БЕОГРАДСКИ УНИВЕРЗИТЕТ
СТОМАТОЛОШКИ ФАКУЛТЕТ
СЕКРЕТАРИЈАТ

ПРИМЉЕНО 20 -07- 2012

Орг. јед.	Број	Прилог	Вредност
03	956/2		

УНИВЕРЗИТЕТ У БЕОГРАДУ

Адреса: Студентски трг 1, 11000 Београд, Република Србија
Тел.: 011 3207400; Факс: 011 2638818; E-mail: officebu@rect.bg.ac.rs

ВЕЋЕ НАУЧНИХ ОБЛАСТИ
МЕДИЦИНСКИХ НАУКА
Тел. 3207-432; 3207-430

Београд, 10.7.2012. год.
02 Број: 06 - 19091/65-12
БТ

На основу чл. 123. став 4 Закона о високом образовању ("Службени гласник РС", број 76/05, 100/07-аутентично тумачење, 97/08 и 44/10), чл. 46. ст. 5. тач. 3. Статута Универзитета у Београду - пречишћен текст ("Гласник Универзитета у Београду", број 162/11) и чл. 14. – 21. Правилника о већима научних области на Универзитету у Београду ("Гласник Универзитета у Београду", број 134/07, 150/9 и 158/11, а на захтев Стоматолошког факултета, број 956/1од 25.06.2012. године,

Веће научних области медицинских наука, на XIV седници одржаној дана 10. јула 2012. године, донело је

О Д Л У К У

ДАЈЕ СЕ сагласност на предлог теме докторске дисертације:

Кандидат

Денис Брајковић

Назив теме:„Ефикасност профилактичке примене нимесулида и левобупивакаина у контроли постоперативног бола после хируршког вађења доњих импактираник умњака".

ПРЕДСЕДНИК ВЕЋА
Проф. др Нада Ковачевић

Доставити:
- Факултету
- секретару Већа
- архиви Универзитета

Nastavno - naučnom veću Stomatološkog fakulteta Univerziteta u Beogradu

Na sednici Nastavno - naučnog veća Stomatološkog fakulteta Univerziteta u Beogradu od 25. 02. 2014. godine, imenovana je komisija (odluka broj 3/8) u sastavu:

Prof. dr Dragica Stojić, Stomatološki fakultet, Beograd

Doc. dr Miroslav Andrić, Stomatološki fakultet, Beograd

Prof. dr Siniša Mirković, Medicinski fakultet, Novi Sad

za ocenu završene doktorske disertacije pod nazivom **EFIKASNOST PROFILAKTIČKE PRIMENE NIMESULIDA I LEVOBUPIVAKAINA U KONTROLI POSTOPERATIVNOG BOLA POSLE HIRURŠKOG VAĐENJA DONJIH IMPAKTIRANIH UMNJAKA,**

Kandidat: dr Denis Brajković

Mentor: doc. dr Božidar Brković.

Imenovana Komisija je proučila doktorsku disertaciju i podnosi Nastavno - naučnom veću Stomatološkog fakulteta Univerziteta u Beogradu sledeći

IZVEŠTAJ

A. Prikaz sadržaja doktorske disertacije

Doktorska disertacija dr Denisa Brajkovića pod nazivom EFIKASNOST PROFILAKTIČKE PRIMENE NIMESULIDA I LEVOBUPIVAKAINA U KONTROLI POSTOPERATIVNOG BOLA POSLE HIRURŠKOG VAĐENJA DONJIH IMPAKTIRANIH UMNJAKA je

napisana na 114 strana na kojima je prikazano 16 tabela, 7 grafikona, 2 dijagrama i 149 referenci iz savremene, značajne naučne literature. Disertacija sadrži: rezime na srpskom i engleskom jeziku, uvod, ciljeve istraživanja, materijal i metode, rezultate, diskusiju, zaključke, literaturu, upotrebljene skraćenice i biografiju.

U **Uvodu** su obrazloženi mehanizmi nastanka periferne i centralne senzitizacije, fenomena odgovornog za pojačanje orofacijalnih bolova. Poseban osvrt je dat na ćelijske mehanizme ovog fenomena, koji uključuju medijatore, i propagaciju nociceptivnih impulsa posle hirurškog vađenja impaktiranih umnjaka. Imajući u vidu da je profilaksa postoperativnog bola noviji terapijski pristup, podrobno su analizirani principi ovakvog terapijskog postupka. S tim u vezi, komparativno su prikazani dosadašnji rezultati kliničkih istraživanja klasične kontrole postoperativnog bola, kao i za sada malobrojni podaci o kliničkom značaju profilaktičke analgezije posle hirurškog vađenja impaktiranih umnjaka. Imajući u vidu da je za profilaksu postoperativnog bola posle hirurškog vađenja impaktiranih donjih umnjaka izabrana kombinacija levobupivakaina, kao lokalnog anestetika dugotrajnog dejstva, i nimesulida, kao nesteroidnog antiinflamatornog leka, prikazana je klinička farmakologija ovih lekova. Posebno je ukazano na kliničku primenu nimesulida kao postoperativnog analgetika u oralnoj hirurgiji, kao i na mali broj podataka koji se odnose na primenu levobupivakaina u intraoralnoj lokalnoj anesteziji, anestetika manje toksičnosti u odnosu na do sada široko korišćeni bupivakain.

Ciljevi istraživanja su precizno definisani: Ispitati efikasnost levobupivakaina (2 ml, 0,5%) za sprovodnu anesteziju donjoviličnog, lingvalnog i bukalnog nerva i uporediti njegove kliničke parametre anestezije sa parametrima bupivakaina (2 ml, 0,5%) kod hirurškog vađenja impaktiranih donjih umnjaka; Ispitati efekte bupivakaina (2 ml, 0,5%) i levobupivakaina (2

ml, 0,5%) na protok krvi kroz pulpu prvog donjeg premolara primenjenog za sprovodnu anesteziju donjoviličnog nerva; Ispitati efikasnost profilaktičke analgezije izazvane kombinovanom primenom nimesulida (100 mg or), 1 sat pre hirurškog vađenja donjih impaktiranih umnjaka, sa levobupivakainom (2 ml, 0,5%) ili bupivakainom (2 ml, 0,5%); Ispitati efikasnost kontrole postoperativnog bola posle kombinovane primene nimesulida (100 mg or), 1 sat posle hirurškog vađenja donjih impaktiranih umnjaka, sa levobupivakainom (2 ml, 0,5%) ili bupivakainom (2 ml, 0,5%); Uporediti efikasnost kombinacije nimesulida, 1 sat pre hirurškog vađenja donjih impaktiranih umnjaka, + levobupivakaina/bupivakaina (profilaktička analgezija) sa efikasnošću levobupivakaina/bupivakaina + nimesulida, 1 sat posle hirurškog vađenja donjih impaktiranih umnjaka (postopeprativna kontrola bola), kao i placebom.

U poglavlju **Materijal i metode** pregledno su date karakteristike klinčkog istraživanja i jasno su definisani faktori za uključivanje i isključivanje ispitanika iz studije primenom *CONSORT* protokola. Posebno su prikazani metodi praćenja kliničkih parametara lokalne anestezije, kao i metod praćenja protoka krvi kroz pulpu zuba, kao parametar vazoaktivnog delovanja lokalnog anestetika. Pored toga, jasno i pregledno su prikazani metodi praćenja postoperativne analgezije. U statističkoj obradi podataka navedeni su svi racionalno upotrebljeni statistički testovi.

Rezultati su prikazani u dva poglavlja koja se odnose na ispitivanje kavaliteta anestezije postignute levobupivakainom i profilaktičke analgezije postignute nimesulidom i levobupivakainom. Prikazani rezultati prate postavljene ciljeve. U prvom poglavlju prikazane su demografske karakteristike zdravih ispitanika i dijagram njihove randomizacije, klinički parametri sprovodne anestezije postignute levobupivakainom i bupivakainom, kao promene

protoka krvi kroz zubnu pulpu pre i posle primene pomenutih anestetika. Drugo poglavlje sadrži prikaz rezultata kvaliteta postignute analgezije profilaktičkom primenom nimesulida u kombinaciji sa levobupivakainom i bupivakainom. Prikazani su rezultati učestalosti i inteziteta postoperativnog bola u prvih 24 sata i 7 dana posle hirurške intervencije, kao i potreba za primenom analgetika.

