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KLINIČKI ZNAČAJ PRIMENE LOKALNIH ANESTETIKA DUGOG DEJSTVA U ORALNOJ HIRURGIJI

CLINICAL SIGNIFICACY OF LONG ACTING LOCAL ANESTHETICS IN ORAL SURGERY

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Kratak sadržaj

Oralno hirurški zahvati uglavnom su praćeni jakim i dugotrajnim bolovima koji se inteziviraju posle intervencije i traju više sati. U oralno hirurškoj praksi se lokalni anestetici dugog dejstva koriste od 1957. godine, a njihova primena umanjuje potrebu za dodavanjem anestetika u toku intervencije, olakšava postoperativni oporavak i smanjuje uzimanje anelgetika. U radu je dat pregled osobina lokalnih anestetika dugog dejstva koji se koriste u oralnoj hirurgiji, kao i naša iskustva u njihovoj primeni.
Ropivakain se po početku dejstva i dužini dejstva anestezije ne razlikuje značajno od bupivakaina, kvalitet anestezije je bolji nego kod bupivakaina, uzrokuje manju motornu blokadu i ima manju KVS i CNS toksičnost. Poređenjem osobina ovih lokalnih anestetika zaključujemo da, ako postoji potreba za lokalnim anestetikom dugog dejstva, ropivakainu treba dati prednost u odnosu na etidokain i bupivakain.

Ključne reči: *lokalni anestetik, ropivakain, bupivakain*

Abstract

Oral surgical procedures are usually accompanied by severe and long lasting pain that intensify after the intervention and lasting several hours. Surgical practice had need for long-acting local anesthetics first applied since 1957. to provide indolence during and after the intervention that have proved to be effective for the suppresion for both intraoperative and postoperative pain. This paper is an overview of characteristics of long acting local anesthetics used in oral surgery, as well as our experience in their implementation.
Ropivacaine and bupivacaine has equal onset of effects and length of action, quality of anesthesia is higher than the bupivacaine, causes less motor block and has a less CVS and CNS toxicity then bupivacaine. We conclude that in case of need for the long acting local anesthetic, priority should be given to ropivacaine over etidocaine and bupivacaine.

Key words: *local anestetic, ropivacaine, bupivacaine*

Uvod

Lokalna anestezija je reverzibilno isključenje osećaja bola u anatomski ograničenom delu tela. Lokalni anestetici prolazno blokiraju sprovođenje nervnog impulsa kroz senzitivna nervna vlakna a pri tome ne dovode do njihovog oštećenja Ovaj efekat postižu tako što dovode do destabilizacije ćelijske membranu i onemogućavaju odvijanje normalnog procesa depolarizacije, zbog smanjena propustljivosti membrane za natrijumove jone[1].

Primenu lokalnog anestetika u stomatologiji je prvi put opisuje dr.Richard J.Hall i njegov

Introduction

Local anesthesia is a reversible exclusion of pain in an anatomically limited part of the body. Local anesthetics temporarily block enforcement of nerve impulses through the sensitive nerve fibers and thereby do not cause their damage. This effect is achieved by destabilization of the cell membrane and normal functioning of the process of depolarization, due to reduced membrane permeability to sodium ions[1].

The use of local anesthetics in dentistry was first described on 6th. December 1884 by Dr. Richard J.Hall and his associate Dr. William Stewart Halsted and it was published in New

Oralno hirurški zahvati uglavnom su praćeni jakim i dugotrajnim bolovima koji se inteziviraju posle intervencije i traju više sati(oko 24 sata, pri čemu su najintenzivniji 6-8 sati od intervencije, zbog pokretanja. kaskadnog procesa sinteze imunomedijatora(prostaglandina i bradikinina)[3,4]. Zato je potrebno anestezirati meka i koštana tkiva na duži vremenski period (6-8h) ili pacijentima omogućiti postoperativnu analgeziju upotrebom oralnih anelgetika u cilju supresije bola. U oralno hirušku praksu se.zbog tih potreba uvode lokalni anestetici dugog dejstva, kojise prvi put primenjuju od 1957. da obezbede bezbolnost u toku i posle intervencije.

Farmakokinetička svojstva molekula LA zavise od rastvorljivosti u mastima, vezivanja za proteine plazme, i disocijacione konstante pKa[5]. Strukturne promene molekula LA dugog dejstva značajno utiču na njihovu tosičnost, potencijal, sposobnost difuzije i dužinu dejstva. Bitna osobina LA je efekat na krvne sudove na mestu aplikacije. Svi LA osim kokaina i ropivakaina izazivaju vazodilataciju na mestu aplikacije, koja smanjuje dužinu dejstva LA i povećava njegovu toksičnost. Vazokonstriktori se dodaju LA kako bi umanjili njihove negativne efekte na lokalnu cirkulaciju na mestu administracije i smanjili toksičnost[6]. Lokalni anestetici dugog dejstva koji se primenjuju u oralnoj hirurgiji su etidokain, bupivakain,levobupivakain i najnoviji LA dugog dejsva ropivakain. Svi su slične structure , ali se značajno razlikuju u kliničkim osobinama.

