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PREGLEDNI RAD
REVIEW

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Nove spoznaje o lokalnoj primjeni tramadola u oralnoj kirurgiji

New Findings on Local Tramadol Use in Oral Surgery

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Sažetak
U oralnoj kirurgiji danas se obavljaju bezbolni zahvati, ali i nakon toga adekvatno kontrolira bol. Jedan od najčešćih operativnih zahvata u oralnoj kirurgiji jest operativno uklanjanje trećeg kutnjaka ili alveotomija umnjaka kada se odiže mukoperiostalni režanj, uklanja kost i rana zašiva. Takvi zahvati praćeni su poslijeoperacijskom boli, oteklinom i trizmusom. Autori mnogobrojnih istraživanja bavili su se smanjenjem boli i što boljom kontrolom one postoperativne, a jedan od najčešćih modela u istraživanjima jest alveotomija umnjaka. Tramadol je dobro poznat centralno djelujući opioidni analgetik koji se upotrebljava u liječenju mnogobrojnih bolnih stanja kao što su poslijeoperacijska bol, bol tijekom poroda, zatim bol u terminalnoj fazi maligne bolesti, koronarna bol i u slučaju neuropatske boli. No to je i atipični opioid koji, primijenjen lokalno, pokazuje analgetska i anestetska svojstva. Cilj ovoga rada jest prezentirati nove spoznaje o lokalnom djelovanju tramadola u oralnoj kirurgiji.

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Uvod

Kontrola boli u oralnoj kirurgiji važan je čimbenik u sprječavanju straha i anksioznosti pacijenata, a dobro kontrolirana bol nakon kirurškog zahvata može olakšati oporavak u smislu životnih i oralnih funkcija (1, 2). Kontrola boli temelji se na korištenju različitih analgetika koje dijelimo na tri glavne skupine lijekova – neopioidne analgetike [nesteroidne protuupalne lijekove (NSPUL), paracetamol (acetaminofen), metamizol] te opioidne i adjuvantne analgetike (antiepileptici, antidepresivi i lokalni anestetici). Uz izbor analgetika vrlo je važan i način primjene lijeka, a on može biti enteralan (sublingvalno, peroralno i rektalno) i parenteralan (intravaskularni, intramuskularni, subkutani i inhalacijski). Ne treba zaboraviti da je i vrijeme davanja analgetika bitan čimbenik u kontroli poslijeopercijske boli, a razlikujemo prijeoperativnu, intraoperativnu i poslijeoperativnu primjenu lijeka. U posljednje se vrijeme također sve više pozornosti posvećuje kombiniranoj analgetskoj (multimodalnoj) terapiji, ali i kombiniranju različitih načina primjena istoga lijeka (npr., lokalno na mjestu ozljede tkiva i sistemski). Tako se želi postići maksimalan analgetski učinak te djelovati i na periferni i na centralni prijenos boli uz smanjenje doze analgetika, a samim time smanjuje se i rizik od pojave neželjenih reakcija. Uporaba perifernih blokova živaca za anesteziju i poslijeoperacijsku analgeziju znatno se povećala u nekoliko posljednjih godina. Dodatcima lokalnim anesteticima često se poboljšava njihova kvaliteta i produljuje anestezija, ali i po-

Introduction

Pain control in oral surgery is a key factor for reducing fear and anxiety in patients. Improved postoperative pain management after oral surgery may lead to faster recovery in terms of lifestyle and oral function (1, 2). Pain management is usually based on different analgesic medications that can be divided into three major drug classes: non-opioid drugs [non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol (acetaminophen), metamizol], opioids and adjuvants (antidepressants, anticonvulsants and local anesthetics). The choice of analgesic drug is as important as the route of administration for a drug. The various routes of administrations are classified into following categories: enteral (sublingual, peroral and rectal) and parenteral (intravascular, intramuscular, subcutaneous and inhalation). Also, time of administration of an analgesic drug plays important role in pain management and it can be preoperative, intraoperative and postoperative. A great deal of attention has recently been directed at combining analgesic drugs (multimodal analgesia) or combining different routes of administration of the same drug (e.g. locally at the site of tissue injury and systemically). Targeting both peripheral and central pain pathways enables to maximize the analgesic effect by using lower doses of drugs and thereby lowering the risk of adverse events. Over the past few years, years there has been a significant increase in the use of local anesthetic peripheral nerve blocks for surgical anesthesia and postoperative analgesia. Adjuvants are frequently

boljšava poslijeoperacijska analgezija. U mnogobrojnim kliničkim istraživanjima ispitan je učinak nekih dodataka kao što su buprenorfin, morfij, fentanil, epinefrin, klonidin, deksamedetomidin, deksametazon, tramadol i magnezij (3).