U **Diskusiji** je naučnom analizom dobijenih rezultata utvrđeno da 0,5% levobupivakain postiže klinički adekvatne parametre za dugotrajnu intraoralnu lokalnu anesteziju u hirurgiji donjih impaktiranih umnjaka. Analiza komparativnih rezultata o efikasnosti profilaktičke primene nimesulida (100 mg) sa 0,5% levobupivakainom, u odnosu na placebo i kombinaciju nimesulida (100 mg) i 0,5% bupivakaina, pokazuje da je ispitivana kombinacija efikasna u kontroli bola posle hirurškog vađenja donjih impaktiranih umnjaka. Istovremeno, dobijeni rezultati su povezani sa nalazima dosadašnjih svremenih istraživanja u ovoj oblasti.

Na osnovu iznetih i diskutovanih rezultata predstavljeni su **zaključci** koji daju jasne odgovore na postavljene ciljeve.

U **literaturi** su navedene relevantne, savremene i značajne naučne reference koje su citirane u radu.

B. Kratak opis postignutih rezultata

Posle primene 3 ml 0,5% levobupivakaina, za hirurško vađenje impaktiranih donjih umnjaka, registrovana je visoka uspešnost anestezije mekog tkiva od 90, 90 i 93% koja je postignuta sprovodnim anestezijama donjoviličnog nerva, bukalnog nerva i jezičnog nerva. Uspešnost anestezije mekog tkiva posle primene 3 ml 0,5% bupivakaina je iznostila 90, 87 i 87% za

sprovodne anestezije pomenutih nerava. S druge strane, uspešnost anestezije pulpe je bila značajno niža u obe grupe pacijenata (73% levobupivakain i 66% za bupivakain). Oba anestetika su pokazala podjednak latentni period, dužinu trajanja sprovodih anestezija, kao i bifazične promene u protoku krvi kroz zubnu pulpu donjeg privog premolara. Značajno bolji intenzitet intraoperativne anestezije postignut je posle primene 3 ml 0,5% levobupivakaina u odnosu na istu dozu bupivakaina. Vreme pojave prvog bola i vreme uzimanja prvog analgetika u postoperativnom periodu je bilo značajno duže posle primene levobupivakaina u odnosu na bupivakain. Ovi rezultati su objavljeni u časopisu Clinical Oral Investigation 2013.

Rezultati ispitivanja efekata profilaktičke analgezije u toku prva 24 sata, su pokazali da preoperativno primenjen nimesulid sa levobupivakainom i bupivakainom prouzrokuje podjednaku učestalost pojave postopertivnog bola, dok se značajno duži bezbolni postoperativni period i vreme do uzimanja prvog i drugog analgetika zapaža posle profilaktičke primene kombinacije nimesulid/levobupivakain. Pomenutom kombinacijom se takođe postiže značajno duži analgetički period i u odnosu na postoperativno dat nimesulid/levobupivakain. Učestalost pojave bola i intenzitet bola u prvih 7 postoperativnih dana su bili značajno niži kod pacijenata koji su profilaktički primili nimesulid/levobupivakain i nimsulid/bupivakain, u odnosu na placebo i primenu ovih kombinacija posle hirurške intervencije. Ukupna doza primenjenog analgetika posle hirurškog vađenja umnjaka je bila značajno manja posle profilaktičke primene nimesulid/levobupivakain, nego posle postoperativne primene nimesulid/levobupivakain, nimesulid/bupivakain ili placeba.

Imajući u vidu novu savremenu terapiju bola (profilaktička analgezija), kao i racionalne metodološke pristupe za analizu njene efikasnosti, celokupni rezultati ove doktorske disertacije ukazuju da je profilaktički primenjen nimesulid (100 mg or.) u kombinaciji sa

levobupivakainom (3 ml, 0,5%) efikasan terapijski pristup u postizanju profilaktičke analgeziji prilikom hirurškog vađenja imapaktiranih umnjaka u donjoj vilici.

C. Uporedna analiza doktorske disertacije

Rezultati ove doktorske disertacije, proistekli iz kliničke, randomizovane, dvostruko-slepe studije, pokazali su uspešnost sprovodnih anestezija postignutih levobupivakainom (3 ml, 0,5%), kao i efikasnost koncepta profilaktičke analgezije postignute preoperativnom primenom nimesulid/levobupivakain (100mg, or./3ml, 0,5%) na modelu hirurškog vađenja impaktiranih umnjaka u donjoj vilici.

Levobupivakain, noviji lokalni anestetik dugotrajnog delovanja, pokazuje manju toksičnost i podjednaku efikasnost u odnosu na bupivakain, čiji je izomer. Rezultati ove doktorske disertacije pokazuju po prvi put da levobupivakain postiže klinički dobre parametre dugotrajne intraoralne lokalne anestezije, kao što je to slučaj sa drugim sprovodnim anestezijama (brahijalni nervni blok, išijadični nervni blok) (Cox i sar. 1998, Casati i sar. 2002).

Savremena preporuka za ispitivanje profilaktičke analgezije za kontrolu postoperativnog bola je komparativna analiza preoperativne i postoperativne primene analgetika, kao i placeba, uz lokalni anestetik dugotrajnog delovanja. Dosadašnje studije Junga i sar. (2005), kao i Kaczmarzyka i sar. (2010) su pokazala da primena analgetika talniflumata (370 mg, or.), odnosno ketoprofena (100 mg, or.), uz primenu lokalnog anestetika srednje dužine delovanja, 2% lidokaina sa epinefrinom (100,000), odnosno 4% artikaina sa epinefrinom (1:200,000), superiornija u odnosu na placebo, što je u saglasnosti sa dobijenim rezultatima u ovoj doktorskoj disertaciji. Međutim, analizirajući preoperativno i posoperativno primenjen analgetik, ovi su autori pokazali značajnu redukciju inteniteta bola, kao i značajno povećanje trajanja analgezije posle postoperativne pirmene analgetika u odnosu na profilaktičku. Ovakav

rezultat nije dobijen u ovoj doktorskoj disertaciji, što bi moglo da se pripiše činjenici da su pomenuti autori koristili lokalni anestetik srednje dužine delovanja, nasuprot levobupivakainu i bupivakainu, koji su anestetici dugotrajnog delovanja i, samim tim, dugotrajnije učestvuju u kontroli postoperativnog bola. Dobijena razlika može da se pripiše i primeni analgetika talniflumata, čija se maksimalna koncentracija u plazmi postiže za 2,35 sati (Park i sar. 2008), i ketoprofena, čija se maksimalna koncentracija u plazmi postiže za 0,5 do 2 sata (Cailleteau 1988, Data Sheet Oruvail® SR Capsules 2011), u odnosu na nimesulid (u doktorskoj disertaciji), čija se maksimalna koncentracija postiže za 0,5 do 1 sat (Ugazio i sar. 1993, Pulkkinen 1993). Imajući to u vidu, postoperativna primena talniflumata i ketoprofena više odgovara konceptu postoperativne kontrole bola, nego konceptu profilaktičke analgezije.

D. Objavljeni rad koji čini deo doktorske disertacije

Denis Brajković, Božidar Brković, Marija Milić, Vladimir Biočanin, Elena Kršljak, Dragica Stojić. Levobupivacaine vs. Bupivacaine for third molar surgery: quality of anaesthesia, postoperative analgesia and local vascular effects. Clin Oral Invest 2013, DOI 10.1007/s00784-013-1114-0.