Na osnovu dostupnih podataka iz literature tj. ranijih i savremenih istraživanja dostupnih na u štampanoj i elektronskoj , (podaci dostupni na Pub Med-u, Med Line-u i Ebsco bazi) , 26 radova o etidokainu, 36 radova o bupivakainu i 13 radova o ropivakainu, analizirali smo efektie lokalnih anestetika dugog dejstva sa ciljem da utvrdimo koje su prednosti i mane LA dugog dejstva i da li je neki od njih adekvatniji za primenu u orlno-hirurškoj praksi,

Na osnovu dobijenih podataka utvrđeno je da postoje sledeći LA dugog dejstva koji se primenjuju u stomatološkoj praksi:

1.Etidokain

2.Bupivakain

2.a. Levobupivakain

3. Ropivakain

Oral surgical procedures are usually accompanied by severe and long-term pain that intensify after the intervention and last several hours (about 24 hours, with the highest intensity 6-8 hours after the intervention, caused by the cascade processes imunomediators (prostaglandins and bradycins)[3,4] synthesis. Therefore, it is necessary to anesthetize soft tissue and bone in the long term (6-8 hr) or provide postoperative analgesia for patients using oral analgesics in order to reduce the pain. Because of these needs, long-acting local anesthetics are applied in oral surgical practice since 1957. to provide indolence during and after the intervention.

Pharmacokinetic properties of local anesthetic molecule depend on its liposolubility, binding for proteins, and pKa[5]. The structural changes of molecule greatly affect their toxicity, potential, diffusion capacity and duration. Very important characteristic of local anesthetic is effect on blood vassals in the place of application. All of LA, except cocaine and ropivacaine, cause vasodilatation. Vasodilatation reduces effect of LA and increases its toxicity. The solution of local anesthetics is prepared with vasoconstrictors in order to eliminate LA negative effect on circulation in the place of administration, prolong effects and make them less toxic[6]. Long acting local anesthetics in oral surgery are etidocaine, bupivacaine, levobupivacaine and the latest long acting LA-ropivacaine. Their structures are alike but they are different in clinical characteristics.

We made the search based on available literature the data from the now days and past , surveys available in printed and electronic form, (information available at the Pub-Med, Med Line and the EBSCO database) .We analyzed 26 studies about etidocaine, 36 studies about bupivacaine, 13 studies about ropivacaine in order to determine what are the advantages and disadvantages of long-acting LA and whether some of them is more adequate for use in oral-surgical practice.

Based on this data these are the long acting-LA applied in oral surgery:

1 .Etidocaine

2 .Bupivacaine

2a Levobupivacaine

3. Ropivacaine

1. **Etidokain** hidrohlorid (2-N-etilpropilamino-2, 6-butiro-ksilidid hidrohlorid) je amidni lokalni anestetik dugog dejstva, sintetisan 1972.godine[7] Lokalni anestetik po strukturi sličan lidokainu od koga se razlikuje po dodatku propil grupe na etil grupu na aminskom kraju molekula i dodatkom etil grupe na atom ugljenika na središnjem delu lanca(slika 1). Etidokain je približno 50 puta liposolubilniji u odnosu na lidokain, a njegova sposobnost vezivanja za proteine plazme (94%), slična je bupivakainu (95%) a znatno veća nego kod lidokaina(65%). Potentnost etidokaina in vitro je približno četiri puta veća u odnosu na lidokain, ali mu je toksičnost skoro tri puta veća[6] Skoro sav metabolizam etidokaina odvija se u jetri, a ekskrecija se odvija putem bubrega. Svega 1% etidokaina u nepromenjenom obliku izbacuje se iz organizma urinom.

Kliničke studije ukazuju na produženo vreme delovanja etidokaina. Donoghue, Doberenz, Jacobsen[8] u studiji sa 14 pacijenata kod kojih je uklonjen treći molar obostrano, ukazuju da 43% pacijenata nije osetilo bilo kakav postoperativni bol na strani koja je anestezirana etidokainom, dok su svi ispitnici osetili manji ili veći bol na strani anesteziranoj lidokainom. Nije bilo pacijenata koji su se žalili na jake postoperativne bolove na strani anesteziranoj etidokainom, dok se 29% pacijenata žalilo na takve bolove na drugoj strani gde je primenjen lidokain. Početak dejstva anestezije je sličan lidokainu. Dužina dejstva anelgezije za etidokain sa epinefrinom prema Donoghue i sar[8] je prosečno 7,6 sati (2-20 h) nasuprot lidokainu kod koga je dužina dejstva prosčno bila 1,8 sati (1,5-4h). Trajanje anestezije (vreme proteklo od početka utrnulosti usne do potpunog vraćanja senzibiliteta) bilo je 9,4h za etidokain i 2,7 za lidokain.