Tramadol-hidroklorid [(1RS; 2RS)-2-[(dimetilamino) metil]-1-(3-metoksifenil)-cikloheksanol hidroklorid] ubraja se u skupinu centralno djelujućih blagih opioidnih analgetika, a koristi se u liječenju umjerene do umjereno jake boli. Prvi put je sintetiziran 1962. godine, a od 1977. u širokoj je uporabi. Smatra se da su glavni mehanizmi djelovanja tramadola agonistički preko μ-opioidnih receptora (μ-OR) i inhibicije ponovne pohrane monoamina (4). Tramadol se na tržištu može nabaviti kao racemična smjesa dvaju enantiomera – (+) tramadol i (-) tramadol, jer se pokazalo da ima bolja analgetska svojstva u usporedbi sa svakim enantiomerom posebno (5). U usporedbi s kodeinom i morfijem, tramadol ima slabiji afinitet prema μ-OR-ima i to otprilike 10 puta manji negoli kodein i 6000 puta manji negoli morfij. Analgetski učinak putem μ-OR-a nije dovoljan za postizanje analgetskog učinka tramadola (6, 7). Identificirana su dvadeset tri metabolita tramadola koji nastaju u jetrima postupcima demetilacije, oksidacije i konjugacije (sulfatom i glukuronatom) (5, 8). O-desmetil tramadol (M1) glavni je metabolit tramadola i ima 400 puta veći afinitet negoli matična tvar prema μ-OR-ima. No taj je afinitet i dalje mnogo manji od afiniteta morfija (6, 9). Inhibicija ponovne pohrane monoamina, u prvom redu norepinefrina (NE) i serotonina [5-hidroksitriptamin (5-HT)] koji se otpuštaju na živčanim završetcima, još je jedan od mehanizama djelovanja tramadola i to neopioidnog tipa. Inhibicijom ponovne pohrane monoamina inhibira se prijenos boli u središnjem živčanom sustavu te se tako pojačava analgetski učinak tramadola (10). Enantiomer (+) tramadol uglavnom je odgovoran za inhibiciju ponovne pohrane serotonina, (-) tramadol za inhibiciju ponovne pohrane norepinefrina, a O-desmetil tramadol (M1) primarno je odgovoran za agonističku aktivaciju μ-OR-a. Novije studije, u kojima su se istraživali ionski kanali i G-protein vezane receptore (GPVR), ne samo da su poboljšale naše razumijevanje njihove fiziologije i farmakologije, nego su i dokazale da su upravo ti receptori ciljna mjesta za analgetike i anestetike. Osim već spomenuta dva glavna mehanizma djelovanja, tramadol posjeduje i dodatne mehanizme djelovanja, no još nam nisu poznati (11).

Nažalost svjedoci smo sve veće i neopravdane uporabe opioidnih analgetika u stomatologiji, a posebice u oralnoj kirurgiji radi kontrole boli nakon zahvata kao što su vađenje zuba i alveotomija umnjaka. U Sjedinjenim Američkim Državama zabilježeno je u 2015. godini 52 404 smrtna slučaja nakon predoziranja, od čega čak 63,1 posto uključuje opijate i opioide (12). U znanstvenim i medicinskim krugovima u SAD-u sve se više pozornosti posvećuje kontroli takozvane opioidne epidemije. Smatra se da su očekivanja pacijenata, kad je riječ o uzimanju opioidnih analgetika nakon stomatološkog zahvata, te strah stomatologa od nezadovoljnih pacijenata najčešći uzroci propisivanja tih lijekova (13). Zabrinjava činjenica da SAD čini 99 posto svjetske konzumacije kombinacije hidrokodona i acetaminofena (14). Mnogobrojni pacijenti svoj prvi doticaj s opioidnim analgeticima imaju nakon

added to local anesthetics to enhance the quality and duration of the anesthetic effect, and also to improve postoperative analgesia. A number of clinical trials have investigated the effects of some adjuvants such as: buprenorphine, morphine, fentanyl, epinephrine, clonidine, dexmedetomidine, dexamethasone, tramadol, and magnesium (3).

Tramadol hydrochloride [(1RS; 2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol hydrochloride] is a centrally acting weak opioid analgesic clinically effective in treating moderate to moderately severe pain. This drug was first synthetized back in 1962, but has not been commercially available until 1977. The main action mechanisms of tramadol are μ-opioid receptors (μ-OR) agonism and inhibition of the monoamine reuptake (4). Commercially, tramadol comes as a racemic mixture of two enantiomers (+) tramadol and (-) tramadol that has superior analgesic properties than either enantiomer alone (5). In comparison to codeine and morphine, tramadol has a very low affinity for the μ-OR and this affinity is estimated to be 10 times lower than that of codeine and 6000 times lower than that of morphine. Tramadol analgesic/opioid action via μ-OR alone is insufficient to represent its analgesic properties (6, 7). There are twenty-three metabolites of tramadol identified as a result of demethylation, oxidation and conjugation (sulphation and glucuronidation) in the liver (5, 8). O-desmethyl tramadol (M1) is the main metabolite of tramadol, and its affinity toward μ-OR is approximately 300-fold higher than that of the parent compound. Nevertheless, its affinity is still lower than that of morphine (6, 9). Non opioid analgesic action mechanism of tramadol had been identified via inhibition of the reuptake of monoamines, such as norepinephrine (NE) and serotonin [5-hydroxytryptamine (5-HT)] that are released from nerve endings. By inhibition of the reuptake of monoamines, tramadol is inhibiting pain transmission in the central nervous system, and in this way contributing to its analgesic effect (10). Enantiomer (+) tramadol is primarily responsible for serotonin reuptake inhibition, (-) tramadol for noradrenaline reuptake inhibition and the metabolite O-desmethyltramadol (M1) is primarily responsible for the agonist activity on the μ-opioid receptor. Recent studies focused on ion channels and G protein-coupled receptor (GPCR) signalling, thus improving our understanding of their physiology and pharmacology. Moreover, it has been discovered that they are also targets for analgesics and anesthetics. Apart from the two main described mechanisms of tramadol action, we do not yet know additional mechanisms of tramadol action (11).

