 : 80,000) (Lidokain-Adrenalin 2%®, Galenika, Serbia). At the end of surgery, the patients were given a study questionnaire with detailed instructions for collecting the protocol parameters of postoperative analgesia. Regular postoperative follow-ups were scheduled for the first and seventh days after the surgery.

The questionnaires were returned back seven days after the surgery, when the patients' sutures were removed.

The postoperative analgesia protocol consisted of clear instructions for analgesic consumption (ibuprofen 400 mg *per os*, Brufen®, Galenika, Serbia) in the case of pain experienced at the surgical site of moderate to severe intenstity, identified at the level of ≥ 4 according to the Verbal Rating Scale (VRS). The VRS consists of a list of six-point scale phrases (0 – no pain; 1 – just notable pain; 2 – weak pain; 3 – moderate pain; 4 – severe pain; 5 – excrutiating pain) which represent the levels of pain intensity. The patients were instructed to grade pain intensity at fixed time points 2, 4, 6, 8, 12, 24 and 48 hours postoperatively. Also, the patients were instructed to record the total amount of analgesics taken in the first 24 hours and over seven days postoperatively.

In order to evaluate the patients satisfaction with the administered analgesia and the overall satisfaction with the treatment, a five-point verbal scale was used: 1 – poor, 2 – fair; 3 – good; 4 – very good; 5 – excellent. The patients evaluated the duration of anaesthesia using a three-point verbal scale: 1 – not enough; 2 – enough; 3 – too long.

Statistical analysis was performed using the statistical software SPSS, version 18.0. The results were presented as the mean ± standard deviation (SD), while χ^2 test was performed to determine the differences in gender and the patient's satisfaction with the treatment and analgesia. Age, weight, the duration of operative procedure and analgesic uptake were compared using parametric one-way ANOVA with *post-hoc* Tukey test. When normal data distribution was not present, non-parametric Kruskal-Wallis and Mann-Whitney tests were used. The difference of $p < 0.05$ was considered significant. The group size was estimated based on a pilot study. In order for the study to have 80% power, with type I errors of 0.05 and assumed differences detected at 40%, the total sample size required was 82 patients. The sample size was calculated using the statistical program G*Power 3.1. (Heinrich-Heine-University, Dusseldorf, Germany).

Results

The flow diagram demonstrates randomisation of patients enrolled in the study (Figure 1). Initially, 125 patients were examined but 102 met the enrollement criteria. The patients were randomised into three groups of 34 each and received either levobupivacaine, bupivacaine or lidocaine with epinephrine. Due to discontinued intervention and the lost of follow-ups, 3, 7, and 7 patients from Lid + Epi, Bup and Lbup groups, respectivelly, were excluded from the study. The subjects' demographic and clinical data are summarised in Table 1.