Upotreba etidokaina može smanjujiti potrebu za uzimanjem oralnih anelgetika nakon intervencije,[9] Duže vreme regresije pri upotrebi etidokaina (vreme od početka regresije anestezije do potpunog oporavka mekih tkiva) može omogućiti lakšu kontrolu bola[6,10]. U određenim okolnostima etidokain ipak ne obezbeđuje adekvatnu hemostazu, što smanjuje vidljivost operativnog polja. Povećano intraoperativno krvarenje pri upotrebi etidokaina javilo se i u oralnoj i u periodontalnoj hirurgiji. I ako se etidokain nalazi u istom odnosu sa epinefrinom (1:200.000) kao i bupivakain, postoje razlike

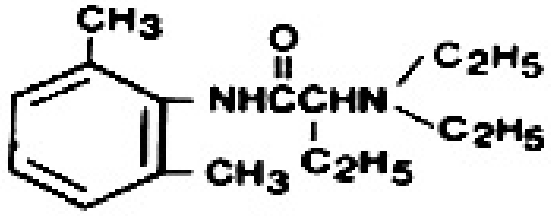
1. **Etidocaine**: Etidocaine hyidrochloride (2-N-etilpropyilamino-2, 6-butiro-ksilidid hydrochloride) is long acting amide local anesthetic , syntetized in 1972.[7] Etidocaine is an amid type local anesthetic and is similar in structure to lidocaine: it differs from lidocaine by the addition of a propyl on an ethyl group at the amine end, and by the addition of an ethyl group on a carbon in the intermidiate chain(figure 1). Etidocaine is approximately 50 times more lipid-soluble than lidocaine, and its plasma proten binding (94%) is similar as bupivacaine(95%), and greather than that of lidocaine(65%).In vitro etidocaine is approximately four times more potent than lidocaine as a local anesthetic agent, but its toxicity is three times higher[6]. Most of metabolism of etidocaine takes place in the liver and excretion occurs via kidneys. Only 1% etidocaine in unaltered form releases from the body through urine.

Clinical studies indicate a prolonged time of etidocaine action. Donoghue, Doberenz, Jacobsen[8] in his study with 14 patients undergoing thirth molar removal, reported that 43% of patients reported no postoperative pain on the side injected with etidocaine, while all patients reported some level of postoperative pain on the lidocaine injected side. No patient reported severe postopertive pain on the side on which etidocaine was injected, whereas 29% of patients reported severe postoperative pain on the side on which lidocaine was injected. The onset of anesthesia is reported to be similar to that of lidocaine. The duration of anelgesia for etidocaine with epinephrine according to Donoghue et al.[8] is in average 7.6 hours range (2-20 hr) versus 1.8 hr (range 1,5-4 hr) for lidocaine with epinephrine. The duration of anesthesia (time from onset until normal lip sensation) was 9.4h (3,8 to 19hr) for the etidocaine solution, versus 2,7 hr (1,3 to 6hr) for lidocaine.

The use of etidocaine may decrease the need for ingestion of oral anelgetics in the postoperative period [9]. The longer regresion time with etidocaine (the time from the start of regresion of anestesia to the return to the normal soft tissue sensation) may provide better pain control.[6,10.] In certain circumstances, etidocaine may not provide adequate hemostasis which causes lower visibility of the operating area. Increased intraoperative bleeding was noted with etidocaine in both third molar extraction

u sposobnosti hemostaze. Etidokain ima manji kardiodepresorni efekat nego bupivakain ali veći nego lidokain.

Za upotrebu u stomatologiji koristi se kao 1% i 1,5% rastvor etidokaina sa adrenalinom 1:200.000. Proizvođači preporučuju max. dozu od is 8 mg/kg do max. 400mg . Etidokain se na tržištu nalazi pod nazivom Duranest® (EvaluatePharma).



Slika 1. Strukturna formula Etidokaina
Figure1. Structural formula of etidocaine

2. **Bupivakain** hidrohlorid (1-n-butil-DL-piperidin-2-karboksilna kiselina-2,6-dimetil-hilanilid hidrohlorid) je amidni lokalni anestetik dugog dejstva, sintetisan 1957.godine od strane Ekenstama[11]. Strukturno je vrlo sličan mepivakainu, od koga se razlikuje jedino po zameni butil grupe metil grupom na aminskom kraju molekula(slika2). Bupivakain je oko 35 puta liposolubilniji u odnosu na mepivakain, što ima presudan značaj kada je u pitanju jačina lokalnog anestetika. Potentnost bupivakaina je oko četiri puta veća u odnosu na lidokain. Do pojave utrnulosti mekih tkiva dolazi u proseku posle 2 minuta po aplikaciji 0,5% bupivakaina sa adrenalinom 1:200.000. Anestezija mekog tkiva posle aplikacije bupivakaina sa adrenalinom traje od 4 do 9 sati, približno 2-3 puta duže nago nakon primene lidokaina sa epinefrinom[12]. Bol se obično javlja i pre nego što potpuno prestane utrnulost mekih tkiva[12]. Od kada su objavljeni prvi izveštaji o upotrebi bupivakaina u oralnoj hirurgij (1966.god. Feldmann i Nordenram)[13], ovaj anestetik se prevashodno koristi kod intervencija kod kojih je poželjan što duži učinak anestetika (hirurgija impaktiranih zuba i dr.), kao i u tretmanu hroničnog orofacijalnog bola (neuralgije).