E. Zaključak (obrazloženje naučnog doprinosa)

Doktorska disertacija „Efikasnost profilaktičke primene nimesulida i levobupivakaina u kontroli postoperativnog bola posle hirurškog vađenja donjih impaktiranih umnjaka“ dr Denisa Brajkovića predstavlja značajan i originalan naučni doprinos u postavljanju kliničkih principa za protokol profilaktičke analgezije u oralnoj hirurgiji. U radu su primenjene savremene kliničke metode za analizu efikasnosti profilaktičke analgezije. Ova doktorska disertacija je urađena prema svim principima naučnog i kliničkog istraživanja, sa precizno

definisanim ciljevima, originalnim naučnim pristupom, savremenom metodologijom rada, adekvatno prikazanim i diskutovanim rezultatima i jasno uobličenim zaključcima.

Na osnovu svega napred navedenog, i imajući u vidu objavljeni rad iz oblasti doktorske disertacije, Komisija predlaže Nastavno - naučnom veću Stomatološkog fakulteta Univerziteta u Beogradu da prihvati doktorsku disertaciju pod naslovom „**Efikasnost profilaktičke primene nimesulida i levobupivakaina u kontroli postoperativnog bola posle hirurškog vađenja donjih impaktiranih umnjaka“** dr Denisa Brajkovića i odobri njenu javnu odbranu radi sticanja akademske titule doktora stomatoloških nauka.

U Beogradu, 24. april 2014. godine

Članovi komisije:

Prof. dr Dragica Stojić

_____

Doc. dr Miroslav Andrić

_____

Prof. dr Siniša Mirković

_____

Na osnovu člana 49. Statuta Stomatološkog fakulteta Univerziteta u Beogradu, Nastavno naučno veće Stomatološkog fakulteta, na IV redovnoj sednici u školskoj 2013/14. godini, održanoj 03.06.2014. godine, donelo je sledeću

O D L U K U

Usvaja se pozitivan izveštaj Komisije za ocenu završene doktorske disertacije **dr Denisa Brajkovića**, pod nazivom „EFIKASNOST PROFILAKTIČKE PRIMENE NIMESULIDA I LEVOBUPIVAKAINA U KONTROLI POSTOPRETIVNOG BOLA POSLE HIRURŠKOG VAĐENJA DONJIH IMPAKTIRANIH UMNJAKA“.

Imenovani/a će javno braniti doktorsku disertaciju, ukoliko dobije pozitivno mišljenje Veća naučnih oblasti medicinskih nauka Univerziteta u Beogradu, pred komisijom u sastavu:

1. prof. dr Dragica Stojić
2. doc. dr Miroslav Andrić
3. prof. dr Siniša Mirković, Medicinski fakultet u Novom Sadu.

O b r a z l o ž e nj e

Veće naučnih oblasti medicinskih nauka, na sednici od 10.07.2012. godine, dalo je saglasnost na predlog teme doktorske disertacije dr Denisa Brajkovića, pod nazivom „EFIKASNOST PROFILAKTIČKE PRIMENE NIMESULIDA I LEVOBUPIVAKAINA U KONTROLI POSTOPRETIVNOG BOLA POSLE HIRURŠKOG VAĐENJA DONJIH IMPAKTIRANIH UMNJAKA“.

Imenovani/a je u časopisu Clin Oral Invest, objavio/la rad pod nazivom: „Levobupivacaine vs. bupivacaine for third molar surgery: quality of anaesthesia, postoperative analgesia and local vaskular effects“ (2013).

Imajući u vidu napred navedeno, Nastavno naučno veće Stomatološkog fakulteta Univerziteta u Beogradu, rešilo je kao u dispozitivu.

Odluku dostaviti: Imenovanom/oj, Univerzitetu u Beogradu, Odseku za nastavu, Veću, Komisiji (3) i Pisarnici.

Referent kadrovskog odseka
Violeta Rastović

Dekan
Stomatološkog fakulteta

Prof. dr Miroslav Vukadinović

Clin Oral Invest (2014) 18:1481–1488
DOI 10.1007/s00784-013-1114-0

ORIGINAL ARTICLE

Levobupivacaine vs. bupivacaine for third molar surgery: quality of anaesthesia, postoperative analgesia and local vascular effects

Denis Brajkovic · Bozidar Brkovic · Marija Milic · Vladimir Biocanin · Elena Krsljak · Dragica Stojic

Received: 2 February 2013 / Accepted: 13 September 2013 / Published online: 6 October 2013

Abstract
Objectives The main purpose of this prospective, double-blind, randomized study was to evaluate anaesthetic parameters, postoperative analgesia and vasoactive properties of levobupivacaine and bupivacaine for lower third molar surgery.
Material and methods Sixty patients (ASA I) were scheduled for lower third molar surgery under inferior alveolar nerve block, lingual nerve block and buccal nerve block (mandibular nerve blocks) obtained with 3 ml of 0.5 % levobupivacaine and 3 ml of 0.5 % bupivacaine. Success rate, onset and duration of three nerve bocks were evaluated by electrical *pulp testing*, *pinprick testing* and signs of soft tissue anaesthesia (patient-reported numbness). Intensity of intraoperative anaesthesia and postoperative analgesia were measured with visual analogue scale (VAS) and numeric rating scale (NRS). The time of first postoperative pain reported and analgesic consumption were also recorded. The laser Doppler flowmetry was used for the measurement of the first premolar pulpal blood flow.
Results There were no differences between levobupivacaine and bupivacaine regarding the success rate, onset and duration of mandibular nerve blocks as well as intensity of postoperative analgesia and analgesic consumption. Intensity of intraoperative anaesthesia and duration of postoperative analgesia were significantly higher in the levobupivacaine than in the bupivacaine group. Both anaesthetics showed similar biphasic vasoactive effect.
Conclusions Levobupivacaine 0.5 % achieved superiority over bupivacaine 0.5 % in the intensity of intraoperative anaesthesia and duration of postoperative analgesia for lower third molar surgery under the mandibular nerve blocks.
Clinical relevance It seems that the plain levobupivacaine (0.5 %) could be an effective alternative to plain bupivacaine (0.5 %) in those dental procedures which require profound bone and soft tissue anaesthesia.

Keywords Levobupivacaine · Bupivacaine · Anaesthetic parameters · Postoperative analgesia · Third molar surgery · Pulpal blood flow

D. Brajkovic · B. Brkovic (✉) · M. Milic
Clinic of Oral Surgery, School of Dental Medicine, University of Belgrade, Belgrade, Serbia
e-mail: brkovic73@yahoo.com

D. Brajkovic
Department of Maxillofacial Surgery, Faculty of Medical Science, University of Kragujevac, Kragujevac, Serbia

V. Biocanin
Division of Oral Surgery, Faculty of Medical Science, University of Kragujevac, Kragujevac, Serbia

E. Krsljak
Department of Oral and General Physiology, School of Dental Medicine, University of Belgrade, Belgrade, Serbia

D. Stojic
Department of Pharmacology in Dentistry, School of Dental Medicine, University of Belgrade, Belgrade, Serbia

Introduction

Bupivacaine, the long-acting amide local anaesthetic, is used to obtain both effective sensory block with long-lasting duration and beneficial postoperative analgesia for surgical extraction of lower third molars. However, after the clinical reports of life-threatening neural and cardiac toxicity of bupivacaine, given for regional nerve blocks such as brachial, femoral or scalene [1–4], it became evident that bupivacaine has a narrow safety margin given its high lipid solubility as opposed to other amide local anaesthetics [5, 6]. The majority of these adverse reactions occurred as a result of a high dose of bupivacaine administered in the aforementioned regional blocks. Since intraoral block anaesthesia does not require large volumes of bupivacaine, and,

consequently, the risk for systemic toxicity associated with the dose of bupivacaine is not an issue, an unwanted intravascular injection still remains a risk factor for possible toxic effects of bupivacaine in intraoral block anaesthesia.

