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A randomized anesthethic potency comparison between ropivacaine and bupivacaine on the perioperative regional anesthesia in lower third molar surgery

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ABSTRACT

Background: Perioperative pain control by means of local anesthesia is an intrinsic part of surgical practice.
Aim: To evaluate the anesthetic potencies between ropivacaine and bupivacaine in the surgery of mandibular horizontally impacted teeth.
Material and method: Outpatients of both sexes, in the age range from 18 to 70 yrs. of age (mean age: 26.48 ± 3.66), participated in this clinical study. After mandibular conduction anesthesia of 0.75% ropivacaine in group I, 0.5% bupivacaine in group II, and 2% lidocaine with 1:100000 epinephrine in group III, the following anesthetics variables were measured: quality of anesthesia score (QAS), success rate of local anesthesia (SLA), onset time of anesthesia (OT), duration of anesthesia (DA), intensity of intraoperative pain (IIP) (VAS scale in mm). Blood pressure, and pulse were measured.
Results: Ninety patients, divided into three equal groups, were enrolled for the study. Ropivacaine gained statistically significant ($p < 0.05$) variables: QAS of 1.77 ± 0.68 and IIP was 18.90 ± 6.11 mm ($p < 0.05$). The SLA of the achieved local anesthesia was 96.6%, 93.3% and, 86.6% for ropivacaine, lidocaine with epinephrine 1:100000, and bupivacaine groups, respectively. OT was 151.50 ± 80.93, 168.27 ± 79.73, and 89.80 ± 27.91 sec, for groups I, II and III, respectively. The DA for ropivacaine was 412.17 ± 110.04 min, while the one for bupivacaine and lidocaine with epinephrine 1:100000 was 376.30 ± 98.51 min., and 216.13 ± 47.69 min., respectively. Hemodynamic parameters were insignificant to cause side effects.
Conclusion: 0.75% ropivacaine provided successful local anesthesia in 96.6% of the patients, better quality and onset of anesthesia with the duration of anesthesia of 412.17 ± 110.04 min and lower intraoperative pain than in the case of 0.5% bupivacaine and 2% lidocaine with epinephrine.

1. Introduction

Intraoperative pain control by means of local anesthesia is an intrinsic part of clinical practice in oral surgery. The management of a patient's postoperative pain after ambulatory surgery of impacted wisdom teeth under local anesthesia is one of the essential goals in the overall treatment of patients with impacted teeth. This is because the third molar extraction of wisdom teeth is a very common surgical procedure, with frequent moderate or severe postoperative pain in terms of its intensity (Barden et al., 2004; Mobilio et al., 2011). The elimination of postoperative pain has led clinicians to use intravenous paracetamol or morphine for the treatment of patients' postoperative pain (Van Aken et al., 2004), and relief of patients' suffering, enabling the patients' socio-economic activity, and increasing overall patient satisfaction (Kumar et al., 2014). There is evidence in literature that, in the postoperative treatment of pain episodes, various local anesthetics provide analgesia after some, but not all surgeries (Gupta, 2010).

For many decades, 2% lidocaine with epinephrine was the usual and preferable local anesthetic in everyday dental practice (Ernberg and Kopp, 2002). Its relatively quick onset (2 min) and a medium range of soft tissue anesthesia (190 min) (Haas, 2002) potentiate it as successful everyday working local anesthetic (Allen, 1979; Malamed, 1986).

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On the other hand, surgical procedures favor local anesthetics for long-lasting local anesthesia, because they reduce the need for postoperative analgesic drugs (Johansson et al., 1994).

One of the regionally well-known and potent long-acting amid type anesthetics which serves this purpose is bupivacaine. Even though the pharmacological structure of bupivacaine provides a long-lasting effect of anesthesia, with local vasodilatation, which does not alter the presence of bupivacaine in blocking the nerve's sodium intracellular voltage dependent channels, the duration of its anesthetic action is 240 and 440 min for mandibular pulp and soft tissue, respectively. However, bupivacaine has demonstrated cardio toxicity and arrhythmogenicity when administered in a higher dose, or accidentally, via intravascular route (Haas, 2002; Hansen, 2004). After the first report on the six cases of almost simultaneous convulsions and heart failure, following an unwanted intravascular application of the clinical doses of bupivacaine (Ahlbright, 1979), as well as subsequent reports of more deaths (Horlocker and Wedel, 2002), the need arose for the development of long-acting local anesthetics that would be safer for application.

Based on previous pharmacological needs for safer local anesthetics, another long-lasting, amide type anesthetic was developed, one as potent as bupivacaine – ropivacaine. (McClure, 1996; Nau and Strichartz, 2002; Hansen, 2004; Dillane and Finucane, 2010). As a long-lasting regional anesthetic, ropivacaine was developed as the successor of bupivacaine in terms of its anesthetic duration and potency, and with a lower toxicity level on the central nervous system (CNS) and cardiovascular system compared to bupivacaine, which has been investigated and proven in animal experiments (Danielsson et al., 1997; Zhang et al., 2003; Zink et al., 2005), and human studies (Knudsen et al., 1997; Mather and Chang, 2001; Ryu et al., 2007). Ropivacaine is a racemate S(−)enantiomer, developed for the purpose of reducing potential toxicity to the central nervous system, as well as cardiotoxicity, improving relative sensory profiles, and enabling lower motor block (Simpson et al., 2005), with an overall better systemic toxicity tolerance when compared to bupivacaine (Hansen, 2004). In preclinical studies, it was shown that ropivacaine caused lower arrhythmogenicity than bupivacaine (Aya et al., 2002), but displayed less anesthetic potency than bupivacaine in terms of the length of analgesia (Juncos et al., 2001). Its duration of anesthetic action is 3.3 ± 0.3 h for the inferior alveolar nerve block required for lower third molar extraction(El-Sharrawy and Yagiela, 2006).

However, a question arises regarding the overall anesthetic potency of ropivacaine for oral surgery use, with the minimum administrated dose of ropivacaine, which enables reducing side effects, but still providing adequate regional anesthesia for surgery. The successful use of ropivacaine as a long-acting anesthetic for various oral surgery operations was previously reported in English literature (Buric, 2006).

Interestingly, the anesthetic evaluation of ropivacaine and bupivacaine in the pain elimination associated with the surgical removal of horizontally impacted lower wisdom teeth has not been exhaustively studied in patients.

The purpose of this study is to evaluate the anesthetic potencies of ropivacaine and bupivacaine, as well as their influence on hemodynamic parameters in the surgery of horizontally impacted lower wisdom teeth.

2. Material and methods

2.1. Subjects

Outpatients of both sexes, in the age range from 18 to 70 yrs., participated in this randomized, double blinded clinical study, following Institutional Ethical Board approval (# of approval: 20/2-2017-3EO, dated 12/02/2018). All patients included in the study were in good health and categorized as physical status Grade I (ASA I), according to the American Society of Anesthesiologists (ASA). Informed consent was obtained for every patient before the administration of conduction anesthesia and surgery of the impacted wisdom tooth. To participate in this study, each patient had to present a mandibular asymptomatic horizontally impacted wisdom tooth, based on the clinical and radiological appearance using Winter's classification (Winter, 1926) (Fig. 1). The exclusion criteria were allergies of any kind to food and drugs, especially to pain killers, ibuprofen, antibiotics, as well as preoperative local inflammation, pregnancy, breast-feeding status and orofacial pain.