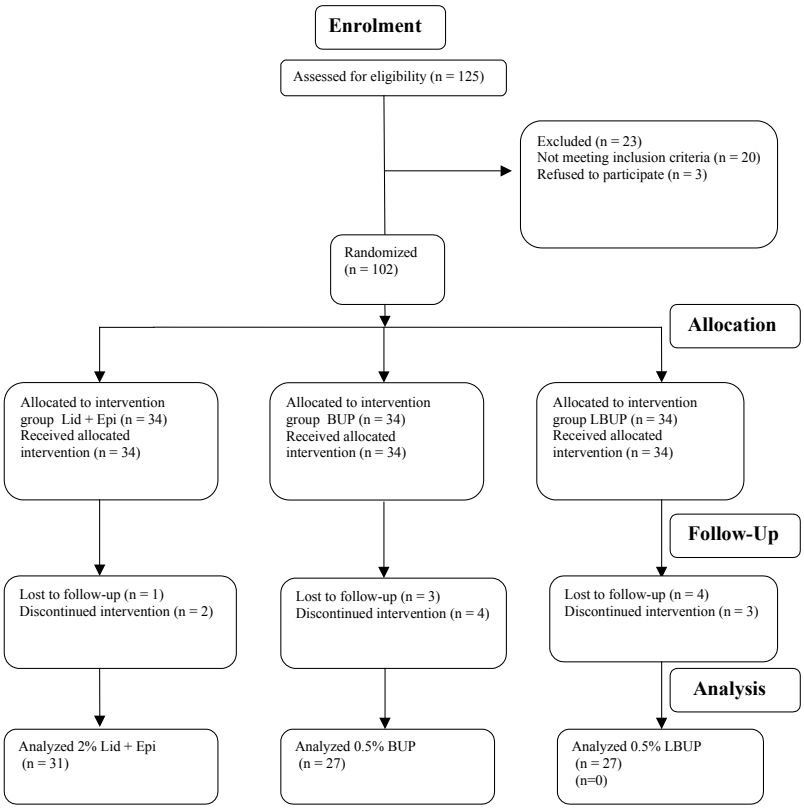

Fig. 1 – Flow diagram of randomization either 2% lidocaine with epinephrine (1 : 100,000) (Lid + Epi), 0.5% bupivacaine (BUP) or 0.5% levobupivacaine (LBUP) for lower third molar surgery.

There were statistically significant differences in postoperative pain intensity among the three investigated groups over 4 to 48 hours. Significantly higher levels of postoperative pain were recorded in the Lid + Epi compared to the Bup and Lbup groups at each time point. The patients in the Bup and Lbup groups experienced similar postoperative pain intensities except during the sixth hour, when pain levels were significantly higher in the Bup cohort (Figure 2). In addition, significantly more patients experienced moderate to severe

Table 1

Patient's demographic and clinical data

Parameters	Lid + Epi	Bup	Lbup
Number of patients	30	27	27
Female/Male, n	19/11	18/9	19/8
Age (years), $\bar{x} \pm SD$	23.6 ± 4.0	23,9 ± 3,5	24,4 ± 5,1
Weight (kg), $\bar{x} \pm SD$	67 ± 13	65 ± 12	68 ± 15
Impacted third molars, n	30	27	27
Duration of operation (min), $\bar{x} \pm SD$	14.3 ± 4.2	13.3 ± 3.9	15.5 ± 4.5
Section of crown and roots (yes/no), n	20/10	19/8	18/9
Bone removal, n			
mesial	6	7	5
distal	16	18	19
oclusal	3	2	2
buccal	0	1	0
lingual			

Lid + Epi : 2% lidocaine with 1 : 100,000 epinephrine; Bup : 0.5% bupivacaine; Lbup : 0.5% levobupivacaine.

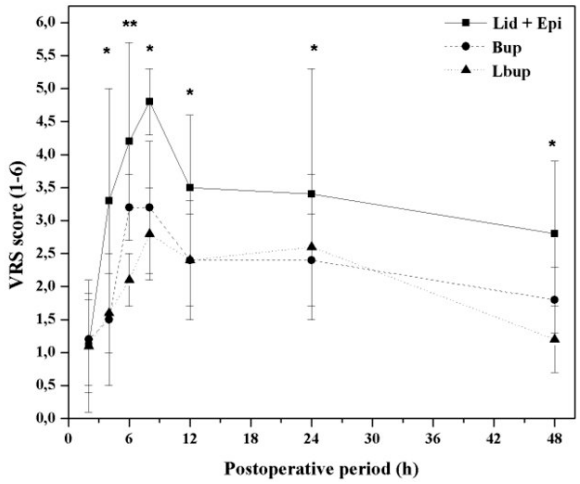

Fig. 2 – Pain intensity according to the verbal rating scale (VRS) after lower third molar surgery. Lid + Epi: 2% lidocaine with 1 : 100,000 epinephrine; Bup: 0.5% bupivacaine; Lbup: 0.5% levobupivacaine; VRS: verbal rating scale; *$p < 0.05$: Lid + Epi vs. 0.5% Bup, Lid + Epi vs. Lbup (Kruskall-Wallis test, Mann-Whitney U test); **$p < 0.05$: Bup vs. LBUP (Kruskall-Wallis test, Mann-Whitney U test).