Commercial preparations of bupivacaine exist as a racemic solution, containing equal amounts of the two enantiomers, R(+) dextrorotatory and S(−) levorotatory stereoisomers. The physicochemical properties of these two enantiomers are identical, but significant differences exist in their interactions with biological receptors; the conformation of which favours interactions with one form over the other [7]. Consequently, vasoactivity and toxicity of the S(−) levorotatory and R(+) dextrorotatory enantiomers of bupivacaine differ, while levorotatory enantiomer are more vasoconstrictive and less toxic [8–10].

Levobupivacaine, as the pure S(−) isomer, has been developed as an alternative to bupivacaine with the desirable blocking properties of racemic bupivacaine, due to a greater margin of safety. Moreover, the comparative clinical studies evaluating levobupivacaine (LBUP) for peripheral nerve blocks have suggested that clinical parameters of regional anaesthesia produced with 0.5 % levobupivacaine might be similar or even better than those produced with an equivalent dose of bupivacaine [11–14]. Levobupivacaine has been also reported to possess advantages in terms of cardiotoxicity and CNS toxicity in animal and human volunteer studies [15, 16].

In dentistry, levobupivacaine (0.5 %) has been compared to bupivacaine (0.5 %), both associated with epinephrine, only in healthy volunteers, showing similar anaesthetic behaviour of these two long-acting anaesthetics regarding success rate, onset and duration of pulpal anaesthesia for inferior alveolar nerve block [17]. For surgical extraction of impacted third molars and the quality of postoperative analgesia, levobupivacaine (0.75 %) was compared with anaesthetics of intermediate duration: lidocaine (2 %) with epinephrine (1:100,000) and mepivacaine (3 %) [18, 19].

Since there are no data concerning the comparative clinical profiles of levobupivacaine vs. bupivacaine for the inferior alveolar nerve block, lingual nerve block and buccal nerve block in patients undergoing surgical extraction of lower third molars, the aim of this study was to investigate parameters of anaesthesia and postoperative analgesia achieved by equal concentrations of 0.5 % levobupivacaine and 0.5 % bupivacaine. In addition, we compared in vivo vasoactive properties of 0.5 % levobupivacaine and 0.5 % bupivacaine using laser Doppler flowmetry.

Material and methods

Patients and study design

After receiving the approval from the Ethical Committee (no. 36/32, School of Dental Medicine, University of Belgrade) and obtaining the informed consent of patients for participation in the study, 60 adult patients were scheduled for the surgical extraction of lower impacted third molars.

The patients were classified as having physical status 1 by the American Society of Anesthesiologists (ASA) classification. Eligibility criteria for participation in the study required patients to be between 18 and 30 years of age. Study exclusion criteria included smokers, nursing mothers, pregnant women, those taking any contraceptive medication or methods and patients who require sedation, general anaesthesia or any other premedication for surgical extractions. Exclusion criteria also included current use of any analgesic agents within 24 h of administration of study medication. Specific inclusion criteria based on the dental examination were patients with fully impacted lower third molars (more than 2/3 of crown covered with alveolar bone confirmed through radiographic analysis) with no signs of acute pericoronitis and with absence of any acute infection of orofacial region. Clinical examination also indicated patients with no dental treatment 24 h previously, and those patients with vital premolars and adjunct gingival tissue on both sites of lower jaw.

The patients were studied using a double-blind, controlled design, randomly allocated into two groups receiving either:

1. 3 ml of 0.5 % levobupivacaine (5 mg/ml) (Chirocaine®, Abbott S.R.L., Campoverde di Aprilia, Italy)—LBUP group (30 patients), or
2. 3 ml of 0.5 % bupivacaine (5 mg/ml) (Marcaine®, AstraZeneca, UK Ltd, United Kingdom)—bupivacaine (BUP) group (30 patients),

for three mandibular nerve blocks (inferior alveolar nerve block (IANB), buccal nerve block (BNB), lingual nerve block (LNB)), responsible for the local anaesthesia of lower third molar extraction, in the following volumes: 2 ml for IANB, 0.5 ml for BNB and 0.5 ml for LNB. The random assignments were done by an independent investigator, according to a computer-generated randomization list with sealed, numbered envelopes. Anaesthetic solutions were prepared for injection by a clinical pharmacist not involved in the administration of local anaesthesia, surgery and evaluation of investigated parameters. The same surgeon performed all blocks. Surgical procedure was standardized for all patients and included creating an envelope of mucoperiosteal flap, bone removal using a drill cooled with saline, extraction with crown or root separation, rinsing the wound with saline after extraction, and suturing after achieving local hemostasis. All patients had a regular daily follow-up during the first 7 days after surgery and instructions for postoperative swelling and pain control were given. Patients were instructed to record any local complications (local irritations, discomforts) or systemic side effects (palpitations, nausea, vomiting, dizziness) during local anaesthetic administration, surgery and postoperatively.

Parameters of anaesthesia and postoperative analgesia

The onset and duration of anaesthesia were studied using *pulp testing*, *pinprick testing* and subjective signs of soft tissue anaesthesia (patient-reported numbness) for IANB, while these anaesthetic parameters for BNB and LNB were investigated only by the pinprick test and report of soft tissue anaesthesia. Pulp testing was performed for the evaluation of complete pulpal anaesthesia of the first premolar at the operating site using tooth vitality tester (Vitality Scanner Model 2006®, Sybron Endo, USA). The tip of the pulp tester probe was placed in the middle third of the buccal side of the tested vital first premolar with fluoride gel (Fluorogal Forte®, Galenika, Belgrade, Serbia), as an electrolyte between the probe and enamel. The experimental tooth and control contralateral premolar were tested three times before the injections were given to record baseline vitality. After the administration of IANB, electrical stimulation of tested tooth was repeated every 1–2 min until the reading became lower than 80 readings (max) to detect the onset time of pulpal anaesthesia. Duration of complete pulpal anaesthesia was the period between the first and the last 80 reading (max) on electrical pulp tester. Anaesthesia was considered successful when two or more consecutive no response at 80 readings (max) was obtained.

Sensory changes for pinprick testing were recorded on the buccal and lingual attached gingiva between mandibular canine and first premolar (for IANB and LNB) and on the buccal mucosa at the third molar area (for BNB) using a 26G sterile injection needle (B-D Microlance®, Becton Dickinson, Ireland). The needle was inserted directly into the periosteum and contacted with the alveolar bone after penetrating the attached gingiva. The onset of anaesthesia was tested every 1–2 min to the time when a pinprick did not elicit any sensation. If onset was not obtained in 15 min, anaesthesia was considered unsuccessful for the tested nerve. Postoperatively, patients were evaluated to establish the duration of anaesthesia, testing every 30 min after surgery to the time when patients felt blunt sensation and continuing every 10 min until sensation was re-established as a response to a pinprick test. The same time protocol was used for testing the onset and duration of soft tissue anaesthesia taken from the patient's subjective reports of tissue numbness.

Intensity of intraoperative anaesthesia and postoperative analgesia were measured only in patients with successful events of all three blocks since the pain control of operating area is determined with adequate IANB, BNB and LNB. Intensity of intraoperative anaesthesia was assessed with two scales, the visual analogue scale (VAS), as a commonly used scale for measuring of pain intensity, and numeric rating scale (NRS), which has shown to be more sensitive and responsive than the VAS [20, 21]. The VAS consists of a horizontal line 100 mm in length, with the end points *no pain* and *worst imaginable pain*. Patients were asked to make the mark on the line that best represents the level of pain intensity that they were experiencing during surgical procedure. The NRS is an 11-point scale consisting of integers from 0 (representing *no pain*) through 10 (representing *the worst pain imaginable*). Patients selected the single number that best represents their pain intensity. Both scales, VAS and NRS, were used as a same time points, immediately after the surgical extraction. If additional anaesthesia was given during the surgery, as a result of unacceptable and intolerable intraoperative pain, the anaesthesia was considered unsuccessful and the patient was excluded from the study. The additional anaesthesia was achieved with 2 % lidocaine+1:80,000 epinephrine (Lidokain 2 % - Adrenalin®, Galenika, Belgrade, Serbia).