Unfortunately, there is an increase in the unjustified use of opioid analgesic drugs in dentistry, especially in oral surgery, prescribed for pain management after tooth extraction or third molar surgery. In 2015 in the United States of America (USA), there were more than 52 404 deaths due to drug overdose, out of which 63.1% were from opiate and opioid drugs (12). In scientific and medical associations in the USA there are more and more discussions on the topic of opioid epidemic and its control. It is estimated that patients' expectations to receive opioid analgesic after dental treatment and dentists' fear of an unsatisfied patient are the main causes for

stomatološkog zahvata kao što je vađenje umnjaka. Procjenjuje se da gotovo dvije trećine pacijenata u dobi od 14 do 17 godina nakon ekstrakcije trećih molara dobiva na recept opioide (15). U Europi se također povećava uporaba medicinski propisanih opioida, ali znatno sporije nego u SAD-u. Štoviše, u Europi je nemedicinska upotraba propisanih opioida, te pojavnost fatalnih incidenata (još uvijek) rijetka (16). U SAD-u se osoblje u dentalnoj medicini tradicionalno poučava da se za blagu do umjerenu bol trebaju ordinirati nesteroidni protuupalni lijekovi (NSPUL) i acetaminofen (paracetamol), a za jaku opioidni analgetiki, iako za takvo stajalište nema uporišta u znanosti (17). Štoviše, istraživanja su pokazala da su NSPUL-i s paracetamolom ili bez njega učinkovitiji u kontroli dentalne boli u odnosu na opioide i kombinacije opioida danih sistemski (18 – 20). U preglednim člancima i metaanalizama analgetskog učinka tramadola u odnosu na NSPUL dan sistemski zaključuje se da tramadol sam ili u kombinaciji s acetaminofenom slabije analgetski djeluje u odnosu na acetaminofen i ibuprofen (21 – 23). U istim studijama također se upozorava na povećanu incidenciju neželjenih reakcija na tramadol, poput mučnine, povraćanja i vrtoglavice. Opioidni analgetici dani sistemski nisu učinkovitiji od NSPUL-a u kontroli boli nakon vađenja zuba ili alveotomije umnjaka. Preporuka stomatolozima je ordinirati NSPUL kao prvi izbor analgetika za liječenje dentalne boli, a ako je bol snažnija, treba ga kombinirati s paracetamolom. No opioidni analgetici mogu biti prvi izbor za pacijente intolerantne na NSPUL ili kada je NSPUL kontraindiciran, kao što je u slučaju alergija, bubrežnog zatajenja i povećanog rizika od gastrointestinalnog krvarenja.

Mehanizmi lokalnog djelovanja tramadola

Lokalno djelovanje tramadola predmet je mnogih istraživanja s obzirom na to da ima atipična svojstva i da mehanizam lokalnog djelovanja još nije razjašnjen u cijelosti. Lokalno bi tramadol mogao imati dva različita načina djelovanja – anestetski i opioidni/analgetski (24). Istraživanjem se došlo do mogućih mehanizama lokalnog djelovanja kao što su: slabo agonističko djelovanje na periferne μ-OR-ove (4, 24) čiji se broj povećava u upalnom tkivu (25, 26); poticanje otvaranja nespecifičnih o voltaži ovisnih kalijevih (K^+) kanala (27); utjecaj na put dušikova oksida (28); agonističko djelovanje na vaniloidni receptor 1 (engl. transient receptor potential vanilloid-1 – TRPV-1), što osim lokalne analgezije rezultira i neželjenim osjećajem pečenja i eritemom (29); blokiranje N-metil-D-aspartatnih receptora (NMDAR), ali u slučaju visoke koncentracije tramadola (30); lokalno anestetsko djelovanje tramadola objašnjava se direktnom blokadom o voltaži ovisnih natrijevih kanala (31)

Godine 1998. među prvima su Pang i suradnici dokazali lokalno anestetsko svojstvo tramadola nakon intradermalne

opioid analgesic prescription (13). A disturbing fact is that the USA consumes 99% of the world's hydrocodone/acetaminophen combination (14). The first experience of a large number of patients with opioids is associated with dental procedures, such as extractions of wisdom teeth. It has been estimated that almost two-thirds of 14 to 17-year-olds receive opioid prescriptions from dentists following the third molar extraction (15). In Europe, the medical use of prescription opioids is also increasing, but at a much slower rate than in the USA. Moreover, non-medical use of prescription opioids and fatal prescription opioid incidents are (still) rare in Europe (16). Traditionally, in the USA, oral health professionals have been taught that nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (paracetamol) should be used for mild to moderate pain, and opioids should be prescribed for severe pain. There is, however, no scientific evidence to support this recommendation (17). In fact, the evidence shows that NSAIDs alone or in combination with acetaminophen are more effective than opioids or their combination administrated systemically in treating dental pain (18-20). In a systematic review and meta-analysis of analgesic efficiency of tramadol compared to NSAID administered systemically, the researchers have concluded that tramadol alone or in combination with acetaminophen has weaker analgesic effect compared to acetaminophen and ibuprofen (21-23). Also, the results of some studies have pointed to the fact that tramadol had an increased risk of adverse effects such as nausea, vomiting and dizziness. Opioid analgesics are not more effective in pain management after tooth extraction or third molar surgery when compared to NSAIDs. The recommendation to dental professionals is to prescribe NSAIDs for dental pain relief, and in a case of severe pain, to prescribe a combination of NSAIDs and paracetamol. However, opioids can be considered a first-line option for patients who are intolerant to NSAIDs or those with some contraindications, such as allergy, renal failure and high-risk of gastrointestinal hemorrhage.