Ranije studije o bupivakainu uglavnom karakterišu ovaj LA kao bezbedan, dok novije kontrolisane studije izveštavaju o mogućnosti pojave naglog kardiovaskularnog kolapsa i njegovu toksičnost koja je veća nego kod lidokaina i ostalih lokalnih anestetika[12,14,15]. Studije na različitim životinjskim modelima ukazuju da

surgery and periodontal surgery. Although etidocaine is marked for dental use with the same concentration of epinerine (1:200,000) as bupivacaine, there appear to be significant differences beetwen these two anesthetic combinations in hemostasis capability. Etidocaine has less cardiodepresant activity than bupivacaine, but greater than lidocaine.

Etidocaine is used in dentistry as 1% and 1,5% solution with epinephrine. Manufacturers reccomend maximum dosage of is 8 mg/kg up to 400mg. Etdocaine is in the market known as Duranest® (EvaluatePharma).

2. **Bupivacaine**: Bupivacaine hydrcohloride (1-n-butyl-DL-pyperidin-2-carboxyl acid-2, 6-dimethylhilanilid hydrochloride) is an amid local anesthetic that is closely related structurally to mepivacaine(figure2) and is sintetised 1957. According to Exentam[11]. Bupivacaine is 35 times more lipid soluble than mepivacaine. Increased lipid solubility is solely due to the elongated aliphatic carbon chain. Bupivacaine is higher protein bound (95%) than mepivacaine (75%). Potency of bupivacaine is four times higher than lidocaine. Soft tissue anesthesia after bupivacaine with epinephrine varies from 5 to 9 hr, approximately 2-3 times longer than anesthesia after lidocaine with epinephrine. Following surgical procedures, the onset of pain is significantly longer for bupivacaine with epinephrine when compared to lidocain with epinephrine. Onset of postoperative pain is usually noted before soft tissue sensation returns to normal[12] since the first published reports on the use of bupivakaina in oral surgery (1966.god. Feldmann and Nordenram) [13], this anesthetic is used primarily in interventions in which the desired effect is long anesthetics, as well as in orofacial chronic pain treatment (neuralgia).

Although most of the early laboratory studies reported on the safety of bupiviacaine, subsequent case reports and controlled studies of cardiovascular collapse have shown that bupivacaine is more cardiotoxic than lidocaine and other local anesthetic [12, 14, 15.] Studies on different animal models indicate that the convulsing doses of bupivacaine unlike lidocaine can cause serious ventricular dhysrhitmias [16, 17]

Benzodiazepine treatment of patients suffering from cardiovascular disease is common in oral surgery now days. There is

konvulzivne doze bupivakaina za razliku od lidokaina mogu izazvati ozbiljne ventrikularne aritmije[16,17]

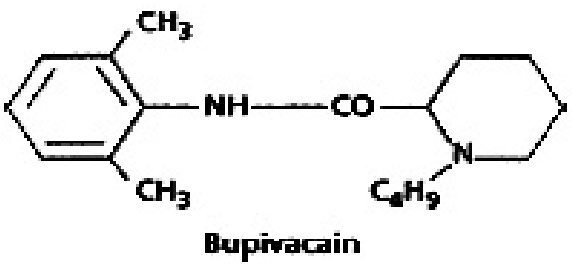
Pacijenti koji pate određenih kardiovaskularnih oboljenja često kao premedikaciju koriste benzodijazepine. U tim slučajevima postoji mogućnost da efekti na CNS ostanu neprepoznati, a samim tim i predoziranje anestetikom, što vodi u hipoksemiju i respiratornu acidozu i direktno povećava kardiotoksičnost [18].

Metabolizam bupivakaina odvija se u jetri, pri čemu 10 % biva ekskretovano putem urina u nepromenjenom obliku.[11]

Bupivakain se ne primenjuje kod dece mlađe od 12 godina. . Doza od 90 mg je predložena maksimalna doza za upotrebu 0,5% bupivakaina sa adrenalinom 1:200.000 u stomatologiji od strane Uprave za hranu i lekove SAD (Food and Drug Administration - FDA). Na tržištu se najčešće nalazi pod zaštićenim imenima Marcaine®, Sensorcaine®, Vexelit® i dr.

2.a.: **Levobupivakain**: Bupivakain ima jedan hiralni centar i proizvodi se kao recemat R i S bupivakain (rac-bupivakain). Oba enantiomera su aktivna, ali S-bupivacaine dovodi do duže neuronske blokade, kao i manje CNS i CVS toksičnosti [19,20], što je dovelo do njegovog uvođenja u praksu kao levobupivakain (*S*)-1-butyl-*N*-(2,6-dimethylphenyl) piperidine-2-carboxamide (slika 3). Paralelnim razvojem je stvoren propil homolog bupivakaina , poznat kao ropivakain.[19].