The postoperative analgesia protocol consisted of 400 mg *per oral* ibuprofen (Brufen®, Galenika, Belgrade, Serbia) taken in case that patients experienced pain at the surgical site of moderate-to-severe intensity (identified with the level ≥4 at NRS and more than 20 mm at VAS). Measured parameters of postoperative analgesia were the following: time at which first pain postoperatively occurred, time of first analgesic dose taken, measurement of postoperative pain intensity at the point of first analgesic dose taken (using the VAS and NRS) and the total amount of analgesic uptake during 48 h postoperatively.

Pulpal laser Doppler flowmetry

The laser Doppler flowmetry (LDF) of dental pulp was carried out on 10 patients (six females and four males) undergoing surgical extraction of lower third molars who satisfied all requirements of study inclusion/exclusion criteria. The specific local criterion was the intraoral evidence of an uninterrupted dental arch in the lower jaw on the investigated site. The investigated teeth to be studied were first mandibular premolars, which were vital (checked by electrical pulp test), non-restored and with physiologically expected pulp chamber dimensions (checked by dental radiographs).

A pulpal blood flow (PBF) was measured by a Periflux System PF 5000 LDF (PF 407 Periflux System®, Perimed, Sweden). The LDF emitted light with a 632.8 nm. Band width was 20 Hz–20 kHz, and sampling frequency was 32 Hz. Calibration was made with the PF 1000 Calibration Device (Perimed) before each measurement. Collected data were analysed by PeriSoft software (version 5.1, Perimed). The PBF was expressed in perfusion units (PU).

The diameter of the probe, which was in direct contact with tooth enamel for recording PBF, was 1 mm (415–159, Perimed). To stabilise the probe, a laboratory-made plastic splint was used to position the probe on the buccal aspect of the premolar crown, 2 mm coronary from the marginal gingiva of the tested tooth. A LDF measurement was made at middle third of clinical crown of the tooth. The rubber dam and cotton rolls were used to isolate the tooth against saliva. The patient rested at least 10 min before measurement in a

quiet, well-ventilated room. Systolic blood pressure, diastolic blood pressure and heart rate were controlled before each measurement.

All participants undergoing surgical third molar extraction were to receive 2 ml of 0.5 % BUP or 0.5 % LBUP for IANB. The PBF measured intervals were before anaesthesia injection and 15, 30, 60, 120, 180, 240, and 300 min after anaesthesia injection. Each measurement lasted 3 min. Average baseline PU value was calculated based on average values measured during these 3 min, expressed in a percentage as a deviation from basic PBF (basic measurement of PBF was expressed as 100 %).

Statistics

Statistical analysis was performed using the statistical software SPSS, version 18.0. The results were presented as the mean±standard deviation (SD). The Chi-square test was performed to determine differences in gender and success rate between groups. Age, weight, duration of surgery, onset, duration and intensity of anaesthesia, time to first postoperative pain, intensity of postoperative pain and first analgesic consumption were compared using parametric Student's *t* test. One-way analysis of variance (ANOVA) was used to determine differences in the PBF at fixed time points within each group while the Student's *t* test was used to compare the differences in PBF between the two anaesthetics.

Group size was estimated based on a pilot study. We estimated that, for detecting of 35 % difference in success rate between the groups, enrolment of 30 patients in each group was necessary in order to have 88.78 % power at two-tailed significance level of 0.05 using the *t* test.

Results

Patient's characteristics

The flow diagram demonstrated the randomization of success rates of pulpal and soft tissue anaesthesia (Fig. 1). Eighty four patients, of whom 24 were excluded, were assessed for eligibility. Sixty patients with fully impacted third molars were randomized to receive either levobupivacaine or bupivacaine. Concerning the fact that clinically adequate anaesthesia for surgical third molar extraction depends on the success rate of three blocks - IANB, LNB and BNB - the consort flow diagram showed that 3 patients had inadequate IANB in both the levobupivacaine and bupivacaine groups during bone removal, while 8 patients in the levobupivacaine and 10 patients in the bupivacaine groups had inadequate pulpal anaesthesia during separation of crown and roots. Additionally, BNB was inadequate for three patients in the levobupivacaine and in four patients in the bupivacaine group during the flap elevation, while LNB failed in two patients treated with levobupivacaine and in four patients treated with bupivacaine before surgical procedure. Subject demographic data of two investigated groups are compared in Table 1.

Parameters of anaesthesia and postoperative analgesia

There were 90, 90 and 93 % success rates of IANB, BNB and LNB in the levobupivacaine group, respectively, and 90, 87 and 87 % success rates of IANB, BNB and LNB in the bupivacaine group, respectively, evaluated by the pinprick test and patient-reported numbness (soft tissue anaesthesia) (Table 2). On the other hand, the success rate of pulpal anaesthesia, measured by pulp testing, was lower (73 % for LBUP and 67 % for BUP) than anaesthetic success rates reached for soft and hard tissue in both the levobupivacaine and bupivacaine groups (Table 2).

The onset time and duration of anaesthesia for sensory blocks are depicted in Table 2. In both groups, the mean onset time for complete sensory blocks ranged between 5 and 9 min. There were no statistically significant differences in the onset time between levobupivacaine and bupivacaine, whether it was measured by the pinprick test, pulp test or patient-reported numbness (soft tissue anaesthesia). Also, the duration of intraoral blocks did not differ between levobupivacaine and bupivacaine groups for all three measured protocols (pinprick test, pulp test and patient-reported numbness) (Table 2).

Anaesthesia obtained with levobupivacaine reached significantly higher intensity during surgical procedures in comparison with bupivacaine-induced anaesthesia when we evaluated this parameter by VAS and NRS. Significantly more patients, in 46 % of the cases, experienced intraoperative pain in the bupivacaine group than in the levobupivacaine group, where pain was present in 26 % of patients (Table 3).

Regarding the response to postoperative pain, it was recorded in almost 44 and 58 % of patients given levobupivacaine and bupivacaine, respectively, with no significant difference between the two groups. Time of the first postoperative pain appearance and time of the first analgesic doses taken (duration of analgesia) were significantly reduced in the group of patients receiving levobupivacaine compared with the bupivacaine-treated patients. However, pain intensity at the time of the first analgesic dose taken (intensity of analgesia), measured by VAS and NRS, did not differ significantly between groups. There was no difference in the number of total pain medication doses taken between two investigated groups (Table 4).

No local or systemic complications were observed in the patients during local anaesthetic administration, surgical procedures and postoperatively.

Pulpal blood flow

Both 0.5 % levobupivacaine and 0.5 % bupivacaine changed the PBF response in the biphasic manner: I phase represented