2.2. Study design and injection administration

Patients were arbitrarily selected, using a sealed envelope technique, to randomly receive either plain 0.75% ropivacaine (Naropin® 0.75%; Astra Zeneca, Sodertalje, Sweden) in group I, plain 0.5% bupivacaine (Marcaine® 0.5%; Astra Zeneca, Sodertalje, Sweden) in group II, and 2% lidocaine with epinephrine 1:100000 (2% lidocaine with 1:100000 epinephrine, AD Galenika, Belgrade, Serbia) in group III, in a double-blind fashion. The expiration date was checked on each of the cartridges and ampoules of anesthetics before use. Preceding the surgery, the syringes with 3 anesthetic solutions were randomly assigned 3-digit numbers, randomly selected by the research staff from the surgical ward included in this study, paying attention to secrecy. The random numbers were subsequently assigned to patients, designating which local anesthetic the patient was to receive.

Sterile disposable plastic 2 mL syringes (Nipro syringe, Shanghai International Holding Corp.GmbH (Europe), Eifestrasse 80, 20537 Hamburg Germany), and 21 GI × 1½ ", 0.8 × 40 needles were used for the administration of local conduction anesthesia belonging to amide type anesthetics. In all groups, mandibular conduction anesthesia, i.e. Halsted's technique (Myer, 1999; Reed, 2002), was used for the administration of 2 mL of each tested local anesthetic in the following fashion: 1.5 mL for inferior alveolar nerve anesthesia, 0.3 mL for lingual nerve anesthesia, and 0.2 ml for buccal nerve anesthesia. In the case of an insufficient effect of the local anesthesia, an additional, second application of conduction anesthesia was performed with 2 mL of the tested anesthetics, in the same manner as the previous procedure, and in the case of its failure, the third attempt was made to achieve successful anesthesia, performed with 2 mL 2% lidocaine with epineprhine 1:100000. All attempts of the infiltration of local anesthetics are noted on the 8-point quality scale for anesthesia.

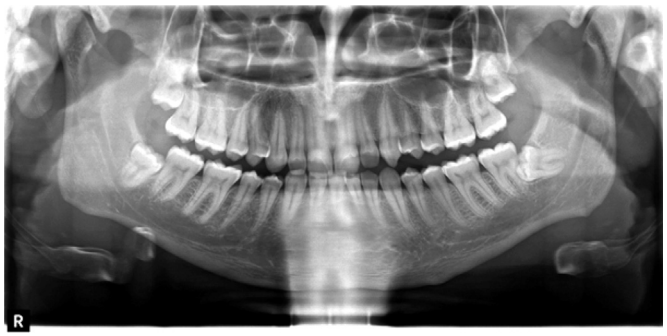

Fig. 1. A horizontally positioned left wisdom impacted tooth.

2.3. Surgery

All the impacted mandibular wisdom teeth in the horizontal position were surgically extracted with the same surgical technique, as follows. Using surgical blade # 15, the mucoperiosteal horizontal envelope flap was extended to the interdental papillae of the first molar. A gingival sulcular incision was performed from the papillae of the first molar, extended distobuccally to the angle of the second molar, with a vertical incision posteriorly and laterally, considering the anterior ramus margin. After the elevation of the mucoperiosteal flap, the bone overlying the impacted wisdom tooth was removed with surgical steel burs (# 167-141, Meisinger HM, Neuss, Germany), with a continuous flow of cold (8 °C), and sterile saline. Wisdom tooth odontectomy was performed, in some cases, with the odontomy and separation of the tooth at the level of the cervical and mesial part of the crown, from the retained roots, followed by subsequent odontomy and the removal of roots. After the debridement of surgical wounds, the mucoperiostel flap was repositioned into its original position, and sutured with single interrupted non-absorbable sutures (Silk USP 3/0 EP 2, SMI AG Steinerberg 8, 4780 St.Vith, Belgium). The sutures were removed on the 7th post-operative day. Patients were instructed to use painkillers in case of intolerable pain (NSAID – Ibuprofen 400 mg, Brufen® 400; Galenika, Belgrade, Serbia), 2 × 400 mg/day, in the postoperative course, only if the pain was severe. All the patients were instructed to preventively use the following antibiotics orally: amoxicillin 875 mg, with 125 mg clavulanic acid (Panklav, Hemofarm, Vršac, Serbia) 2 × 1 g/day for at least 5 days. In case of a known allergy to amoxicillin, it was replaced by clindamycin (Clindamycine MIP, 66386 St. Ingbert, Germany), 3 × 600 mg every 8 h per day, for at least 5 days.

2.4. Parameters of anesthesia and analgesia

After the injection into the pterygomandibular space, and reaching the mandibular nerve's periforaminal area, negative aspiration was conducted through a needle. To determine the onset time (OT) of conduction mandibular anesthesia, we minutely measured the time immediately after the infiltration of the anesthetic to the moment of the patient subjectively beginning to feel lower lip numbness. This procedure was repeated until the full effects of anesthesia were achieved, i.e. the absence of any reactions to a stab on the lip with a sharp instrument.

To objectively measure the anesthetic potency of anesthetics during surgery, we used an 8-point quality on the anesthesia score scale (QAS), according to Sisk (1986). The following parameters were rated: 1. Successful – no pain throughout the procedure; 2. Successful – some pain during the procedure, but reinjection was not necessary after the beginning of the surgery; 3. Successful – pain during the procedure, beginning after the first injection, no pain after the second injection; 4. Limited success – pain during the procedure, beginning after the first injection, pain also during the procedure, after the second injection, but surgery completed without the third injection; 5. Limited success – pain during the procedure, beginning after two injections, but surgery completed without a third injection; 6. Failure – pain during the procedure, beginning after the first injection, pain also during the procedure after the second injection, third injection required; 7. Failure – pain during the procedure, beginning after two injections, third injection required; 8. Failure – no anesthesia after two injections, third injection required or treatment suspended. The assessment of rated parameters was conducted by the authors.

To measure the success of local anesthesia (SLA), we measured the success rate of the achieved local anesthesia, expressed in percentages.

The intensity of intraoperative pain (IIP) during wisdom tooth surgery was assessed by patients postoperatively, by their marking a visual analogue scale (VAS) (Briggs and Closs, 1999), with a straight horizontal line from 0 to 100 mm (10 cm) (0 = no pain and 100 mm = worst imaginable pain). On the line, the patients marked the experienced pain by their sensation. The VAS scale was also used for the determination of the analgesic effects of the tested local anesthetics by assessing the intensity of the first pain and the pain 6 h after the infiltration of local anesthesia, with a measurement of the time of first pain onset. The mandibular block was considered successful if the patient's tooth was surgically extracted with no pain (up to 4 mm) or a pain rating of up to 44 mm, which is considered mild pain (Jensen et al., 2003).

Analgesia assessment was performed by patients' recording the time of the first postoperative pain and the measurement of pain by VAS, first postoperative use of analgesics, as well as the number of the total consumption of analgesics postoperatively after 24 h.

The duration of conduction mandibular anesthesia (DA) was determined from its onset up to the moment when lip numbness was terminated. All the side effects of the tested local anesthetics were recorded in the research paper over 7 days postoperatively.

2.5. Haemodynamic parameters

The blood pressure values (systolic and diastolic blood pressure) and pulse values were obtained before the administration of local anesthetics, 5 and 10 min post-infiltration of local anesthetics, and at the end of wisdom tooth extraction surgery.

All hemodynamic parameters were obtained with an automatic sphygmomanometer (Omron M7 Intelli IT, OMRON Healthcare Group, Kyoto, Japan).