Studije o intradermalnom aplikovanju R i S bupivacaina sugerišu da, u poređenju sa R-bupivacainom S-bupivakain ima veću vazokonstriktornu aktivnost u niskim koncentracijama i manje vazodilatatornih aktivnosti u visokim koncentracijama[21]. Na ovoj osnovi, sistemska absorpcija S-bupivakaina bi trebalo da bude sporija od rac- bupivakaina, a samim tim i veći LA učinak, ipak prema većini studija između rac- bupivakaina i S-bupivakaina nema razlike



Bupivacain

Slika 2. Strukturna formula Bupivakaina

Figure 2. Structure formula of bupivacaine

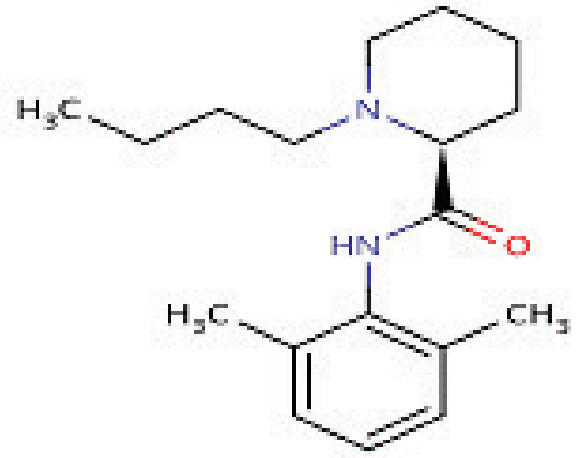
possibility that a benzodiazepine may mask CNS effects and delay recognition of overdose of bupivacaine , it may contribute to hypoxemia and acidosis by respiratory depression, and it may also cause cardiovascular system toxicity[18].

Metabolism of bupivacaine takes place in the liver, while 10% is through urine unchanged [11].

Bupivacaine is not applicated to the children younger then 12 years. Maximum proposed dose of bupivacaine with 1:200,000 adrenaline corresponding Food and Drug Administration - FDA is 90 mg. Bupivacaine is on market under the name Marcaine®, Sensorcaine®, Vexelit®.

2.a: **Levobupivacaine**: Bupivacaine has a single chiral centre and is produced as a recemate of R and S bupivacaine. Both enantiomers are active, but S-bupivacaine produces a longer neural blockade, and less CNS and CVS toxicity[19,20], so it is introduced in clinical practice as levobupivacaine(*S*)-1-butyl-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide(figure 3). With a parallel development the propyl homolog of bupivacaine known as ropivacaine.[19] occured.

Studies of intradermal use of R and S bupivacaine suggest that , compared with R-bupivacaine, S-bupivacaine has more vasoconstrictor activity at low concentration and less vasodilatator activity at high concentration [21]. On this bases, systemic absorption of S-bupivacaine should be slower than of rac bupivacaine therefore leading to greater local anesthetic activity. However, most of the studies report that there is no difference in blood flow, duration and onset



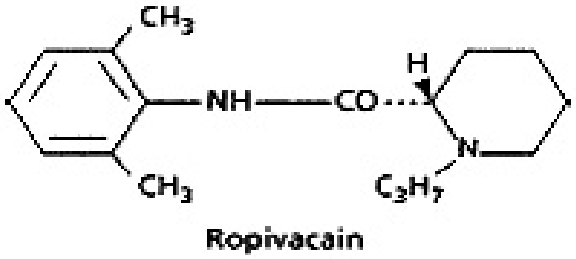
Sika 3. Struturna formula levobupivakaina

Figure 3.Structure formula of levobupivacaine

u krvarenju, trajanju i početku dejstva anestezije.

Na tržištu se nalazi pod imenom Chirocaine® (Astra-Zeneca).

3 **Ropivakain**: Sintetisan je istovremeneo sa bupivakainom 1957. god. ali nije dalje razvijan za kliničku upotrbu. U kliničku praksu je uveden 1996. god. Ropivakain je po strukturi je sličan bupivakainu i mepivakainu, a sva tri anestetika pripadaju hemijskoj grupi – pipekolil ksilidini, koji kombinuju piperidinski prsten kokaina sa ksilidinom iz lidokaina. Substitucijom metil, butil i propil grupa na piperidinskom prstenu nastali su mepivakain, bupivakain i ropivakain.(slika 4)[22]. Ropivakain je S-enan-



Slika 4. Strukturna formula Ropivakaina
Figure 4. Structure of Ropivacaine

tiomer propivakaina (1-propil-2',6'-pipekoloksilidid hidrohlorid monohidrat). Ovaj i neki drugi lokalni anestetici postoje u formi dva lika u ogledalu ili kao enantiomeri. Levo i desnostrani enantiomeri označeni su terminima S i R (sinister i rectus). Prefiksi L i D ili '' + '' i '' – '' odnose se na pravac u kojem enantiomeri rotiraju polarizovanu svetlost.[23] Do sada su lokalni anestetici pripremani kao racemati, mešavine koje sadrže jednake količine S i R oblika, dok su pojedinačni enantiomeri pripremani samo za potrebe istraživanja. Napretkom u tehnici ekstahovanja i stereoselektivne sinteze postala je moguća komercijalna priprema samo jednog enantiomera lokalnog anestetika. Ropivakain je prvi lokalni anestetik označen kao ''čisti'' enantiomer, koji sadrži više od 99% S oblika. Ovo je od značaja jer je mnogobrojnim laboratorijskim ispitivanjima utvrđeno da S-enantiomeri poseduju znatno manju kardiotoksičnost u odnosu na R formu.