Local action mechanisms of tramadol

Research has tended to focus on local mechanisms of action of tramadol. Tramadol is an atypical opioid and its local mechanisms of action have not yet been fully elucidated. The local anaesthetic effects of tramadol are as follows: anesthetic and opioid/analgesic (24). Studies have shown the following possible local mechanisms of action of tramadol:

- weak peripheral agonism over peripheral μ-OR (4, 24), the number of which is enhanced in hyperalgesic and inflammatory conditions (25, 26)
- favouring the opening of nonspecific voltage-dependent potassium (K^+) channels (27)
- acting in the nitric oxide pathway (28)
- agonistic action on vanilloid receptor 1 (TRPV-1 transient receptor potential vanilloid-1) that apart from local analgesic effect, can exert undesired local side effects, such as burning pain and erythema (29)
- with high concentration of tramadol blockade of the N-methyl-D-aspartate (NMDA) receptors (30)
- local anesthetic effect of tramadol can be explained by di-

injekcije (32). Tsai i suradnici postigli su kod štakora direktnom aplikacijom tramadola blokadu neuralne provodljivosti ishijadičnog živca. No postignuti blok nije se mogao poništiti naloksonom, pa navode da je najvjerojatnije u pitanju drukčiji lokalni mehanizam djelovanja tramadola od opioidnoga (33). Slične rezultate dobili su Mert i suradnici. Oni su usporedili anestetski učinak tramadola s lokalnim anestetikom na ishijadičnom živcu žaba. Tramadol je postigao sličnu blokadu živčane provodljivosti kao i lidokain, iako je bila nešto slabija. Zaključili su da bi tramadol mogao imati druga mjesta vezanja ili drukčiji mehanizam djelovanja u odnosu na lidokain (34). Altunkaya i suradnici u svojim su istraživanjima zaključili da 5-postotni tramadol ima slična lokalna anestetska svojstva kao i 2-postotni prilokain kad je riječ o intradermalnoj aplikaciji u slučaju kožne ekscizije. Također navode da tramadol produljuje bezbolno poslijeoperativno razdoblje, uz smanjenje potrošnje analgetika (35, 36). Lokalna anestetska svojstva tramadola dokazao je i Kargi sa suradnicima koristeći se njime kao lokalnim anestetikom u kirurgiji popravka tetive šake (37). Submukozna aplikacija tramadola nakon tonzilektomije, omogućila je kod djece u općoj anesteziji bolju poslijeoperacijsku analgeziju (38). Tramadol kao dodatak mepivakainu za brahijalni pleksusni blok rezultira produženim djelovanjem bloka i, ovisno o dozi tramadola, poboljšava poslijeoperacijsku analgeziju (39, 40).

Lokalno djelovanje tramadola u oralnoj kirurgiji

Kad je riječ o oralnoj kirurgiji, samo se u nekoliko istraživanja ispitivalo lokalno djelovanje tramadola (tablica 1). Godine 2006. objavili su Pozos i suradnici istraživanje u kojemu su ispitivali utjecaj tramadola dodanoga artikainu na duljinu trajanja anestezije tijekom alveotomije donjih umnjaka. Tramadol (50 mg) su dodali 4-postotnom artikainu s epinefrinom (1 : 100,000) te su takvu kombinaciju aplicirali u bukalnu sluznicu u području ekstrakcijske rane neposredno nakon bloka donjega alveolarnog živca. Autori navode da na mjestu aplikacije te kombinacije nisu uočili nikakvo štetno lokalno djelovanje. Također su zaključili da tramadol dodan artikainu i dan submukozno pokraj ekstrakcijske alveole produljuje anestetski učinak artikaina, te da bi takva aplikacija tramadola mogla poboljšati kontrolu poslijeoperacijske boli (41). Isti autori ispitali su 2007. godine utjecaj tramadola danog na različite načine sistemski (intramuskularno) i lokalno (submukozno) na smanjenje poslijeoperacijske boli nakon uklanjanja impaktiranih donjih umnjaka. Rezultati su pokazali da je tramadol (50 mg) dan submukozno u kirurško polje produljio anesteziju (artikaina), te je u kombinaciji lokalne i sistemske primjene poboljšao kvalitetu poslijeoperacijske analgezije. Tramadol apliciran na oba načina (intramuskularno i submukozno) rezultirao je poboljšanim analgetskim učinkom ne samo u usporedbi s kontrolnom grupom, nego sa sistemskom i lokalnom. Kako bismo isključili mogućnost da je rezultat poboljšanog analgetskog učinka nastao zbog dvostruke doze li-

rect blocking of voltage-dependent sodium (Na^+) channels (31)