2.6. Sample size

Sample sizes were based on an equal 3-group amide type local anesthetics comparison (ropivacaine, bupivacaine and lidocaine with 1:100000 epinephrine), for mandibular conduction anesthesia, with the outcome of several variables of anesthetic measures. The measured anesthetic variables were the frequency of successful anesthesia (FA), onset time (OT) and the duration of anesthesia (DA). Analgesia (pain) assessment was performed on the visual analogue scale (VAS), 0–100 mm (10 cm) (0 = no pain and 100 mm = worst imaginable pain), by recording the intensity of intraoperative pain (IIO), intensity of first postoperative pain (IFP), and the intensity of pain 6 h after the operation (IPAO), with a standard divergence ranging from 1 to 2. In addition, the monitored variables were the first postoperative use of analgesics, and the number of the total consumption of analgesics 24 h postoperatively.

The sample size calculation was based on the following parameters: estimated medium effect size – partial $\eta^2 = 0.06$, α error: 0.05, and power of the study: 95%, three groups, and four repeated measurements. The medium effect size of the tested subjects would be sufficient to recommend a change in clinical practice. The calculated sample size of 45 was doubled because of the potential variability of the anesthetic's variables, as well as the systolic and diastolic blood pressure and heart rate. In this study, we enrolled 30 subjects for each group of local anesthetics investigation because this number of participants provided us with a safer clinical (practical) relevance for the tested variables of local anesthetics. The calculation was conducted in G*Power 3.1.9.2 software (Faul et al., 2007).

The power analysis was conducted to ensure that the study groups were large enough and fit for the purpose. The calculation was based on the partial η^2 of mixed model interaction, and the number of subjects per group. A type-I error was set at 0.05 (p

-value). The final sample size of 90 participants would achieve 100% power of the study. A study power analysis was done in G*Power software, version 3.1.9.2 (Faul et al., 2007).

2.7. Statistical analysis

A statistical analysis was performed using SPSS (version 15.0; SPSS, Chicago, IL, USA). Continuous variables are presented as the results given as means ± SD (standard deviation). The Shapiro-Wilk test was performed as a test of continuous variable normality. Categorical variables were presented as absolute numbers (N). The statistical significance was defined as $p < 0.05$. Independent sample t-tests or Mann–Whitney test (depending on data distribution normality for continuous variables) and chi-square tests were used to assess for group differences at baseline. The significance of the differences of continuous variables within groups was analyzed using the Student's t-test for paired samples or Wilcoxon signed ranks test, depending on data distribution normality.

A repeated measurement and mixed ANOVA model were used to examine the effect of time and treatment group. Within-group changes were tested using pairwise comparisons for each variable. The effect size was assessed based on partial η^2 values.

3. Results

Ninety-eight patients were randomly assessed for the fulfillment of eligibility criteria of this study. Eight were ineligible based on the exclusion criteria; a study cohort of ninety patients, divided into three equal groups of patients (30 + 30+30), was registered for the investigation and the analysis of effectiveness of 0.75% ropivacaine (group I), 0.5% bupivacaine (group II), and lidocaine with 1:100000 epinephrine (group III). A total group of ninety patients completed the surgery of lower wisdom teeth with an anesthesia investigation of the tested anesthetics, without any side effects concerning the local anesthetics. The patients' demographic characteristics and the duration of the surgical intervention are presented in Table 1. No statistical significance was found considering the sex and age of the patients. The mean quality of the anesthesia rating score (Table 2) showed statistically significant results of the score (1.77 ± 0.68) ($p < 0.05$), i.e. no pain or some pain (rate 1 and 2) in 80% (24/20) of the patients in the ropivacaine group, with an overall frequency of SLA in 96.6 % (29/30; rating rates 1 to 3) of the patients, with the supplemental second local anesthesia in 6 (20%) patients. In the bupivacaine group, SLA occurred in 86.6 % (26/30) of the patients, with an additional second anesthesia in 11 (36.7%) patients, and with a worse mean anesthesia quality result score (2.37 ± 1.22), when compared to the ropivacaine group. The lidocaine group revealed a better mean quality of the anesthesia rating score (2.00 ± 11) than the bupivacaine group, with an overall SLA in 93.3% success of local anesthesia among the patients, with an additional second anesthesia in 6 (20%) patients, while in 1 patient (3.3%), a third anesthesia was needed. A greater intensity of the mean intraoperative pain during surgery was recorded in the bupivacaine group than in the lidocaine and ropivacaine groups (25.40 ± 12.99 mm, 20.27 ± 14.31 mm and 18.90 ± 6.11 mm, respectively) with statistically (Mann–Whitney) significantly lower pain in favor of ropivacaine ($p < 0.05$).

Analyzing the quality of the anesthesia rating score, and the number of the received injections of local anesthetics (Table 2) from the point of view of clinical significance, it is worth emphasizing that, in all three groups, a supplemental injection of local anesthetics was necessary. In the ropivacaine group, 6 patients (20%) received a supplemental second injection of 2 mL 0.75% ropivacaine, intraoperatively, with the rating of 3 (success), and 4 (limited success) for 5 patients and 1 patient, respectively. In the bupivacaine group, supplemental second injections of 2 mL 0.5% bupivacaine were received by 9 (30 %) patients, with the rating of 3 (success) and 4 (limited success), for 7 and 2 patients, respectively. One patient (3.3%) received double injections of bupivacaine, with the rating of 5 (limited success), while another patient (3.3%) received the third injection with 2 mL 2% lidocaine with epinephrine 1:100000, with the rating of 6 (failure), but with subsequent surgeries completed. The lidocaine group showed better results than the bupivacaine group in terms of the received additional injections of anesthetics. Six (20%) patients received a supplemental second injection of 2 mL 2% lidocaine with epinephrine 1:100000, with the ratings of 3 (success) and 4 (limited success), while one patient (3.3%) received the third injection of the same dose of lidocaine, with the rating of 6 (failure). Overall supplemental injections of the tested local anesthetics in the ropivacaine, lidocaine, and bupivacaine groups were 6 (20%), 7 (23.3%), and 11 (36.6%), respectively.

Table 3 summarizes all the anesthetic variables monitored in this study. The longest mean duration of anesthesia, measured by the termination of lower lip numbness, was observed in the ropivacaine group (412.17 ± 110.04 min) compared to the bupivacaine group (376.30 ± 98.51 min) and, with a statistically and clinically significant duration of the anesthesia in the ropivacaine and bupivacaine groups, compared with the lidocaine group (216.13 ± 47.69 min, $p < 0.001$). The longest mean time of the onset of the first postoperative pain was observed in the ropivacaine group: 340.97 ± 78.70 min, while the bupivacaine groups exhibited 317.30 ± 82.14 min, and the lidocaine group exhibited 157.30 ± 56.51 min. In group I and II, the intensity of the first postoperative pain and of the pain 6 h after the intervention was lower than the intensity of pain during the intervention, and significantly lower ($p < 0.001$) than in group III. The time taken for the first analgesic intake since the end of the intervention was approximately the same in groups I and II, and significantly lower ($p < 0.001$) compared with the same variables in group III. It is interesting that, in the ropivacaine group, 5 patients did not take analgesics at all in the first 24 h, the same as the ones in the group with bupivacaine 3. In group III, with the exception of the mean intensity of intraoperative pain (20.27 ± 14.31 mm), which is lower than in the bupivacaine group (25.40 ± 12.99 mm), but higher than in the ropivacaine group (18.90 ± 6.11 mm), all the aforementioned variables were significantly lower in comparison with the ropivacaine and bupivacaine groups. All the characteristics of the variables for the aforementioned study parameters are shown in Table 3.

Hemodynamic parameters were consistent in both groups and, clinically, showed no systemic side effects which could lead to the termination of the procedure.

After the injection of 2 mL 2% lidocaine with 1: 100000 epinephrine in the first 5 min, there was an increase in systolic

Table 1
Demographic and surgical data.