postoperative pain (VRS ≥ 4) in the Lid + Epi group for all the measured time intervals (Table 2). A significant reduction in the need for rescue medication in the first 24 hours postoperatively was seen in both the Lbup and Bup groups (50% of patients required pain medication) as compared to the Lid + Epi patient sample where 80% of patients required pain medication (Table 3). A total analgesic consumption, measured after the first 24 hours till the seventh day following the surgical procedure was significantly less in the Lbup and Bup groups compared to the Lid + Epi group (Table 3).

Regarding the patient's satisfaction with the achieved postoperative analgesia, 60% (16/27) and 63% (17/27) of patients in the groups Bup and Lbup, respectively, declared achieved analgesia as excellent, compared to 10% (3/31) in the Lid + Epi group. This difference was statistically significant (Figure 3). The five-point verbal scale measurement showed that the mean score for the achieved analgesia was 3.00 ± 1.05, 4.52 ± 0.89 and 4.41 ± 0.91 in the Lid + Epi, Bup and Lbup group, respectively ($p < 0.05$; Kruskal-Wallis rank test), with a significant decrease in the Lid + Epi group compared to both the Lbup and Bup groups [($p < 0.05$, Mann-Whitney test); (data on patient's satisfaction with the

Table 2

Percentage of patients experiencing moderate-to-severe postoperative pain according to the verbal rating scale (VRS ≥ 4) over 48-hour period after 2% lidocaine with 1 : 100,000 epinephrine (Lid + Epi), 0.5% bupivacaine (Bup) and 0.5% levobupivacaine (Lbup)

Groups	2h	4h*	6h*	8h*	12h*	24h*	48h*
Lid + Epi	6	16	48	42	35	26	16
Bup	0	4	11	15	4	4	4
Lbup	0	4	7	11	7	4	6

***$p < 0,05$, χ^2 test.**

Table 3

Postoperative analgesic consumption after anesthesia with 2% lidocaine with 1:100,000 epinephrine (Lid+ Epi), 0.5% bupivacaine (Bup) and 0.5% levobupivacaine (Lbup)

Parameters	Lid + Epi	Bup	Lbup
N_1	25/30*	14/27	14/27
N_2	29/30	20/30	21/30
Pain medcation 24 h (mg), $\bar{x} \pm SD$	1280 ± 450**	630 ± 243	543 ± 277
Pain medication 7 days (mg), $\bar{x} \pm SD$	3430 ± 1633**	1788 ± 832	1640 ± 759

N_1 – number of patients requiring pain medication during 24 hours; N_2 – number of patients requiring pain medication during 7 days; *$p < 0.05$ (Chi-square test), **$p < 0.05$ – Lid + Epi vs. Bup; Lid+Epi vs Lbup (One-way ANOVA, *post hoc* Tukey test).

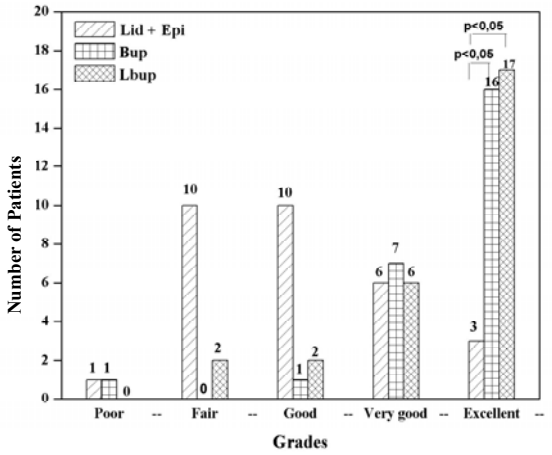

Fig. 3 – Subject's satisfaction with the achieved analgesia. Lid + Epi: 2% lidocaine with 1 : 100,000 epinephrine: Bup : 0.5% bupivacaine; Lbup: 0.5% levobupivacaine; *$p < 0.05$, χ^2 test.