In 1998, Pang et al. were the first to demonstrate a local analgesic effect of tramadol following intradermal injection (32). Tsai et al. demonstrated anesthetic effect of tramadol by its direct application on sciatic nerves of rats. Tramadol produced a neural conduction block that could not be reversed by naloxone. This finding suggested that an underlying mechanism of action of tramadol must differ from its opioid action (33). Similar results have been reported by Mert et al. They have compared anesthetic effect of tramadol with local anesthetic on frog sciatic nerves. Nerve conduction blockade with tramadol was similar to that of lidocaine, although it was weaker. In conclusion, the authors have stated that tramadol could have different binding sites or different action mechanism than lidocaine (34). Altunkaya et al. in theirs studies concluded that 5 % tramadol has a local anesthetic effect similar to 2 % prilocaine when used intradermally for excision of cutaneous lesions. Furthermore, they suggested that tramadol extends postoperative pain free time and reduces analgesic consumption (35, 36). Local anesthetic effect of tramadol was also demonstrated by Kargi et al. in tendon repair surgery of the hand, where tramadol was used as a local anesthetic (36). Submucosal administration of tramadol after paediatric tonsillectomy surgery in general aesthesia has reduced the need for postsurgical analgesia (38). Tramadol as an adjuvant to mepivacaine for axillary brachial plexus block prolongs the duration of aesthesia and depending on the dosage improves postoperative analgesia (39, 40).

Local effects of tramadol in oral surgery

Only few studies have investigated the local effects of tramadol in oral surgery (Table 1). In 2006, Pozos et al. conducted a study to evaluate the effects of tramadol added to articaine on aesthesia duration in mandibular third molar surgery. Tramadol (50 mg) was added to 4 % articaine with epinephrine (1:100,000), and injected into surgical site into the buccal mucosa, adjacent to extraction wound, immediately after the inferior alveolar nerve block. The authors reported that they did not notice any local harmful effect of tramadol as an adjuvant to articaine at the site of application. In this study, the authors demonstrated that tramadol injected submucosally next to the extraction socket prolongs the anesthetic effect of articaine and that such administration could improve the management of postoperative pain (41). In 2007, the same authors published a paper in which they evaluated the effects of tramadol administered systemically (intramuscular) and locally (submucosal) on reducing pain after the removal of an impacted mandibular third molar. The results showed that tramadol (50 mg) administered locally into the surgical site significantly prolonged the duration of the anesthetic effect (articaine) and when used in combination of routes (locally and systemically), improved the quality of postoperative analgesia. Tramadol administered through both routes resulted in an improved analgesic effect not only compared to control group but also compared to both systemic and local groups. In order to examine the fact that better analgesia

Tablica 1. Istraživanja lokalnog djelovanja tramadola u oralnoj kirurgiji

Istraživanje	Način primjene	Grupe	Neželjene reakcija	Rezultati
Pozos i sur., 2006. (41) Utjecaj tramadola na trajanje anestezije tijekom alveotomije donjeg umnjaka	Tramadol dodan 4-postotnom artikainu s epi. (1 : 100 000) i dan u bukalnu mukozu pokraj ekstrakcije nakon mandibularnog bloka	Tram. 50 mg (1 ml) + artikain (2,7 ml) n = 24 i FO (1ml) + artikain (2,7 ml) n = 24	Tramadol: mučnina n = 3 Kontrolna skupina: mučnina n = 2	Produljuje anestetsko djelovanje artikaina Nema utjecaja na poslijeoperacijsku analgeziju
Pozos i sur., 2007. (42) Utjecaj tramadola danog sistemski (intramuskularno i.m.) i lokalno (u bukalnu mukozu) na analgeziju nakon alveotomije donjih umnjaka	Tramadol dan i.m. 1 sat prije zahvata, te tramadol dan u kirurško polje u submukozu odmah nakon početka lokalne anestezije (4-postotni artikain s epi. 1 : 100 000)	Tram. 50 mg i.m. + FO 1 ml subm. n = 12 FO i.m. + tram. 50 mg subm. n = 12 Tram. 50 mg i.m. + tram. 50 mg subm. n = 12 FO i.m. + FO 1 ml subm. n = 12	U svim ispitanim skupinama pojavljivale su se neželjene reakcije kao što su pospanost, vrtoglavica i mučnina	Produljuje anestetsko djelovanje artikaina nakon lokalne aplikacije U kombiniranoj aplikaciji lokalno i sistemski analgetski učinak je bio najbolji
Isiordia-Espinoza i sur., 2011. (43) Preemptivni analgetski učinak oralnog ketorlaka plus lokalno tramadola nakon alveotomije impaktiranog donjeg umnjaka	Ketorlak per os 10 mg 30 minuta prije zahvata + tramadol 50 mg submukozno u operativno polje nakon mandibularnog bloka (4-postotni artikain s epi. 1 : 100 000)	Keto 10 mg per os + FO 1 ml subm. n = 15 Keto 10 mg per os + tram. 50 mg subm. n = 15	Nema	Ketorlak per os plus tramadol subm. znatno poboljšavaju poslijeoperacijsku analgeziju i smanjuju potrošnju analgetika
Isiordia-Espinoza i sur., 2012. (44) Utjecaj submukozne aplikacije tramadola na anestetski učinak mepivakaina s epinefrinom u slučaju bloka donjega alveolarnog živca	Nakon aplikacije 2 % mepivakaina s epi. 1 : 100 000 za mandibularnu anesteziju submukozno je apliciran tramadol na isti način (1. min. nakon početka bloka)	Tram. 50 mg 1 ml n = 20 FO 1 ml n = 20	Tramadol: vrtoglavica n = 2 mučnina n = 1 vrtoglavica i mučnina n = 2 Kontrolna: vrtoglavica n=1 vrtoglavica i mučnina n=1	Poboljšan anestetski blok
Ceccheti i sur., 2014. (45) Analgetski i dodatni anestetski učinak submukozne aplikacije tramadola nakon alveotomije donjeg umnjaka	Nakon alveotomije umnjaka tramadol je apliciran u bukalnu mukozu pokraj alveole umnjaka; za mandibularnu anesteziju korišten je 2-postotni mepivakain s levonorfedrinom 1 : 80 000	Tram. 100 mg 2 ml n = 52 FO 2 ml n = 52	Tramadol: vrtoglavica i mučnina n = 3 Kontrolna: vrtoglavica i mučnina n = 1	Poboljšava analgetski učinak, ali bez produženog anestetskog učinka mepivakaina
Gonul i sur., 2015. (46) Utjecaj submukozne aplikacije tramadola na poslijeopercijsku bol nakon alveotomije donjeg umnjaka	Nakon alveotomije umnjaka tramadol je apliciran u obliku malih kapi na ekstakcijsku alveolu i okolnu kost; za mandibularnu anesteziju korišten je 4-postotni artikain s epinefrinom 1 : 100 000	Tram. 1mg/kg razrijeđen s FO-om do 2 ml n = 30 FO 2 ml n = 30	Tramadol: mučnina n = 5 Kontrolna: mučnina n = 2 povraćanje n = 2 pečenje n = 3	Poboljšava poslijeoperacijski analgetski učinak
Al-Haideri, 2013. (47) Usporedba anestetskog učinka tramadol-hidroklorida s adrenalinom i bez njega tijekom ekstrakcije gornjih molara	Tramadol-hidroklorid aplicira se supraperiostalno kao lokalni anestetik	Tram. 50 mg s adrenalinom (1 : 80 000) n = 50 Tram. 50 mg n = 50	Tram. s adrenalinom: mučnina n = 2 povraćanje n = 1 Tram: mučnina n = 1	Tramadol s adrenalnom omogućuje anestetski učinak dovoljan za ekstrakciju gornjih molara