Parameters	Ropivacaine	Bupivacaine	Lidocaine/ Epinephrine	Total
N (number of patients)	30	30	30	90
Sex (male/ female)	14/16	13/17	16/14	43/47
Age (years)	26.60 ± 4.34	25.73 ± 3.10	27.10 ± 3.44	26.48 ± 3.66
Duration of surgery (min)	32.93 ± 9.58	34.47 ± 8.60	37.13 ± 11.42	34.84 ± 9.98
Root sectioning (yes/no)	11/19	13/17	14/16	38/52

Table 2
Quality of anesthesia score.

ANESTHETIC	MARK								Mean quality of anesthesia (mean ± SD)
	1	2	3	4	5	6	7	8	
Ropivacaine 0,75%	14	10	5	1	–	–	–	–	**1.77 ± 0.68**[*B]
Bupivacaine 0,5%	7	12	7	2	1	1	–	–	**2.37 ± 1.22**
Lidocaine 2%- epinephrine	11	12	5	1	-	1	-	-	**2.00 ± 1.11**

[*] – $p < 0.05$ (Mann–Whitney Test), B-vs Bupivacaine.
1-successful - without pain. 2-successful- minimal pain during procedure without additional anesthesia after the start of surgery. 3- successful - minimal pain after first anesthesia, no pain after another anesthesia. 4- limited success - pain during surgery after first anesthesia and after second anesthesia, but surgery completed without third anesthesia 5- limited success - pain during surgery begins after two anesthesia but surgery completed without third anesthesia 6- failure - pain during surgery after first anesthesia, pain during surgery after second anesthesia, needed third anesthesia 7- failure - pain during surgery begins immediately after two anesthesia required third anesthesia 8- failure – No anesthesia achieved after two local anesthesia administration, required third anesthesia or surgery postponed.

Table 3
Parameters related to anesthesia and postoperative analgesia (mean ± sd).

Parameters	Ropivacaine	Bupivacaine	Lid/Epi	p
Success rate of anesthesia (%)	96.6	86.6	93.3	NS
Onset time (sec)	151.50 ± 80.93	168.27 ± 79.73	89.80 ± 27.91	$p < 0.001$[b,c]
Duration of anesthesia	412.17 ± 110.04	376.30 ± 98.51	216.13 ± 47.69	$p < 0.001$[b,c]
Quality of anesthesia	1.77 ± 0.68	2.37 ± 1.22	2.00 ± 11	$p < 0.05$[a]
Additional anesthesia	6	11	7	
Intensity of intraoperative pain VAS (mm)	18.90 ± 6.11	25.40 ± 12.99	20,27 ± 14.31	$p < 0.05$[a,c]
Time of the first pain (min)	340.97 ± 78.70	317.30 ± 82.14	157.30 ± 56.51	$p < 0.001$[b,c]
Intensity of first postoperative pain VAS (mm)	15.13 ± 11.85	17.20 ± 10.64	34.47 ± 19.31	$p < 0.001$[b,c]
Intensity of pain 6 h after operation VAS (mm)	17.77 ± 14.53	17.70 ± 11.35	33.10 ± 19.68	$p < 0.001$[b,c]
Time of the first analgesic (min)	352.40 ± 63.51	325.53 ± 64.33	171.97 ± 51.35	$p < 0.001$[b,c]
First analgesic taken (yes/no)	25/5	27/3	30/0	
Number of analgesic taken 24 h postoperatively	1.53 ± 1.04	1.83 ± 0.87	2.53 ± 0.78	$p < 0.001$[b,c]

Lid/Epi- Lidocaine with epinephrine.
NS not significant.
[a] Ropivacaine vs Bupivacaine.
[b] Ropivacai vs Lid/Epi.
[c] Bup vs Lid/Epi.

(Fig. 2) and diastolic pressure (Fig. 3), followed by a decrease in the systolic pressure after 5 min, and an increase in the diastolic pressure up to 10 min. In the end, the diastolic pressure began to drop as well until the end of the monitored blood pressure values.

After administering bupivacaine, the systolic pressure dropped within the first 5 min and then slightly increased. A slight increase in the diastolic pressure was observed in the first 5 min in bupivacaine, or in the first 10 min in the case of lidocaine, after which there was a mild drop in its value.

During the examined period, there were no statistically significant changes in the values of the systolic and diastolic pressure, regardless of the type of the applied anesthetic (Table 4).

By monitoring pulse values, it was observed that it changed significantly in the group receiving lidocaine, and in the group receiving ropivacaine.

In the lidocaine group, five minutes after the administration of anesthetics, there was a statistically significant increase in the pulse relative to the values before administering the anesthetic ($p < 0.001$) (Fig. 4), which persisted for 10 min after administration ($p = 0.011$), and then there was a statistically significant reduction between the 10th minute and the last measurement ($p = 0.022$).

In the ropivacaine group, there was firstly a slight increase in pulse in the first 5 min ($p = 0.490$) (Fig. 4), which lasted for up to 10 min, followed by a statistically significant decrease in the pulse value at a follow-up time of 5 min ($p = 0.005$), as well as at a follow-up time of 10 min ($p = 0.001$) when compared to the last measurement.

The pulse values in the bupivacaine group did not significantly differ statistically at different time intervals. The effect of the pulse change was higher in the group receiving lidocaine compared to the ropivacaine group (Partial η^2 0.724, or Partial η^2 0.473) (Table 4).

The mixed-model ANOVA showed that there was a statistically significant difference in the pulse values over time in the tested groups ($p < 0.001$, Partial $\eta^2 = 0.448$), and that there was an interaction between time and the groups ($p = 0.001$, Partial

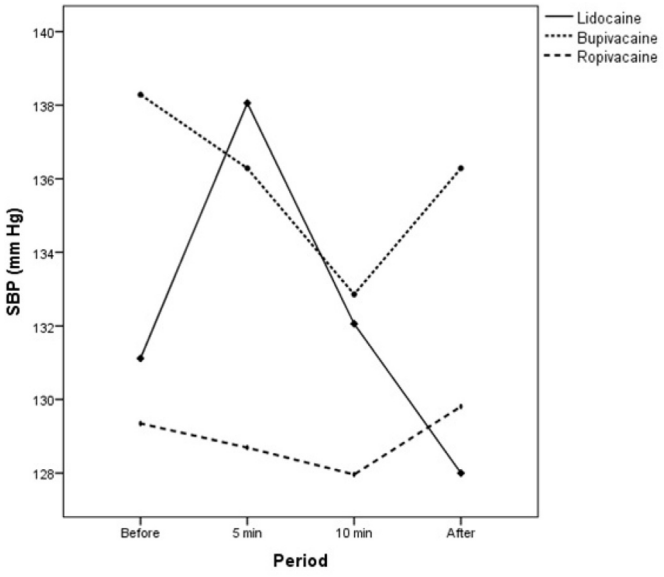

Fig. 2. Systolic arterial blood pressure (SBP) values during the examined period, depending on the used anesthetics. There was no significant difference in SBP values in all groups.

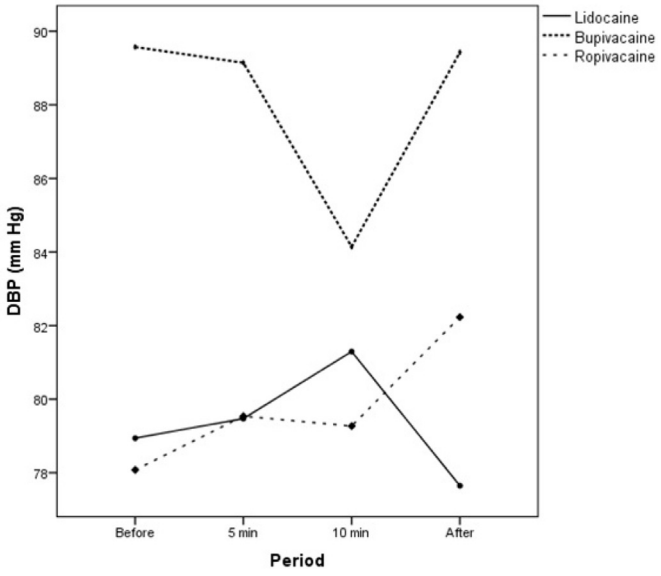

Fig. 3. Diastolic arterial blood pressure (DBP) values during the examined period, depending on the used anesthetics. There was no significant difference in DBP values in all groups.