Disocijaciona konstanta je slična kao kod bupivakaina(pKa=8). Početak dejstva i dužina trajanja anestezije su slični kao kod bupivakaina, ali ropivakain izaziva manju motornu blokadu zahvaljujući liposolubilnosti i teže prolazi kroz deblja mijelinska vlakna, što je bitna

of anesthesia between Rac-bupivacaine and S-bupivacaine.

Levobupivacaine is marketed as Chirocaine. (Astra-Zeneca).

3. **Ropivacaine**: Ropivacaine is synthesized along with bupivacaine in 1957. , but it was no longer developed for clinical use. Ropivacaine is applied in clilical practice 1996. Ropivacaine is structurally similar to bupivacaine and mepivacaine (figure 4) and they belong to the group of anesthetics called pipecolil ksilidins, which combine piperidinski cocaine ring with ksilidinom. With substitution of methyl, butyl and propyl groups on the ring piperidne mepivacaine, bupivakain and ropivakain[22] were made.

Ropivacaine is the S-enantiomer of propivacaine (1-propyl-2 ', 6'-pypecoloxyilidid hydrochloride monohydrate). This and some other local anesthetics exist in the form of two characters in a mirror or as enantiomers. Left and right-side of the enantiomers are indicated by the terms of S and R (rectus and sinister). The prefixes D and L or '' + '' i '' - '' refer to the direction in which the enantiomers rotate polarized light[23.] So far, local anesthetic are prepared as racemat, a mixture containing equal amounts of S and R forms, while the individual enantiomers are prepared for research purposes. With the extracttions and stereoselective synthesis technique advance, commercial preparation of a single enantiomer local anesthetics became possible. Ropivakain local anesthetic is the first labeled as a ''clean'' enantiomer, which has more than 99% of S shape. This is important because a number of laboratory tests confirmed that S-enantiomers have significantly less cardiotoxicity compared to the R form.

Dissociation constant (pKa 8.1) of ropivacaine is similar to pKa of bupivacaine. Onset of anesthesia and anesthetic effect duration is similar to bupivacaine, but ropivacaine causes less motor blockade thanks to liposolubility, and passes with more difficulty into thicker nerve membranes, which is useful in procedures that need preservation of motor. The second important property of ropivacaine is that it causes vasoconstriction, without adding vasoconstrictor. Kopatz at al[24] studied cutaneous capillary bleeding in pigs injected with ropivacaine or bupivacaine, and these agents combinated with epinephrine. Ropivacaine is eather 0, 25% and

osobina u slučajevima u kojima je potrebno očuvanje motorike. Druga važna osobina ropivakaina je da izaziva vazokonsrikciu na mestu primene pri upotrebi bez adrenalina. Kopatzi sar. [24] su u studiji na svinjama određivali krvarenje iz kapilara kože nakon primene ropivakaina i bupivakaina , bez vazokonsrtiktora i ova dva agensa sa vaokonsriktorom. Ropivakain je i u conc. 0,25% I 0,5% smanjio krvarenje za polovinu. Bupivakain je pri istim konc. povećao krvarenje za oko 85%. Ova sposobnost vazokonstrikcije dolazi do izražaja više pri manjim (0,25% i 0,5%) nego pri većim koncentracijama(1%)[21].

Na nasoj Klinici prva iskustva su objavljena 2006. god kada se ropivakain koristio kao anestetik izbora u operaciji maksilarnog sinusa kod pacijenta sa oroantralnom fistulom. Prof. N. Burić[25] u svom radu opisuje njegove pozitivne efekte- dobru hemostazu i dugotrajnu postoperatvnu anelgeziju u trjanju od 240 min.