*epi. – epinefrin; Tram. – tramadol; FO – fiziološka otopina; i.m. – intramuskularno; subm. –submukozno; keto – Ketorlac; per os – peroralno

jeka, autori su pri lokalnoj primjeni tramadola mjerili razinu tramadola u plazmi s pomoću tekuće kromatografije. S obzirom na to da su vrijednosti tramadola u plazmi bile nemjerljive, zaključili su da je poboljšani analgetski učinak tramadola danog u kombinaciji lokalne i sistemske primjene najvjerojatnije rezultat različitih farmakodinamskih mehanizama djelovanja (42). Isiordia-Espinoza i suradnici ispitali su preemptivnu analgeziju za koju su kombinirali ketorolak (peroralno 30 min. prije zahvata) i tramadol lokalno (submukozno) tijekom operacije impaktiranih donjih umnjaka. Zaključili su da je takva preemptivna kombinacija rezultirala ublažavanjm poslijeoperacijske boli te smanjenjem poslijeoperacijske potrošnje analgetika (43). U *crossover* istraživanju ispitan je utjecaj tramadola kao dodatka 2-postotnom mepivakainu s epinefrinom kod bloka donjega alveolarnog živca. Tramadol je

was not the result of doubled drug dosage, the authors have measured tramadol plasma levels when administered locally by liquid chromatography. As tramadol levels were unmeasurable in plasma, the authors suggested that improved analgesia, as a result of tramadol administered in combination of routes could be a result of different pharmacodynamic mechanisms (42). Isiordia-Espinoza et al. investigated the preemptive analgesic effectiveness of oral ketorolac (given orally 30 minutes before surgery) and local tramadol (submucosal) in mandibular third molar surgery. They have concluded that preemtive ketorolac plus submucosal local tramadol resulted in better postoperative treatment of acute pain and in reduction in the consumption of postoperative analgesics (43). In a crossover clinical trial, the effect of submucosal tramadol as an adjuvant of 2 % mepivacaine with epinephrine in infe-