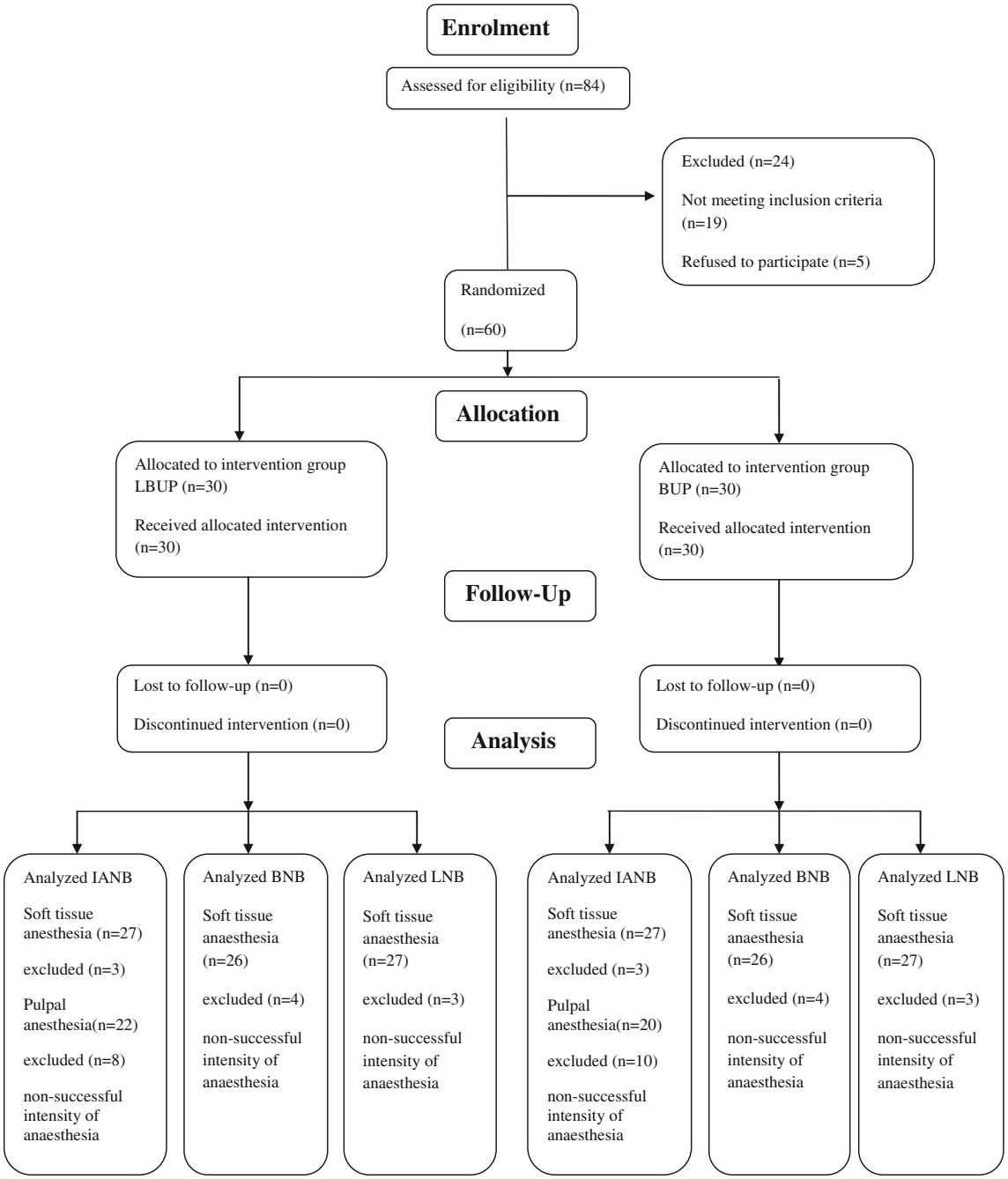

Fig. 1 Flow diagram of randomization either 0.5 % bupivacaine (*BUP*) or 0.5 % levobupivacaine (*LBUP*) for the analysis of inferior alveolar nerve block (*IANB*), buccal nerve block (*BNB*) and lingual nerve block (*LNB*) in the term of soft tissue and pulpal anaesthesia

as a vasoconstriction, and II phase represented as a vasodilation. The maximum blood flow reduction, with the peak of 12 % at 30 min, was recorded in the levobupivacaine-treated patients. The PBF increased after first hour in both groups, reaching the highest values in the second hour after anaesthesia injection (120 % in LBUP and 124 % in BUP) and gradually decreased to baseline values after the third hour of anaesthetic injection in both groups. However, the observed changes in the PBF, registered in both phases, did not show statistically significant differences between two investigated anaesthetics as well as between basal and observed values at observation period of 300 min (Fig. 2).

Discussion

The present prospective, randomized, double-blind study demonstrated that plain 0.5 % levobupivacaine and 0.5 %

Table 1 Subject demographic and clinical data

Parameters	BUP	LBUP
N	30	30
M/F	10/20	12/18
Age (years)	23.9±3.0	24.4±4.0
Weight (kg)	65.9±11.7	71.4±17.2
Duration of treatment (min)	26.8±3.6	25.8±4.5
Impacted third molars	30	30
Section of crown and roots	27	25
No. section of crown and roots	3	5

Values given as mean±SD

N number of patients, *M* male, *F* female, *BUP* bupivacaine, *LBUP* levobupivacaine

Table 3 Intensity of anaesthesia performed by 0.5 % bupivacaine (BUP) and 0.5 % levobupivacaine (LBUP)

Parameters	Treatment (mean±SD)		
		BUP	LBUP
N/success blocks		12/26	7/27*
Intraoperative pain intensity	VAS (mm)	28±9	9±3*
	NRS	4.7±1.3	2.9±0.7*
Presence of pain during:			
Flap elevation		7	5
Bone removal		6	2
Section of crown and roots		3	3
Tooth luxation		6	5

*p<0.05 (Student's *t* test)

VAS visual analogue scale, *NRS* numerical rating scale, *N* number of patients experienced intraoperative pain

bupivacaine achieved effective local anaesthetic parameters in patients undergoing lower third molar surgery. However, evaluation of the success rate of pulpal anaesthesia after the IANB in our study showed relatively low rate of success for both levobupivacaine (73 %) and bupivacaine (67 %) what is less than clinically acceptable success rate for intraoral local anaesthesia (90 %) [22]. In connection with our results, many clinical studies showed a high percentage of failure of pulpal anaesthesia after the IANB, even in combination with local anaesthetic and vasoconstrictor [17, 23, 24]. It was suggested that the reason for such failure is due to anatomical considerations at the injection site and anaesthetic technique principles during the completion of the IANB [25]. Factors which also contribute to the pulpal anaesthesia success depend on the rate of anaesthetic diffusion and concentration gradient which could obtain complete conduction blockade of all nerve fibres especially those in the middle part of a peripheral nerve which are responsible for the pulpal anaesthesia developing [26]. Since the partition coefficient of local anaesthetics is a measure of their lipid solubility, it is interesting to note that the partition coefficient of levobupivacaine (346.0) is equal to that of bupivacaine [5, 27]. It seems, therefore, possible that both anaesthetics, because of their high liposolubility, could be absorbed by the mucosal tissue, leaving little free drug to diffuse into bone and nerves.

It is also interesting to note that the study of Branco et al. [17], evaluating the efficacy of 0.5 % levobupivacaine and 0.5 % bupivacaine, both associated with epinephrine (1:200, 000) as a vasoconstrictor, for the IANB showed equal success rates of 77 % for tested anaesthetics. Since these success rates for both levobupivacaine and bupivacaine are comparable to the success rate presented in our study with plain levobupivacaine and bupivacaine, it seems that the presence of epinephrine does not change the success rate of pulpal anaesthesia significantly. Results obtained by laser Doppler flowmetry showed similar biphasic vasoactive profile of levobupivacaine and bupivacaine: I phase of vasoconstriction (15–30 min after injection) and II phase of vasodilation (2 h after injection). Since slight vasoconstriction for both anaesthetics lasted 15 to 30 min, it could be postulated that this vasoconstricting effect is qualitatively

Table 2 Success rate, onset and duration of mandibular nerve blocks performed by 0.5 % bupivacaine (BUP) and 0.5 % levobupivacaine (LBUP)

Blocks		Parameters of anaesthesia (mean±SD)					
		Onset (min)			Duration (min)		
		Numbness (n)	Pin prick (n)	Pulp test (n)	Numbness (n)	Pin prick (n)	Pulp test (n)
IANB	BUP	8.7±2.1 (27/30)	6.7±2.2 (27/30)	9.1±1.1 (20/30)	689±178 (27/30)	551±189 (27/30)	420±87 (20/30)
	LBUP	7.3±0.6 (27/30)	5.2±0.8 (27/30)	8.3±0.6 (22/30)	691±174 (27/30)	621±117 (27/30)	443±112 (22/30)
BNB	BUP	6.9±3.2 (26/30)	6.8±1.9 (26/30)	–	472±71 (26/30)	420±81 (26/30)	–
	LBUP	5.2±1.5 (27/30)	4.8±2.9 (27/30)	–	521±149 (27/30)	440±114 (27/30)	–
LNB	BUP	7.8±2.2 (26/30)	5.2±2.5 (26/30)	–	425±117 (26/30)	382±118 (26/30)	–
	LBUP	7.2±1.5 (28/30)	5.0±0.7 (28/30)	–	468±140 (28/30)	392±112 (28/30)	–