Tijanić[26] u kliničkoj studiji kod ispitanika je dobio značajno pozitivne efekte ropivakaina: Utrnulost mekih tkiva najduže je trajala nakon aplikacije 0,75% rastvora ropivakaina i prosečno je iznosila 321 min.(90-600min.). Nešto kraće anestetičko dejstvo imao je 0,5% rastvor bupivakaina bez adrenalina - 296,5 min. (210-420). Između 0,75% ropivakaina i 0,5% bupivakaina nije bilo statistički značajne razlike u pogledu dužine dejstva. Najkraću prosečnu vrednost trajanja anestezije imao je 2% rastvor lidokaina sa adrenalinom kod koga ona iznosila 151 min.(75-210), što je statistički signifikantno ($p<0,001$) u odnosu na oba preostala primenjena anestetika. Statistički značajno lošiji kvalitet anestezije bio je nakon aplikacije 0,5% rastvora bupivakaina, kako u odnosu na 0,75% ropivakain ($p<0,01$), tako i u odnosu na 2% lidokain sa adrenalinom ($p<0,001$). Nije bilo statistički značajne razlike u kvalitetu anestezije između ropivakaina i lidokaina. Statistički značajno niža vrednost intenziteta bola u toku intervencije na vizuelno analognoj skali (VAS) utvrđena je kod ispitanika čiji je anestetik bio 2% lidokain sa adrenalinom, u odnosu na ropivakain $p<0,05$, a u odnosu na bupivakain $p<0,001$. Ropivakain je takođe imao statistički značajno nižu srednju vrednost intenziteta bola u toku intervencije u odnosu na bupivakain ($p<0,001$). Najmanje intraoperativno krvarenje bilo je pri primeni 2% lidokaina sa adrenalinom, statistički značajno izraženije ($p<0,001$) bilo je pri primeni 0,75% ropivakaina, a najveće krvarenje je zabeleženo pri korišćenju 0,5% bupivakaina kao anestetika.

0,5% concentrations decreased half of bleeding. Bupivacaine in same concentration decreased bleeding by approximately 85%. This ability is more noticeable at the light concentrated solutions (0, 5% or 0,25%) than more concentrated solutions(1%)[21]

In our case, the first clinical experience was published in 2006. when ropivacaine was used as anesthetic in maxillary sinus surgery in patients with oroantral communication. Prof. N. Burić [25] in his work described its positive effects- fine hemostasis and a long-term postoperative anelgesys for a period of 240 min.

In a clinical study Tijanic [26] got significantly positive effects of ropivacaine: the numbness of soft tissues was the longest after the application the 0,75% solution of ropivacaine and was in average 321 min. long (from 90 to 600 min.). Shorter anesthetic effects had 0,5% bupivacaine solution without adrenaline - 296,5 min. (from 210 to 420min.). Between 0,75% ropivacaine i 0,5% bupivacaine there was no statistical diferences regarding the lenght of the effects. The shortest average lenght of effect had 2% solution of lidocaine with adrenaline and it was 151 minut (from 75min to 210 min.), which was statistically sighnificant ($p<0,001$) compared to the other two analized anesthetics. Quality of anethesia was significantly statistically worse after application of 0,5% solution of bupivacaine, compared to 0,75% ropivacaine ($p<0,01$), and 2% lidocaine with adrenaline ($p<0,001$). Statistically lower pain intensity on the VAS, during the intervention was noticed on examinees with 2% lidocaine with adrenaline compared to ropivacaine $p<0,05$ and bupivacaine $p<0,001$. Ropivacaine also had statistically lower value of intensity of pain compared to bupivacaine($p<0,001$). Intraoperative bleeding was significantly higher in group applied 0,5% bupivacaine than in other two groups($p<0,001$).

The cardiodepresant effect of riopivacane is less severe and shorter than with bupivacaine. The dose that causes cardiovascular collapse and convulsions is higher for ropivacaine than for bupivacaine. Ropivacaine was reported to have approxymately a 75% greater margin of safety than bupivacaine.

Ropivacain is primarily metabolized in liver. The most of the excretion is going through kidneys. [27]

tika, statistički značajno obilnije u odnosu na oba prethodno navedena anestetika (p<0,001).

Kardiodepresorni efekat ropivakaina je manje izražen nego kod bupivakaina. Doza koja izaziva kardiovaskularni kolaps i konvulzije veća je kod ropivakaina. Neke studije objavljuju da je ropivakain 75% bezbedniji za upotrebu nego bupivakaina.

Ropivakain se prvenstveno metaboliše u jetri. Ekskrecija se u najvećem procentu odvija putem bubrega.[27]

Ropivakain se na tržištu nalazi pod zaštićenim imenom Naropin ® (Astra-Zeneca) u koncentracijama 0,25%, 0,5%, 0,75% i 1%. Na evropskom tržištu nije dostupan u koncentraciji 0,5%. Za sada se proizvodi bez dodatka vazokonstriktora u anestetičkom rastvoru. . Maksimalna preporučena doza za ropivakain iznosi 150-200 mg, odnosno 1-2,5 mg/kg, u zavisnosti od mesta aplikacije.

Tabela 1. Prikazuje vreme proizvodnje LA i vreme početka primene LA na odeljenju Oralne hirurgije, Stomatološke klinike u Nišu.

Diskusija

Primena anestetika dugog dejstva je od značaja u orlno-hirurškoj praksi, jer umanjuje potrebu za dodavanjem anesteika u toku intervencije, olakšava postoperativni oporavak nakon intervencije i smanjuje opasnost od nekontrolisanog uzimanja anelgetika. Prostaglandini(PGE_2, PGD_2, PGF_{2a}, PGI2(prostakalcin) i tromboksan(TXA_2) kao imunomedijatori, između ostalog, deluju u mnogim inflamatornim procesima. Nastaju De

Ropivacaine is marketed under the protected name Naropin ® (Astra-ZENECA) in concentrations of 0.25%, 0.5%, 0.75%, and 1%. On the European market it is not available in the concentration of 0.5%. Ropivacaine is produced without the addition of vasoconstrictors. . The maximum recommended dose for ropivacaine is 150-200 mg, 1 to 2.5 mg / kg, depending on the place of application.