Table 1 Studies of local administration of tramadol in oral surgery

Study	Routh of administration	Groups	Adverse events	Results
Pozos et al., 2006 (41) The effects of tramadol added to articaine on anesthesia duration	Tramadol added to 4% articaine with epi. (1:100 000) injected into surgical site into the buccal mucosa adjacent to the extraction	Tram 50mg (1 ml) + articaine (2.7 ml) n=24 SA (1ml) + artikain (2.7 ml) n=24	Tramadol: nausea n=3 Control: nausea n=2	prolongs the effect of local anesthetic articaine no difference between 2 groups for pain intensity value
Pozos et al., 2007 (42) Tramadol administered in a combination of routes for reducing pain after removal of an impacted mandibular third molar	Tramadol administered i.m. 1 hour befor surgery, and tramadol injected into surgical site submucous after IAN block obtained using 4% articaine with epi. (1:100 000)	Tram 50mg i.m. + SA 1 ml subm n=12 SA i.m. + tram 50mg subm n=12 Tram 50mg i.m. + tram 50mg subm n=12 SA i.m. + SA 1ml subm n=12	Adverse events such as drowsiness, diziness and nausea were reported equally across the treamtent groups	Locally injected prolongs the effect of local anesthetic articaine In combination of routes (local and sistemic) improves the quality of postoperative analgesia
Isiordia-Espinoza et al., 2011 (43) Preemptive analgesic effectiveness of oral ketorolac plus local tramadol after impacted mandibular third molar surgery	Ketorlac per os 10 mg 30 minutes before surgery + tramadol 50 mg injected into surgical site submucous after IAN block obtained using 4% articaine with epi. (1:100 000)	Ketorlac 10 mg per os + SA 1ml subm n=15 Ketorlac 10 mg per os + tram 50 mg subm n= 15	No patients reported adverse events	Ketorlac per os plus local tramadol resulted in better postoperative pain management and reduced analgesic consumption
Isiordia-Espinoza et al., 2012 (44) Submucous tramadol increases the anesthetic efficacy of mepivacaine with epinephrine in inferior alveolar nerve block.	submucous administration of tramadol was done 1 minute after that patient informed anesthesia of lower lip in the same way as was done anesthetic IAN block using 2% mepivacaine with epi (1:100 000)	Tram 50 mg 1 ml n=20 SA 1 ml n=20	Tramadol: dizziness n=2 nausea n=1 dizziness and nausea n=2 Placebo: dizziness n=1 dizziness and nausea n=1	Increased anesthetic efficancy of mepivacaine withough prolonging the duration of anesthesia of soft tissue nor affecting the onset of anesthesia
Ceccheti et al., 2014 (45) Analgesic and adjuvant anesthetic effect of submucosal tramadol after mandibular third molar surgery	tramadol was injected into the buccal mucosa adjacent to the third molar alveolus immediately after extraction; IAN block done using 2% mepivakain with levonorfedrinom (1:80 000)	Tram 100 mg 2 ml n=52 SA 2 ml n=52	Tramadol: dizziness and nausea n=3 Control: dizziness and nausea n=1	Contributes to provide a pain-free postoperative period of 3.5-4 h with no effect in leghtening the sensory blockade produced with mepivacaine
Gonul et al., 2015 (46) Effect of submucosal application of tramadol on postoperative pain after third molar surgery	tramadol (1 mg/kg) was applied after extraction to the extraction socket and the bone surface by means of small drops; IAN block was obtained using 4 % articaine with epinephrine (1:100 000)	Tram 1mg/kg diluted with SA do 2 ml n=30 SA 2 ml n=30	Tramadol: nausea n=5 Control: nausea n=2 vomiting n=2 burning n=3	Reduces postoperative acute facial pain
Al-Haideri, 2013 (47) Comparison of local anesthetic efficacy of tramadol hydrochloride (with adrenaline) versus plain tramadol hydrochloride in the extraction of upper molar teeth	tramadol is injected supraperiosteally as a local anestethic	Tram 50 mg with adrenaline (1:80 000) n=50 Tram plain (without adrenaline) 50 mg n=50	Tram with adrenaline: nausea n=2 vomiting n=1 Tram: nausea n=1	Tramadol with adrenaline was shown to be a very effective local anesthetic for extration of upper molar teeth

*epi-epinephrine; Tram-tramadol; SA-saline; i.m.-intramuscular; subm-submucosal; per os-peroral; IAN-inferior alveolar nerve

dan lokalno submukozno jednu minutu nakon što je pacijent potvrdio anesteziju donje usnice i to na isti način na koji je apliciran lokalni anestetik za mandibularnu anesteziju. U ovom istraživanju tramadol nije apliciran submukozno u operativno polje kao što se to činilo u ranijim istraživanjima. Autori su zaključili da je tako primijenjeni tramadol poboljšao kvalitetu anestetskog učinka mepivakaina u prva dva sata, bez utjecaja na vrijeme početka anestezije (vrijeme latencije) i bez produžene anestezije mekoga tkiva (44). Ceccheti i surad-

rior alveolar nerve block was evaluated. The submucous administration of tramadol was performed 1 minute after the patient had made informed decision about anesthesia of the lower lip. It was administered in the same manner as anesthetic block. In this study, submucous administration of tramadol was not applied into the surgical site, as it was the case with previous studies. The authors have concluded that tramadol applied submucosally in this manner increased the anesthetic efficacy of mepivacaine during the first 2 hours

nici ispitali su analgetski i dodatni anestetski učinak tramadola apliciranog submukozno nakon alveotomije donjih umnjaka. Tramadol su primijenili lokalno submukozno neposredno uz alveolu umnjaka odmah nakon alveotomije. Zaključili su da submukozna aplikacija tramadola pridonosi bezbolnom poslijeoperativnom razdoblju od 3,5 do 4 sata nakon operacije, s rijetkim neželjenim reakcijama. Dakle, pacijenti ga dobro prihvaćaju. No nije uočeno poboljšanje u produljenju trajanja senzornog bloka donjeg alveolarnog živca postignutog 2-postotnim mepivakainom (45). Slično istraživanje obavili su Gönül i suradnici – oni su tramadol (1 mg/kg) aplicirali nakon alveotomije donjih umnjaka u ekstrakcijsku ranu i na površinu kosti u obliku malih kapi. Za blok donjega alveolarnog živca koristili su se 4-postotnim artikainom s epinefrinom, a iz prosječne težine pacijenata uključenih u istraživanje bilo je vidljivo da je korištena prosječna količina tramadola iznosila 65 mg. Autori su zaključili da su poslijeoperacijske VAS-vrijednosti za bol u prvih 12 sati bile značajno manje, uzimanje prvog analgetika značajno kasnije, a ukupna potrošnja analgetika znatno manja u tramadolskoj skupni u odnosu na kontrolnu (46). Zanimljivo istraživanje proveo je Al-Haideri – istražio je i usporedio lokalni anestetski učinak tramadola s adrenalinom i bez adrenalina tijekom ekstrakcije gornjih molara. Zaključio je da tramadol s adrenalinom infiltriran supraperiostalno može biti vrlo učinkovit lokalni anestetik u slučaju vađenja gornjih molara. S obzirom na to da tramadol bez adrenalina ima slab anestetski učinak, smatra da učinak adrenalina, u prvom redu vazokonstrikcija, omogućuje tramadolu zadržavanje na mjestu aplikacije i djelovanje na živčane završetke. Također navodi da se studija odnosi samo na manje oralne i maksilofacijalne kirurške zahvate tj. na vađenje zuba. Iako statistički bez značajne razlike među grupama, neželjene reakcije na tramadol (4 % ukupno – mučnina i povraćanje) mogle bi ograničiti njegovu kliničku uporabu kao lokalnog anestetika (47).