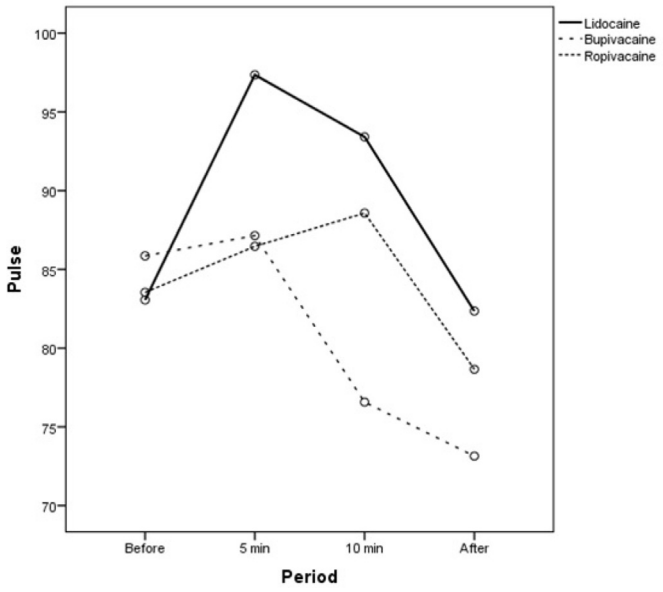

Fig. 4. Pulse values during examined period, depending on the used anesthetics. Five minutes after application of anesthetics, there is significant increase in pulse in lidocaine with epinephrine ($p < 0.001$) and ropivacaine group ($p = 0.490$).

Table 4
Systolic and diastolic arterial blood pressure and pulse rate values during the examined period, depending on the used anesthetics.

	Lidocaine	Bupivacaine	Ropivacaine
SBP			
Before	131,12 ± 17,71	138,29 ± 14,30	129,35 ± 12,13
5min	138,06 ± 25,30	136,29 ± 20,50	128,69 ± 15,41
10 min	132,0 ± 20,54	132,86 ± 24,87	127,96 ± 16,45
After	128,00 ± 14,79	136,29 ± 17,46	129,81 ± 16,21
p-value[a]	0,327	0,982	0,825
Partial η^2	0,212	0,036	0,038
DBP			
Before	78,94 ± 10,17	89,57 ± 12,58	78,08 ± 8,79
5min	79,47 ± 14,03	89,14 ± 12,57	79,54 ± 9,75
10 min	81,29 ± 14,29	84,14 ± 19,38	79,27 ± 9,89
After	77,65 ± 10,82	89,43 ± 8,79	82,23 ± 13,16
p-value[a]	0,678	0,938	0,433
Partial η^2	0,100	0,088	0,110
Pulse			
Before	83,06 ± 12,40	85,86 ± 17,48	83,54 ± 14,49
5min	97,35 ± 15,58	87,14 ± 22,03	86,46 ± 13,21
10 min	93,41 ± 14,39	76,57 ± 11,66	88,58 ± 15,99
After	82,35 ± 12,92	73,14 ± 13,40	78,65 ± 12,59
p-value[a]	<0,001	0,141	0,002
Partial η^2	0,724	0,710	0,473

SBP- systolic arterial blood pressure, DBP- diastolic arterial blood pressure.
[a] ANOVA for repeated measure.

$\eta^2 = 0.220$). In both cases, the effect of the change was large because Partial $\eta^2 > 0.14$.

Hemodynamic parameters were fully within the limits that clinically showed no side effects which could lead to the termination of the procedure.

4. Discussion

This study demonstrates the magnitude of more successful local anesthetics in the surgery of mandibular wisdom teeth, and an analgesic efficacy of 0.75% ropivacaine, compared to 0.5% bupivacaine and 2% lidocaine with 1:100000 epinephrine.

In the lidocaine group, the investigated variable of the mean onset time was statistically faster (almost 2 min) compared to the ropivacaine group (almost 2.5 min) and the bupivacaine group (almost 3 min). Available literature data demonstrated that non-ionized molecules of the local anesthetics, with pKa close to physiologic values, are capable of realizing faster diffusion through the nerve cell's membrane (Mc Lure and Rubin, 2005). That is why the faster onset of local anesthesia with 2% lidocaine with 1:100000 epinephrine is not a surprise in this study; lidocaine's onset is dependent on its lower dissociation constant – pKa (7.7), which is very close to the physiologic values of tissue pKa (7.4), enabling more lidocaine molecules to penetrate the nerve faster per unit of time (Mc Lure and Rubin, 2005). The pKa for ropivacaine and bupivacaine is 8.1, so the gained onset values in this study for ropivacaine and bupivacaine are, therefore, slower than lidocaine, but still rapid due to their pharmacokinetic properties (Casati and Putzu, 2005). The higher concentration of ropivacaine and its lower lipid solubility leave enough free local anesthetic molecules to bind and penetrate the nerve sheet faster per unit of time (Casati et al., 1999). These cellular events were clinically manifested in our study, with the fast onset of local anesthesia in the case of ropivacaine.

The other investigated parameters also favor the use of ropivacaine for local anesthesia: 0.75% ropivacaine provided successful local anesthesia in 96.6% of the patients, which is much better than 0.5% bupivacaine and 2% lidocaine with 1:100000 epinephrine, which accounted for 86.6% and 93.3 % of the realized successful local anesthesia, respectively. The mean duration of the achieved conduction anesthesia for ropivacaine was almost 7 h, while the one for bupivacaine was almost 6 h, and about 3 ½ hours for lidocaine anesthesia. The mean time of the first pain occurrence was almost 6 h in the ropivacaine group, slightly more than 5 h in the bupivacaine group, and 2 ½ hours in the group that received lidocaine with epinephrine. Ropivacaine also contributed to the fact that the patients experienced a lower intensity of the first post-operative pain (VAS).

There is an insufficient number of papers regarding the use of ropivacaine in oral surgery (Buric, 2006; El-Sharrawy and Yagiela,

2006; Brkovic et al., 2010; Tijanić et al., 2010, 2012; Espitalier et al., 2011), and only a few of them have investigated the use of ropivacaine for the surgical extraction of the lower wisdom molar (Mansour et al., 2012; Budharapu et al., 2015; Crincoli et al., 2015; Brković et al., 2017). In this study, in the ropivacaine group, interventions were performed with minimum pain, with the achieved full effectiveness of local anesthesia with ropivacaine in 96.6% ($p < 0.05$) of the patients. In 80% of the patients, the quality of the anesthesia score obtained in this study was between 1 and 2 ($p < 0.05$), which is very similar to the results of El-Sharrawy and Yagiela (2006). The same authors obtained a score between 1 and 2 on the slightly modified rating scale. Statistically, the successful local anesthesia in the bupivacaine group is 86.6%, and has a significantly worse mean anesthetic score quality among the tested anesthetics, with a score of 2.37 ± 1.22. The lidocaine group yielded successful local anesthesia in 93.3% of the patients, and realized a better anesthetic score quality of 2.00 ± 11, compared with the bupivacaine group. The better clinical results of ropivacaine than those of bupivacaine and lidocaine may be explained by the several following facts.