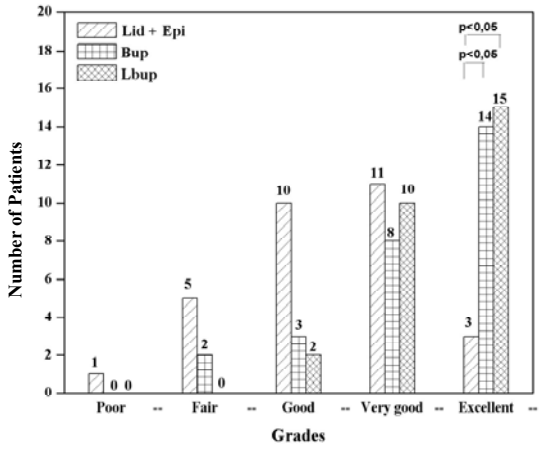

Fig 5 – Overall satisfaction with quality of the treatment. Lid + Epi: 2% lidocaine with 1 : 100,000 epinephrine: Bup : 0.5% bupivacaine; Lbup : 0.5% levobupivacaine; *$p < 0.05$, χ^2 test.

achieved postoperative analgesia are not presented)]. Regarding the patients' evaluation of the duration of anaesthesia, significantly more patients in the Lbup and Bup groups (40% in both groups) found local anaesthesia lasted too long in comparison to the Lid + Epi group (13%) (Figure 4). The patients' overall satisfaction was significantly lower in the Lid + Epi group (10% of patients declared an excellent level) than in the Lbup (56% excellent) and Bup (52% excellent) (Figure 5). The mean scores for overall satisfaction with the treatment quality were 3.22 ± 0.65, 4.26 ± 0.75 and 4.48 ± 0.82 for the Lid + Epi, Bup and Lbup groups, respectively ($p < 0.05$; Kruskal-Wallis rank test), with a significant decrease in the Lid + Epi group compared to the other two groups [($p < 0.05$, Mann-Whitney test); (data for overall satisfaction are not presented)].

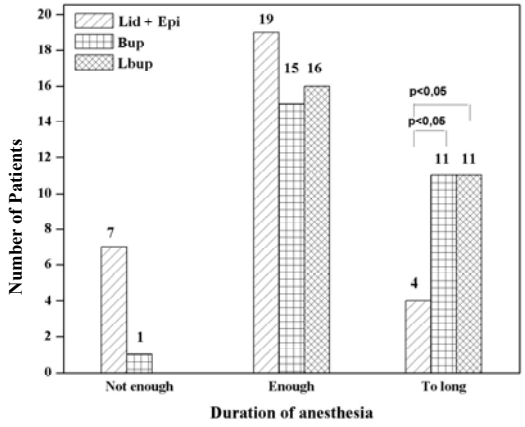

Fig. 4 – Subject's satisfaction with the duration of anesthesia. Lid + Epi: 2% lidocaine with 1 : 100,000 epinephrine; Bup: 0.5% bupivacaine; Lbup: 0.5% levobupivacaine; *$p < 0.05$, χ^2 test.

Discussion

The present, randomised, prospective, double-blind study demonstrated that 0.5% levobupivacaine, as a new long-acting local anaesthetic for use in oral surgery, was effective in achieving postoperative analgesia after lower third molar surgery, as it has been well known for 0.5% bupivacaine [6, 20]. On the other hand, intermediate anaesthetic, such as 2% lidocaine with epinephrine, did not show clinically relevant postoperative analgesic effects, because its duration of action duration did not cover the early postoperative period which is determined by a significant intensity of postoperative pain. Since postoperative pain after third molar surgery reaches its maximal intensity in the first 12 hours [21], and due to the high frequency of third molar surgery, it would be of great importance to use a local anaesthetic that provides prolonged analgesia and decreases patient discomfort. Furthermore, the reduction of postoperative pain improves quality of life, reduces morbidity and allows for the rapid return to daily activities [2].