IAN inferior alveolar nerve block, *BNB* buccal nerve block, *LNB* lingual nerve block, *n* number of successfully achieved nerve blocks

Table 4 Postoperative analgesia after 0.5 % bupivacaine (BUP) and 0.5 % levobupivacaine (LBUP) anaesthesia

Parameters	Treatment (mean±SD)		
		BUP	LBUP
Time of first postoperative pain report (min)		375±110	547±203*
(N_1/success blocks)		(15/26)	(12/27)
Time of first analgesic consumption (min)		402±164	626±247*
(N_2/success blocks)		(13/26)	(11/27)
Postoperative pain intensity	VAS (mm)	25±14	20±11
	NRS	4.5±2.2	4.1±1.8
No. of pain medication doses taken:			
First		9	10
Second		3	1
Third		1	0
Total analgesic consumption		13	11

*p<0.05 (Student's *t* test)

VAS visual analogue scale, *NRS* numerical rating scale, N_1 number of patients experienced postoperative pain, N_2 number of patients required pain medication

sufficient to ensure a similar success rate as it was achieved with the combination of levobupivacaine+epinephrine and bupivacaine+epinephrine.

The onset of achieved intraoral blocks showed similar non-significant onset time as result of equal pK_a of 8.1 for both levobupivacaine and bupivacaine [28]. When considering the duration of anaesthesia, both anaesthetics showed a long-acting effect without significant difference between levobupivacaine and bupivacaine. Most probably, it is the consequence of similar pharmacokinetic property—protein binding of bupivacaine (95 %) and levobupivacaine (95 %) [5], and similar pharmacodynamic vasoactive effect although both anaesthetics posses

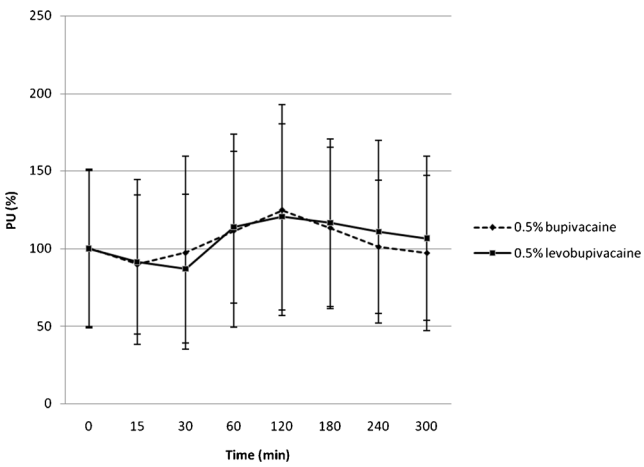

Fig. 2 Changes in pulpal blood flow of lower first premolar after the IANB achieved by 2 ml of 0.5 % bupivacaine (*broken line*) and 0.5 % levobupivacaine (*solid line*). Data were presented as percentages with whiskers representing the statistical range. *PU* perfusion units

delayed vasodilation [29]. Our results concerning the duration of mandibular anaesthesia are in agreement with those obtained for other peripheral nerve blocks. Namely, 0.5 % levobupivacaine and 0.5 % bupivacaine achieved similar duration of axillary brachial plexus block [13] or sciatic nerve block [12].

The basic difference in the design of our study, in comparison to the previous studies, is exhibited in the following. Namely, for the analysis of the intensity of the intraoperative anaesthesia and postoperative analgesia, we included patients with all three successful blocks (IANB, LNB and BNB), the condition necessary for painless surgical third molar extraction as well as control of long-lasting postoperative pain. In contrast to anaesthetic duration, levobupivacaine and bupivacaine differ in the intensity of intraoperative anaesthesia. Our results showed that 0.5 % levobupivacaine produced significantly more effective surgical block than 0.5 % bupivacaine when intensity of mandibular nerve blocks was measured by VAS, as a standard, and by NRS, as the most responsive scale [20, 21]. Although our study stated a comparison of equal concentrations of bupivacaine and levobupivacaine, it should be noted that the concentration of levobupivacaine (Chirocaine®) is denoted on the drug label as the concentration of the base of the molecule and not as the concentrate of the hydrochloride of the molecule, as is the case with racemic bupivacaine. Thus, as ampoule of levobupivacaine contains 13 % more molecules of local anaesthetic than an ampoule of racemic bupivacaine of the same concentration [30], it could be proposed that the higher anaesthetic intensity of levobupivacaine vs. bupivacaine is the consequence of slightly increased levobupivacaine concentrations, not the result of higher potency of levobupivacaine since partition coefficients of both anaesthetics, as a marker of anaesthetic potency, are equal [5]. Concerning the response to postoperative pain, it is interesting to note that part of these parameters, the time of first postoperative pain report and time of first analgesic dose taken, is significantly prolonged in the levobupivacaine group vs. bupivacaine group. On the other hand, the part regarding the intensity of postoperative analgesia, such as the intensity of pain at the time of first analgesic consumption as well as the number of total analgesic doses taken, is similar for both anaesthetics. Therefore, slightly increased levobupivacaine concentration could be responsible for the prolonged postoperative analgesia but not for its intensity. Upon reviewing the results of postoperative pain analysis, from the clinical point of view, it could be said that both anaesthetics with successful anaesthesia reached by all three nerve blocks responsible for surgical third molar extraction showed similar profiles of postoperative pain control. Results coming from other studies of third molar surgery cannot be easily extrapolated to ours, since a higher concentration of levobupivacaine (0.75 %) was used [18, 19] and, in the study of Rood et al. [18], patients underwent general anaesthesia for surgical extraction of third molars.

Conclusion

In conclusion, 3 ml of 0.5 % levobupivacaine induces the IANB, BNB and LNB of similar success rate, onset, duration of anaesthesia, postoperative pain intensity and analgesic consumption as well as similar vascular response within oral tissue as blocks produced with the same volume and concentration of bupivacaine. Differences between two anaesthetics were seen in the intraoperative intensity of anaesthesia, prolonged time of first postoperative pain report and time of first analgesic consumption. However, further studies are needed to compare the safety profile of levobupivacaine and bupivacaine during mandibular nerve blocks in oral surgery.