The higher concentration of 0.75% ropivacaine could be contributed to better local anesthetic effects, owing to the physiochemical properties of ropivacaine, even though there is evidence that 0.5% ropivacaine is of the same potency as the one of 0.75%, and yields the same final clinical results, but with a greater overall anesthetic efficiency than 0.5% bupivacaine (El-Sharrawy and Yagiela, 2006). Ropivacaine has the ability to separate sensory and motor neurological pathways, which are concentration dependable (Wildsmith, 1997). In addition, ropivacaine of a lower concentration has the ability, which is more efficient than that of bupivacaine (McClure, 1996), to anesthetically block myelinated Aδ (acute pain, first pain) (Skljarevski and Ramadan, 2002) and C unmyelinated nerve fibers (slow, second pain) more efficiently than large myelinated Aβ nerve fibers (stretch receptors/mechanoreceptors) (Wildsmith et al., 1989; Hall, 2011).

As elaborated above, the physicochemical properties and the obtained results of the successful intraoperative ropivacaine local anesthesia and postoperative analgesia in the duration of 412.17 ± 110.04 min, with pain relief and the onset of first postoperative pain after 376.30 ± 98.51 min for bupivacaine anesthesia and, 216.13 ± 47.69 min for lidocaine anesthesia, justified the use of 0.75% ropivacaine for mandibular wisdom tooth surgery.

An additional, but less administrated local anesthesia was necessary in the ropivacaine group only for 6 patients, compared with 7 and 11 patients in the lidocaine and bupivacaine groups. The time of the first pain was 340.97 ± 78.70 min in the ropivacaine group, and 317.30 ± 82.14 min in the bupivacaine group, while the fastest first pain episodes were noted in the group that received lidocaine with epinephrine (157.30 ± 56.51 min.). Ropivacaine also contributed to the fact that the patients experienced the lowest intensity of first postoperative pain (15.13 ± 11.85, VAS).

A weaker ropivacaine physicochemical potency to bind to the extra neural and neural lipids (fat) and faster transfer to the target site in the nerve are pharmacokinetic advantages over other tested local anesthetics. This is in agreement with the previous reports and opinions of other researchers concerning ropivacaine and its anesthetic properties (Akerman et al., 1988). It is worth emphasizing the pharmacokinetic fact that less than 3% of the infiltrated local anesthetics penetrate the nerve, and that the rest of the anesthetic volume (97%) is absorbed in the systemic circulation in the subsequent 30 min after the injection (Berde, 2004).

The duration of anesthesia in this study showed that the ropivacaine group gained 412.17 ± 110.04 min of anesthesia, which was clinically (not statistically) more significant when compared with the bupivacaine group, which exhibited 376.30 ± 98.51 min. Ropivacaine and bupivacaine showed identical nerve blocking activities at higher concentrations (Rosenberg et al., 1986). However, in this study, we focused on the minimal volume and the lower concentration of anesthetics for perineural deposition, which provided successful local anesthesia and post-operative analgesia, and discovered that 2 mL of 0.75% ropivacaine may provide favorable nerve blocking.

The surgical extraction of the lower horizontally impacted wisdom tooth often represents an aggressive intervention in which, apart from soft tissue disturbance, it is necessary to remove a greater or smaller part of the bone surrounding the impacted tooth, and to perform tooth sectioning. In oral surgery, primary hyperalgesia occurs due to the peripheral sensitization of receptors in the mucosa and periosteum in a series of inflammatory mediators, such as prostaglandins (Kaczmarzyk et al., 2010), which are synthesized immediately after tissue damage, and occur at higher concentrations for one hour after trauma (Savage and Henry, 2004). The accumulation of prostaglandin E_2 at the site of the surgery is associated with the onset of pain and inflammation after wisdom tooth extraction (Gordon et al., 2008). The anesthetic effect of medium-lasting local anesthetics (such as 2 mL of 2% lidocaine with 1:100000 epinephrine) usually terminates 1–2 h after the end of the surgery, which coincides with the maximum release of major pain mediators, such as prostaglandin and bradykinin (Ong and Seymour, 2003). It is known that, after surgical extraction of the wisdom tooth, pain usually occurs before soft tissue sensitivity returns to normal (Respect, 1976), and is the strongest between 3 and 8 h after the termination of the operation (Seymour et al., 1985; Fisher et al., 1988; Bjørnsson et al., 2003). The use of long-lasting local anesthetics is a way to serve as an analgesic and block postoperative pain for hours after surgery, delaying the return of pain sensitivity in the region being operated on until the maximum level of the major pain mediators decreases. Long-lasting local anesthetics, such as ropivacaine and bupivacaine, are used in order to prolong perioperative securitization and decrease postoperative sensitization that manifests itself as hyperalgesia after the cessation of local anesthetic action, thereby reducing postoperative pain and accelerating recovery (Gordon et al., 2008). Some authors believe that the use of local long-acting anesthetics reduces the use of analgesics in the postoperative period, and that long-acting anesthetics with a gradual onset of pain make pain control easier (Respect, 1976; Laskin, 1978; Marković and Todorović, 2006; Duka et al., 2007). A combination of long-lasting local anesthetics, and analgesics from the group of non-steroidal anti-inflammatory drugs (NSAIDs), seems to be effective in controlling postoperative pain (Hyrkäs et al., 1994). Although some authors (Marković and Todorović, 2006) recommend that NSAIDs should not be used due to their adverse effects, the administration of analgesics seems to be justified, and in some cases, necessary. The concept of the application of a long-lasting local anesthetic after the end of the surgery to prolong post-operative analgesia (Brković et al., 2017), as well as the application of liposomal anesthetic formulation (Franz-Montan et al., 2012; Lieblich and Danesi, 2017), is interesting. In this study, both long-lasting anesthetics exhibited a certain analgesic effect in the postoperative period. The time taken for the first analgesic was over 5 h after surgery as a result of the long effect of the applied anesthetics, with 16.7% of the subjects in the ropivacaine group, and 10% in the bupivacaine group who did not take analgesics in the first 24 h postoperative period. This prolonged and favorable duration of ropivacaine local anesthesia could be explained with its lipid solubility, with less plasma protein binding than bupivacaine, with the same pKa characteristics as bupivacaine.

There is evidence in literature that, by virtue of its vasoconstrictor effect, ropivacaine has a lower potential to cause cerebral toxicity and cardiotoxicity when compared to bupivacaine (Zink

and Graf, 2004; Casati and Putzu, 2005; Simpson et al., 2005; Dillane and Finucane, 2010). Clinical trials have shown that higher doses of ropivacaine are required up to 25%, compared to bupivacaine, prior to the onset of cerebral toxicity (Scott et al., 1989; Knudsen et al., 1997). Owing to the lower doses, the use of ropivacaine in the orofacial region does not cause a significant change in cardiovascular parameters (Oliveira et al., 2006; Brkovic et al., 2010; Krzemiński et al., 2011), while the addition of epineprhine 1:200.000 to ropivacaine may cause a transient increase in blood pressure and pulse 2 min after injection (Oliveira et al., 2006). During our study, there was no statistically significant change in the values of systolic and diastolic pressure, regardless of the type of anesthetic applied. Five minutes after the application of anesthetics, there was an increase in pulse values in all groups. In the group with ropivacaine, the pulse rate at the end of the examined period was statistically lower in relation to the measured value of 10 min after the application of anesthetics ($p < 0.001$). Furthermore, the hemodynamic changes that occurred could probably have been due to the increased serum epinephrine and are stress dependent. The half-life of plasma epinephrine is short and less than 1 min, while pharmacotherapeutically administered epinephrine is eliminated from the bloodstream in about 10 min or less, due to the decomposition by catechol-O-methyl transferase (COMT) in the blood, liver, lungs and other tissues. (Pallasch, 1998).