Zaključak

Imperativ moderne oralne kirurgije jest adekvatna i učinkovita kontrola poslijeoperacijske boli te što kvalitetnija lokalna anestezija. Pojedine studije i metaanalize pokazale su prednost NSPUL-a u usporedbi s opioidnim analgeticima pri sistemskoj primjeni, te se opioidi ne bi trebali rutinski ordinirati za akutnu dentalnu bol. S druge strane, lokalna primjena atipičnoga opioida tramadola otvara sasvim nove mogućnosti u kontroli poslijeoperacijske boli i poboljšanju lokalne anestezije. Tako tramadol apliciran lokalno submukozno, supraperiostalno, topikalno u obliku kapi ili kao dodatak lokalnim anesteticima, daje obećavajuće rezultate. Daljnja istraživanja nužna su da bi se objasnili mehanizmi lokalnog djelovanja tramadola, a velike kliničke studije potrebne su radi pronalaženja sigurnih i učinkovitih protokola lokalne primjene tramadola u svakodnevnoj praksi.

without affecting the onset of anesthesia (latency time), and without prolonging the duration of anesthesia of soft tissues (44). Ceccheti et al. have investigated analgesic and the adjuvant anesthetic effect of submucosal tramadol after mandibular third molar surgery. Tramadol was injected into the buccal mucosa adjacent to the third molar alveolus, immediately after extraction. They concluded that submucosal administration of tramadol contributed to providing a pain free period of 3.5-4 hours after extraction, with rare adverse effects and good patient acceptance. Nevertheless, no beneficial effect of tramadol in lengthening the sensory blockade produced with 2 % mepivacaine was observed (45). A similar investigation was conducted by Gönül et al. in which they applied tramadol (1 mg/kg) after mandibular third molar extraction to the extraction socket and the bone surface topically in small drops. An inferior alveolar nerve block was obtained using 4 % articaine with epinephrine. From the mean weight of the patients included in the study, it can be concluded that the average tramadol dosage was 65 mg. The authors concluded that postsurgical pain VAS scores were significantly lower in first 12 hours, first analgesic intake was significantly later, and total analgesic intake was significantly lower, in the tramadol group compared to the control groups (46). A very interesting study was conducted by Al-Haideri in which he investigated and compared local anesthetic efficacy of tramadol with adrenaline versus plain tramadol in the extraction of maxillary molar teeth. He concluded that tramadol with adrenaline injected supraperiosteally proved to be an effective local anesthetic for the extraction of upper molar teeth. Due to weak local anesthesia of plain tramadol (without adrenaline), the author stated that the presence of adrenaline, which produces vasoconstriction, thus deterring tramadol locally, is crucial for producing its anesthetic effects on the nerve. It was also highlighted that the study involved minor oral and maxillofacial surgery (teeth extraction). Although statistically non-significant (4 % overall), the side effects of tramadol (nausea and vomiting) could limit the clinical use of this drug as a local anesthetic (47).

Conclusion

The imperative of modern oral surgery is to ensure high quality local anesthesia and to adequately and efficiently control a patient's pain post operatively. A large number of studies and meta-analysis have shown NSAIDs advantages over systemically administrated opioid analgesics, and concluded that opioids should not be prescribed as the first line of pain control for treatment of acute dental pain. On the other side, local administration of atypical opioid tramadol opens new possibilities in postsurgical pain management, and an improvement in local anesthetics properties. In this regard, tramadol applied locally submucosally, supraperiosteally, topically by means of small drops or as an adjuvant to local anesthetic, could provide promising results. However, further studies are required to elucidate local mechanisms of action of tramadol. Furthermore, there is a need for large clinical studies to investigate safe and effective protocols for local administration of tramadol in everyday practices.

Abstract
In modern times, all procedures in oral surgery need to be painless and management of postoperative pain needs to be adequate. The surgical extraction of the third molar or alveolectomy of the wisdom tooth is one of the most common surgical procedures carried out in oral surgery and it includes rising a flap, bone removal and suturing. These surgical procedures usually cause swelling, trismus and moderate to severe pain. Third molar surgery is often used as a model in clinical trials that are directed toward reducing postoperative pain and improving its management. Tramadol is a well-known central acting opioid analgesic that produces analgesia against multiple pain conditions such as postsurgical pain, obstetric pain, terminal cancer pain, pain of coronary origin and neuropathic pain. Tramadol is an atypical opioid. When administered locally, it has both analgesic and anesthetic properties. The aim of this paper was to present new findings on local effects of tramadol in oral surgery.

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