Acknowledgments This study was supported by the Serbian Ministry of Education and Science, grant no. 175021.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Brown DL, Ransom DM, Hall JA, Leicht CH, Schroeder DR, Oford KP (1995) Regional anesthesia and local anesthetic-induced systemic toxicity: seizure frequency and accompanying cardiovascular changes. Anesth Analg 81:321–328
2. Kopp SL, Wynd KP, Horlocker TT, Hebl JR, Wilson JL (2009) Regional blockade in patients with history of a seizure disorder. Anesth Analg 109:271–278. doi:10.1213/ane.0b013e3181a832da
3. Marwick PC, Levin AI, Coetzee AR (2009) Recurrence of cardiotoxicity after lipid rescue from bupivacaine-induced cardiac arrest. Anesth Analg 108:1344–1346. doi:10.1213/ane.0b013e3181979e17
4. Dudley MH, Fleming SW, Garg U, Edwards JM (2011) Fatality involving complications of bupivacaine toxicity and hypersensitivity reaction. J Forensic Sci 56:1376–1379. doi:10.1111/j.1556-4029.2011.01829.x
5. Leone S, Di Cianni S, Casati A, Fanelli G (2008) Pharmacology, toxicology, and clinical use of new long acting local anesthetic, ropivacaine and levobupivacaine. Acta Biomed 79:92–105
6. Werdehausen R, Braun S, Fazeli S, Hermanns H, Hollmann MW, Bauer I, Stevens MF (2012) Lipophilicity but not stereospecificity is a major determinant of local anaesthetic-induced cytotoxicity in human T-lymphoma cells. Eur J Anaesthesiol 29:35–41. doi:10.1097/EJA.0b013e32834cd6c4
7. McLeod GA, Burke D (2001) Levobupivacaine. Anaesthetic 56:331–341
8. Aps C, Reynolds F (1978) An intradermal study of the local anaesthetic and vascular effects of the isomers of bupivacaine. Br J Clin Pharmacol 6:63–68
9. Vanhoutte F, Vereecke J, Verbeke N, Carmeliet E (1991) Stereoselective effects of the enantiomers of bupivacaine on electrophysiological properties of the guinea-pig papillary muscle. Br J Pharmacol 103:1275–1278
10. Mazoit JX, Boico O, Samii K (1993) Myocardial uptake of bupivacaine: pharmacodynamics of bupivacaine enantiomers in the isolated perfused rabbit heart. Anesth Analg 77:477–482
11. Cox CR, Checketts MR, Mackenizie N, Scott NB, Bannister J (1998) Comparison of S(−) - bupivacaine with racemic (RS) – bupivacaine in supraclavicular brachial plexus block. Br J Anaesth 80:594–598
12. Casati A, Chelly JE, Cerchierini E, Santorsola R, Nobili F, Grispigni C, Di Benedetto P, Torri G (2002) Clinical properties of levobupivacaine or racemic bupivacaine for sciatic nerve block. J Clin Anesth 14:111–114
13. Liisanantti O, Luukkonen J, Rosenberg PH (2004) High-dose bupivacaine, levobupivacaine and ropivacaine in axillary brachial plexus block. Acta Anaesthesiol Scand 48:601–606. doi:10.1111/j.1399-6576.2004.00393.x
14. Novak-Jankovic V, Milan Z, Potocnik I, Stupnik T, Maric S, Stopar-Pintaric T, Kremzar B (2012) A prospective, randomized, double-blinded comparison between multimodal thoracic paravertebral bupivacaine and levobupivacaine analgesia in patients undergoing lung surgery. J Cardiothorac Vasc Anesth 26:863–867. doi:10.1053/.j.jvca.2012.01.050
15. Huang YF, Pryor ME, Veering BT, Mather LE (1998) Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep. Anesth Analg 86:797–804
16. Bardsley H, Griswood R, Baker H, Watson N, Nimmo W (1998) A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. Br J Clin Pharm 46:245–249
17. Branco FP, Ranali J, Ambrosano GMB, Volpato MC (2006) A double-blind comparison of 0.5 % bupivacaine with 1:200,000 epinephrine and 0.5 % levobupivacaine with 1:200,000 epinephrine for the inferior alveolar nerve block. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 101:442–447. doi:10.1016/j.tripleo.2005.06.005
18. Rood JP, Snowdon AT, Gennery BA (2002) Safety and efficacy of levobupivacaine for postoperative pain relief after surgical removal of impacted third molars: a comparison with lignocaine and adrenaline. Br J Oral Maxillofac Surg 40:491–496. doi:10.1016/S0266-4356(02)00184-5
19. Crincoli V, Di Bisceglie MB, Massaro M, Giuliani R, Favia G, Brienza N (2009) Postoperative pain relief after surgical removal of impacted third molars: a single-blind, randomized, controlled study to compare levobupivacaine and mepivacaine. J Orofac Pain 23:325–329
20. Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP (2011) Validity of four pain intensity rating scales. Pain 152:2399–2404. doi:10.1016/l.pain.2011.07.005
21. Gagliese L, Weizblit N, Ellis W, Chan VWS (2005) The measurement of postoperative pain: a comparison of intensity scales in younger and older surgical patients. Pain 117:412–420. doi:10.1016/j.pain.2005.07.004
22. Ray K (1973) Local anaesthesia in dental surgery. In: Green RA (ed) Anaesthesia and analgesia in dentistry, 1st edn. HK Lewis & Co, Ltd, London, pp 295–343
23. Teplitsky PE, Hablichek CA, Kushneriuk JS (1987) A comparison of bupivacaine to lidocaine with respect to duration in the maxilla and mandible. J Can Dent Assoc 53:475–478
24. Volpato MC, Ranali J, Ramacciato JC, de Oliveira PC, Ambrosano GMB, Groppo FC (2005) Anesthetic efficacy of bupivacaine solutions in inferior alveolar nerve block. Anesth Prog 52:132–135
25. Bangerter C, Mines P, Sweet M (2009) The use of intraosseous anesthesia among endodontists: results of a questionnaire. J Endod 35:15–18. doi:10.1016/j.oen.2008.10.003
26. Malamed SF (2004) Clinical action of specific agents. In: Malamed SF (ed) Handbook of local anesthesia, 5th edn. Mosby, St. Louis, pp 255–261
27. Whiteside JB, Wildsmith JAW (2001) Developments in local anaesthetic drugs. Br J Anaesth 87:27–35
28. Casati A, Putzu M (2005) Bupivacaine, levobupivacaine and ropivacaine: are they clinically different? Best Pract Res Clin Anaesthesiol 19:247–268. doi:10.1016/j.bpa.2004.12.003
29. Foster RH, Markham A (2000) Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. Drugs 59:551–579
30. Schung SA (2001) Correction factor for comparison between levobupivacaine and racemic bupivacaine. Reg Anesth Pain Med 26:91

Obrazac 1.

Fakultet STOMATOLOŠKI

UNIVERZITET U BEOGRADU

Stručno veće za medicinske nauke

Broj zahteva

(naziv stručnog veća kome se zahtev upućuje , shodno čl.6 Statuta Univerziteta u Beogradu i čl. 7. st.1 ovog pravilnika)

..god.

(Datum)

ZAHTEV

za davanje saglasnosti na izveštaj o urađenoj doktorskoj disertaciji

Molimo da, shodno članu 68. st.3. Zakona o univerzitetu ("Službeni glasnik RS" br. 20/98), date saglasnost na

izveštaj o urađenoj doktorskoj disertaciji kandidata BRAJKOVIĆ OLIVER DENISA
(ime, ime jednog od roditelja i prezime)

KANDIDAT BRAJKOVIĆ OLIVER DENIS prijavio je doktorsku disertaciju pod nazivom
(ime, ime jednog od roditelja i prezime)

„EFIKASNOST PROFILAKTIČKE PRIMENE NIMESULIDA I LEVOBUPIVAKAINA U KONTROLI POSTOPERATIVNOG BOLA POSLE HIRURŠKOG VAĐENJA DONJIH IMPAKTIRANIH UMNJAKA“

Univerzitet je dana 10.07.2012 svojim aktom pod br. 06-19091/65-12 dao saglasnost na predlog teme

doktorske disertacije koja je glasila

„EFIKASNOST PROFILAKTIČKE PRIMENE NIMESULIDA I LEVOBUPIVAKAINA U KONTROLI POSTOPERATIVNOG BOLA POSLE HIRURŠKOG VAĐENJA DONJIH IMPAKTIRANIH UMNJAKA“

Komisija za ocenu i odbranu doktorske disertacije kandidata BRAJKOVIĆ OLIVER DENISA
(ime, ime jednog od roditelja i prezime)

obrazovana je na sednici održanoj 25.02.2014 odlukom fakulteta pod br. 3/8

u sastavu:

ime i prezime člana komisije:	zvanje:	naučna oblast:
DRAGICA STOJIĆ	PROFESOR	BAZIČNE STOM. NAUKE
MIROSLAV ANDRIĆ	DOCENT	KLINIČKE STOM. NAUKE
SINIŠA MIRKOVIĆ	DOCENT	KLINIČKE STOM. NAUKE

Nastavno-naučno veće fakulteta prihvatilo je izveštaj Komisije za ocenu i odbranu doktorske disertacije na sednici održanoj dana 03.06.2014.

DEKAN FAKULTETA

Prof. dr Miroslav Vukadinović

Prilog:
1. **Izveštaj komisije sa predlogom**
2. **Akt Nastavno-naučnog veća fakulteta o usvajanju izveštaja**
3. **Primedbe date u toku stavljanja izveštaja na uvid javnosti, ukoliko je takvih primedbi bilo.**