4.1. Strengths and weaknesses of the study

The presented study has certain limitations. Most of the treated patients were in the 2nd and 3rd decades of their lives, with the same or similar demographic characteristics. The results of this study, therefore, cannot be extended to other (older) age groups with and without other dental or medical problems. We were also unable to get blood samples from the subjects (ethical reasons and unwillingness of the patients to allow blood screenings), for measuring the total and, more importantly, the plasma free concentration of ropivacaine, which is bound to plasma α 1-acid glycoprotein, which increases following surgery (Yokogawa et al., 2007), and correlate the obtained results with the clinical effectiveness of the tested anesthetics. Even though the presented results are clinically valid and statistically significant, an investigation involving a bigger group of subjects could be beneficial for researchers and clinicians, so further investigation is required concerning the clinical use of long lasting local anesthetics for different clinical indications in orofacial surgery.

5. Conclusion

Following the results of our study, the use of 2 mL 0.75% of ropivacaine, can be successfully administered in long-lasting oral surgery, which is followed by intense postoperative pain. The magnitude of perioperative pain reduction during the surgery of the lower wisdom tooth is realized through the local long-lasting anesthetic 0.75% ropivacaine, over 2 mL 0.5% long-lasting bupivacaine, and medium-lasting 2 mL 2% lidocaine with 1: 100000 epineprhine. Ropivacaine provided successful local conduction anesthesia in 96.6% of the patients, exhibited the duration of anesthesia of near 7h, better quality and the shorter onset of local anesthesia, as well as success of local anesthesia with the less intense intraoperative pain, which persisted in the cases of bupivacaine and lidocaine.

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Conflict of interest

None.

References

Ahlbright GA: Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 51: 285–287, 1979

Akerman B, Hellbetg IB, Trossvik C: Primary evaluation of the local anesthetics properties of the amino amide agent ropivacaine (lea 103). Acta Anaesthesiol Scand 32: 571–578, 1988

Allen GD: Dental anesthesia and analgesia: local and general, 2rd ed. Baltimore,MD: Williams and Wilkins, 64–77, 1979

Aya AG, de la Coussaye JE, Robert E, Rampart J, Cuvillon P, Mazoit JX, et al: Comparison of the effects of racemic bupivacaine, levobupivacaine, and ropivacaine on ventricular conduction, refractoriness, and wavelength: an epicardial mapping study. Anesthesiology 96: 641–650, 2002

Barden J, Edwards JE, McQuay HJ, Andrew Moore R: Pain and analgesic response after third molar extraction and other postsurgical pain. Pain 107: 86–90, 2004

Berde C: Local anesthetics in infants and children: an update. Paediatr Anaesth 14: 387–393, 2004

Bjørnsson GA, Haanaes HR, Skoglund LA: Ketoprofen 75 mg qid versus acetaminophen 1000 mg qid for 3 days on swelling, pain, and other postoperative events after third-molar surgery. J Clin Pharmacol 43(3): 305–314, 2003

Briggs M, Closs JS: A descriptive study of the use of visual analogue scales and verbal rating scales for the assessment of postoperative pain in orthopedic patients. J Pain Symptom Manag 18: 438–446, 1999

Brkovic BM, Zlatkovic M, Jovanovic D, Stojic D: Maxillary infiltration anaesthesia by ropivacaine for upper third molar surgery. Int J Oral Maxillofac Surg 39(1): 36–41, 2010

Brković B, Andrić M, Ćalasan D, Mali M, Stepić J, Vučetić M, et al: Efficacy and safety of 1% ropivacaine for postoperative analgesia after lower third molar surgery: a prospective, randomized, double-blinded clinical study. Clin Oral Investig 21: 779–785, 2017

Budharapu A, Sinha R, Uppada UK, Subramanya Kumar AV: Ropivacaine: a new local anaesthetic agent in maxillofacial surgery. Br J Oral Maxillofac Surg 53(5): 451–454. https://doi.org/10.1016/j.bjoms.2015.02.021, 2015

Buric N: The assesment of anesthetic efficiacy of ropivacaine in oral surgery. N Y State Dent J 72(3): 36–39, 2006

Casati A, Fanelli G, Aldegheri G, Berti M, Colnagi E, Cedrati V, et al: Interscalene brachial plexus anesthesia with 0.5%, 0.75% or 1% ropivacaine: double – blind comparison with 2% mepivacaine. Br J Anaesth 83: 872–875, 1999

Casati A, Putzu M: Bupivacaine, levobupivacaine and ropivacaine: are they clinically different? Best Pract Res Clin Anaesthesiol 19(2): 247–268, 2005

Crincoli V, Favia G, LImongelli L, Tempesta A, Brienza N: The effectiveness of ropivacaine and mepivacaine in the postoperative pain after third lower molar surgery. Int J Med Sci 12(11): 862–866. https://doi.org/10.7150/ijms.13072, 2015 16

Danielsson BR, Danielson MK, Böö EL, Arvidsson T: Halldin MM Toxicity of bupivacaine and ropivacaine in relation to free plasma concentrations in pregnant rats: a comparative study. Pharmacol Toxicol 81: 90–96, 1997

Dillane D, Finucane BT: Local anesthetic systemic toxicity. J Can Anesth 57: 368–380, 2010

Duka M, Lazić Z, Stamatović N, Tatić Z, Bubalo M, Veljović M: Clinical parameters of the local anesthetic effects of bupivacaine applied with and without a vasoconstrictor in oral implantology. Vojnosanit Pregl 64(9): 611–615, 2007

El-Sharrawy, Yagiela A: Anesthetic efficiacy of different ropivacaine concentrations for inferior alveolar nerve block. Anesth Prog 53: 3–7, 2006

Ernberg M, Kopp S: Ropivacaine for dental anesthesia:a dose –finding study. J Oral Maxillofac Surg 60: 1004–1010, 2002

Espitalier F, Remerand F, Dubost AF, Laffon M, Fusciardi J, Goga D: Mandibular nerve block can improve intraoperative inferior alveolar nerve visualization during sagittal split mandibular osteotomy. J Cranio-Maxillofacial Surg 39(3): 164–168, 2011

Faul F, Erdfelder E, Lang AG, Buchner A: G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 39: 175–191, 2007

Fisher SE, Frame JW, Rout PG, McEntegart DJ: Factors affecting the onset and severity of pain following the surgical removal of unilateral impacted mandibular third molar teeth. Br Dent J 164(11): 351–354, 1988

Franz-Montan M, de Paula E, Groppo FC, Ranali J, Volpato MC: Efficacy of liposome-encapsulated 0.5% ropivacaine in maxillary dental anaesthesia. Br J Oral Maxillofac Surg 50(5): 454–458, 2012

Gordon SM, Chuang BP, Wang XM, Hamza MA, Rowan JS, Brahim JS, et al: The differential effects of bupivacaine and lidocaine on prostaglandin E2 release, cyclooxygenase gene expression and pain in a clinical pain model. Anesth Analg 106(1): 321–327, 2008

Gupta A: Wound infiltration with local anaesthetics in ambulatory surgery. Curr Opin Anesthesiol 23: 708–713, 2010

Haas DA: An update on local anesthetics in dentistry. Can Dent Assoc 68(9): 546–551, 2002

Hall John: In Guyton and Hall textbook of medical physiology, 12th ed. Philadelphia, Pa: Saunders/Elsevier, 563–564, 2011