Previously published results on the analgesic effect of levobupivacaine in third molar surgery may not be compared easily to our research, due to different concentrations of levobupivacaine used (0.75%) [22, 23], whilst in the study of Rood et al. [22], third molars were extracted under general anaesthesia and for postoperative pain relief either 0.75% levobupivacaine, 2% lignocerine with adrenaline 1 : 80,000, or placebo. However, at clinical concentrations of 0.5% and 0.75%, levobupivacaine does produce long-lasting block anaesthesia [22, 23]. This long-lasting effect of both levobupivacaine and bupivacaine can be attributed to the drugs' pharmacokinetic properties. Specifically, the protein-binding coefficient of lidocaine is 64%, which is much lower than the 96% of bupivacaine and levobupivacainen [24]. The high protein-binding coefficient of bupivacaine and levobupivacaine allows local anaesthetics' molecules to bond to tissue proteins and ensure increased concentrations of anaesthetic molecules at the site of injection which are responsible for prolonging the duration of anaesthesia [25, 26].

It is well-documented that surgical trauma and subsequent inflammation induce the sensitivity of peripheral nociceptors (primary hyperalgesia), a notion which has been clinically observed as increased postoperative pain emanating from the site of surgery [27]. Inadequate and short-lasting

nerve blocks may cause prolonged and enhanced postoperative pain, leading to central neural sensitisation [27, 28], which results in pain hypersensitivity beyond the area of surgery (secondary hyperalgesia) and the presence of pain after stimulus (allodynia)3. Juhl et al. [4, 28] showed that third molar surgery was followed by long-lasting mechanical, thermal and electrical sensitisation 30 days after intervention, even in the absence of spontaneous pain and consumption of postoperative analgesics. These findings suggest that anaesthetic blocks should last until inputs from peripheral surgical sites drop below the level that can maintain central sensitisation, especially in the hours immediately following lower third molar extraction. It is also recommended that long-acting local anaesthetics should be a part of the pre-emptive analgesia protocol, because it starts before surgery (anaesthetic injection before surgery) and lasts a good deal of time after surgery, in order to prevent postoperative pain and to reduce administration of postoperative analgesic therapy [29, 30]. Our results show that the analgesic efficacy of long-acting local anaesthetics is seen up to 48 hours postoperatively, long after local anaesthetic action has finished. In addition, the total amount of rescue analgesics is significantly lower with bupivacaine and levobupivacaine treatment over a seven-day period. These results could presents the indirect proof of the suppression of central sensitisation. Conversely, the use of lidocaine with epinephrine which is an intermediate local anaesthetic, does not provide sufficient blockage of postoperative neural hyperexcitability.

Regarding the patient's satisfaction with the overall treatment, significantly higher number of patients marked bupivacaine and levobupivacaine higher than lidocaine with epinephrine. It could be postulated that the overall patient's satisfaction is in strong correlation with satisfaction with the achieved analgesia, while prolonged analgesia seemed to favour the patients' choice of a better anaesthetic. Moreover, the quality of life after oral surgical interventions can have a major impact on a patient's future perception of pain and preoperative anxiety [31].

Conclusion

In our study, 0.5% levobupivacaine and 0.5% bupivacaine provided more pronounced postoperative analgesic effects in comparison to 2% lidocaine with epinephrine (1:80,000), due to the reduced levels of postoperative pain and the need for postoperative analgesic consumption. In addition, 0.5% levobupivacaine provided an analgesic effect similar to 0.5% bupivacaine after third molar surgery.

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