Table 1. shows the manufacturing and application time of LA in the department of Oral Surgery on Dental Clinic of Nis.

Discusion

The application of long-acting local anesthetics is of great importance in oral-surgical practice, as it reduces the need for anesthetics during the intervention, facilitates postoperative recovery after interventions and reduce the risk of uncontrolled anelgethics taking. Prostaglandins (PGE2, PGD2, PGF2a, PGI2 (prostakalcin) and thromboxan (TXA2) as imunomediators, among other things, act in many inflammatory processes. They are made de novo in damaged cells during the metabolism of arachidonic acid, with enzyme phospholipase A2 and are released by the cell wall (prostaglandins are present in all white blood cells, platelets and endothelium).As effect of PGI2 (prostakalcin) vasodilatation and edema occurs. PGE2 acts synergistically with other mediators, which increase during the inflammation. PGE2 has no

Tabela 1. Vreme proizvodnje i vreme početka primene lokalnih anestetika na odeljenju Oralne hirurgije Stomatološke klinike u Nišu.

Lokalni anestetik	Godina proizvodnje	Godina primene
Etidokain	1972.	-
Bupivakain	1957.	1997.
Ropivakain	1957.(1996.- početak primene)	2002.

Tabele 1. Manufacturing and aplication time of the long-acting LA In the Department of Oral Surgery on Dental Clinic in Nis

Local anesthetics	Manufacturing time	Application time
Etidocaine	1972.	-
Bupivavacine	1957.	1997.
Ropivacaine	1957.(1996- aplied for the first time)	2002.

novo u oštećenim ćelijama u toku metabolizma arahidonske kisline uz pomoć enzima fosfolipaze A2 i oslobađaju de iz njihovog zida (nalaze se u svim leukocitima, trombocitima i endotelu). Dejstvom PGI_2 (prostakalcin) nastaje vazodilatacija i edem. PGE2 deluje sinergistički sa drugim posrednicima koji pojačavaju bol u toku inflamacije. PGE2 nema direktnu ulogu u stvaranju osećeja bola, ali čini osetljivijim aferentna nervna vlakna na dejstvo bradikinina i histamina[28]. Prostaglandin tromboksan A_2 uzrokuje vazokonstrikciju i pospešuje agregaciju trombocita, Upotreba anelgetika, naročito iz grupe nesteroidnih antiinflamatornih lekova blokira stvaranje tromboksana A_2 u trombocitima, što proizvodi inhibitorni efekat na agregaciju trombocita, i produžava krvarenje. Zbog toga je u postoperativnom tretmanu bolje imati obezbeđenu anelgeziju uz pomoć LA nego ordinirati anelgetike. Etidokain ne obezbeđuje zadovoljavajuću intraoperativnu hemostazu uprkos dodatom vazokonstriktoru. Bupivakain ima naglašeniji konvulzivni i kardiodepresorni efekat i duže vreme početka dejstva anestezije od etidokaina. Ropivakain ima manje naglašene negatvne efekte, i ima vazokonstriktorna svojstva.

Zaključak

Ropivakain se po početku dejstva i dužini dejstva anestezije ne razlikuje značajno od bupivakaina, kvalitet anestezije je bolji nego kod bupivakaina, uzrokuje manju motornu blokadu i ima manju KVS i CNS toksičnost kao i manje krvarenje u toku inervencije. Poređenjem osobina ovih lokalnih anestetika zaključujemo da, ako postoji potreb za LA dugog dejstva, u toku kliničko rada, ropivakainu treba dati prednost u odnosu na etidokain i bupivakain.

direct role in emerging of feel of pain, but it makes afferent nerve fibers more irritated on effect of bradykinin and hystamine[28]. Thromboxan A2 causes vasoconstriction and stimulates platelet aggregation. The use of anelgetics, especially from a group of non anti-inflammatory drugs, blocks the creation of thromboxan A2 in platelets, producing an inhibitory effect on platelet aggregation and prolonging bleeding. Therefore, in the postoperative treatment, it is better to have secured anelgesia with LA than to ordinate anelgetics.

Etidocaine does not provide a satisfactory intraoperative hemostasis despite the addition of vasoconstrictor. Bupivacaine has better convulsant and cardiodepressive effect and the onset of effects is slower compared to etidocaine.

Conclusion

Ropivacaine and bupivacaine have equal onset of effects and length of action. The quality of ropivacaine anesthesia is higher than the bupivacaine, causes less motor block and has a smaller CVS and CNS toxicity. Ropivacaine causes less blood flow than etidocaine so as bupivacaine, despite it does not contain vasoconstrictor. Comparing the properties of local anesthetics, we conclude that in case of need for the long acting LA during clinical practice, ropivakacaine should be given priority over etidocaine and bupivacaine.

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