Hansen TG: Ropivacaine: a pharmacological review. Expert Rev Neurother 4: 781–791, 2004
Horlocker T, Wedel D: Local anesthetic toxicity-does product labeling reflect actual risk? Regional Anesth Pain Med 27(6): 562–567, 2002
Hyrkäs T, Ylipaavalniemi P, Oikarinen VJ, Paakkari I: Effective postoperative pain prevention through administration of bupivacaine and diclofenac. Anesth Prog 41(1): 6–10, 1994
Jensen MP, Chen C, Brugger AM: Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain 4: 407–414, 2003
Johansson B, Glise H, Hallerbäck B, Dalman P, Kristoffersson A: Preoperative local infiltration with ropivacaine for postoperative pain relief after cholecystectomy. Anesth Analg 78: 210–214, 1994
Juncos A, Marret E, Goursot G, Mazoit X, Bonnet F: A comparison of ropivacaine and bupivacaine for cervical plexus block. Anesth Analg 92: 720–724, 2001
Kaczmarzyk T, Wichlinski J, Stypulkowska J, Zaleska M, Woron J: Preemptive effect of ketoprofen on postoperative pain following third molar surgery. A prospective, randomized, double-blinded clinical trial. Int J Oral Maxillofac Surg 39: 647–652, 2010
Knudsen K, Beckman Suurkula M, Blomberg S, Sjovall J, Edvardsson N: Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. Br J Anaesth 78: 507–514, 1997
Krzemiński TF, Gilowski L, Wiench R, Płocica I, Kondzielnik P, Sielańczyk A: Comparison of ropivacaine and articaine with epinephrine for infiltration anaesthesia in dentistry- a randomized study. Int Endod J 44(8): 746–751, 2011
Kumar S, Palaria U, Sinha AK, Punera DC, Pandey V: Comparative evaluation of ropivacaine and ropivacaine with dexamethasone in supraclavicular brachial plexus block for postoperative analgesia. Anesth Essays Res 8: 202–208, 2014
Laskin J: Use of etidocaine hydrochloride in oral surgery: a clinical study. J Oral Surg 36: 863–865, 1978
Lieblich SE, Danesi H: Liposomal bupivacaine use in third molar impaction surgery: innovate study. Anesth Prog 64(3): 127–135. https://doi.org/10.2344/anpr-64-02-03, 2017
Malamed SF: Handbook of local anesthesia, 2rd ed. St Louis, MO: CV Mosby, 42 66, 1986
Mansour NA, Al-Mahdy Al-Belasy F, Abdel-Monem MT, Marzook HA: Ropivacaine versus bupivacaine in postoperative pain control. J Biotechnol Biomater 2(4): 1–7, 2012
Marković AB, Todorović L: Postoperative analgesia after lower third molar surgery: contribution of the use of long-acting local anesthetics, low-power laser, and diclofenac. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 102(5): e4–e8, 2006
Mather LE, Chang DH: Cardiotoxicity with modern local anaesthetics: is there a safer choice? Drugs 61: 333–342, 2001
Mc Lure HA, Rubin AP: Review of local anaesthetic agents. Minerva Anesthesiologica 71: 59–74, 2005
McClure JH: Ropivacaine. Br J Anesth 76: 300–307, 1996
Mobilio N, Gremigni P, Pramstraller M, Vecchiatini R, Calura G, Catapano S: Explaining pain after lower third molar extraction by preoperative pain assessment. J Oral Maxillofac Surg 69(11): 2731–2738, 2011
Myer SL: The story of local anesthesia, http://www.dentaleconomics.com/articles/print/volume-89/issue-3/features/the-story-of-local-anesthesia.html; 1999
Nau C, Strichartz GR: Drug chirality in anesthesia. Anesthesiology 97: 497–502, 2002
Oliveira NE, Lima Filho NS, Lima EG, Vasquez EC: Effects of regional anesthesia with ropivacaine on arterial pressure and heart rate in healthy subjects. Eur J Oral Sci 114: 27–32, 2006
Ong C, Seymour RA: Pathogenesis of postoperative oral surgical pain. Anesth Prog 50: 5–17, 2003
Pallasch T: Vasoconstrictors and the heart. J Calif Dent Assoc 26, 1998 668-673, 676
Reed KL: A brief history of anesthesiology in dentistry. Tex Dent J 119(3): 219–224, 2002
Respect J: Clinical trials with bupivacaine in oral surgery. Oral Surg 42(3): 301–306, 1976
Rosenberg PH, Keta J, Dalila A: Absorption of bupivacaine, etidocaine, lignocaine and ropivacaine into n-heptane, rat sciatic nerve, and human extradural and subcutaneous fat. Br J Anesth 58: 310–314, 1986
Ryu HY, Kim JY, Lim HK, Yoon J, Yoo BS, Choe KH, et al: Bupivacaine induced cardiac toxicity mimicking an acute non-ST segment elevation myocardial infarction. Yonsei Med J 30: 331–336, 2007
Savage MG, Henry MA: Preoperative nonsteroidal anti-inflammatory agents: review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 98(2): 146–152, 2004
Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R: Acute toxicity of ropivacaine compared with that of bupivacaine. Anesth Analg 69: 563–569, 1989
Seymour RA, Meechan JG, Blair GS: An investigation into post-operative pain after third molar surgery under local analgesia. Br J Oral Maxillofac Surg 23(6): 410–418, 1985
Simpson D, Curran MP, Oldfield V, Keating GM: Ropivacaine a review of its use in regional anaesthesia and acute pain managment. Drugs 65(18): 2675–2717, 2005
Sisk AL: Evaluation of the Akinosi mandibular block technique in oral surgery. J Oral Maxillofac Surg 44: 113–115, 1986
Skljarevski V, Ramadan NM: The nociceptive flexion reflex in humans – review article. Pain 96(1): 3–8, 2002
Tijanić M, Burić N, Jovanović G: Evaluation of anesthetic effect of ropivacaine in surgery of chronic periapical lessions. Med Pregl 63(5–6): 366–370, 2010
Tijanić M, Burić N, Jovanović G, Stojanović S, Spasić M: Assessment of ropivacaine postoperative analgesic effect after periapical maxillary incisors surgery. Vojnosanit Pregl 69(5): 405–408, 2012
Van Aken H, Thys L, Veekman L, Buerkle H: Assessing analgesia in single and repeated administrations of propacetamol for postoperative pain: comparison with morphine after dental surgery. Anesth Analg 98: 159–165, 2004
Wildsmith JAW, Brown DT, Paul D, Johnson S: Structure –activity relationships in differential nerve block at high and low frequency stimulation. Br J Anesth 63: 444–452, 1989
Wildsmith JAW: Peripheral nerve block and ropivacaine. Am J Anesthesiol 24: 14–17, 1997
Winter GB: Impacted mandibular third molar. St Louis: American Medical Book Co., 1926
Yokogawa K, Shimomura S, Ishizaki J, Shimada T, Fukuwa C, Kawada M, et al: Involvement of alpha1-acid glycoprotein in inter-individual variation of disposition kinetics of ropivacaine following epidural infusion in off-pump coronary artery bypass grafting. J Pharm Pharmacol 59: 67–73, 2007
Zhang S, Yao S, Li Q: Effects of ropivacaine and bupivacaine on rabbit myocardial energetic metabolism and mitochondria oxidation. J Huazhong Univ Sci Technol Med Sci 23: 178–179, 2003
Zink W, Bohl JR, Hacke N, Sinner B, Martin E, Graf BM: The long term myotoxic effects of bupivacaine and ropivacaine after continuous peripheral nerve blocks. Anesth Analg 101: 548–554, 2005
Zink W, Graf BM: Benefit-risk assessment of ropivacaine in the managment of postoperative pain. Drug Saf 27(14): 1093–1114, 2004