ACTA
STOMATOLOGICA
CROATICA
www.ascro.hr

Acta stomatol Croat. 2024;58(3):267-290.
DOI: 10.15644/asc58/3/7

ORIGINAL SCIENTIFIC PAPER
IZVORNI ZNANSTVENI RAD

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Nonsteroidal Anti-Inflammatory Drugs for Oral Surgery: A Systematic Review and Meta-Analysis

Nesteroidni protuupalni lijekovi za oralno-kirurške zahvate: sustavni pregled i metaanaliza

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Abstract

Objectives: The aim of the present study was to investigate if there are differences in mitigation acute pain following oral surgery procedures within a hospital setting and regarding various medication regimens. **Materials and methods:** A systematic literature search was performed between the years 2013 and 2023, including the databases PUBMED, Cochrane and Scopus, to identify the clinical trials investigating the prescription of non-steroidal (NSAID's) anti-inflammatory drugs before or after an oral surgery. A meta-analysis with meta-regression model was employed on the primary and secondary outcomes, such as pain, swelling and trismus. **Results:** Thirty-six articles were included, 6 of them being retrospective and 30 prospective, with a higher proportion of women than men, at a ratio of 1.34:1 and an average age of 31.9 years. Drugs with medium duration of action demonstrated lower values for pain and swelling. Regarding these parameters, pain and swelling, propionic acid derivatives and acetic acid derivatives exhibited lower values respectively. **Conclusions:** The quality of evidence was low to very low-certainty. The meta-analysis suggests that postoperative pain, swelling and trismus following oral surgery management may be effectively treated with the following drugs: NSAID medium-duration action drugs; propionic acid derivatives for lower pain levels and acetic acid derivatives for lower swelling measures; and Ibuprofen 400mg every 8h for 3 days or less. **Clinical Relevance:** Anti-inflammatory and analgesic drugs are prescribed to prevent or treat dental pain. Ibuprofen 400mg was the most prescribed drug after or before an oral surgery procedure. However, the evidence is indirect and needs to be interpreted with caution.

Received: June 9, 2024
Accepted: September 2, 2024

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MeSH Terms: Acute Pain; Analgesics; Postoperative Pain; Anti-Inflammatory Agents
Author Keywords: Anti-inflammatory; Analgesic; Oral surgery; Post-operative pain.

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Introduction

Acute dental pain can involve both the hard and soft tissues of the oral cavity and may arise from underlying conditions or dental procedures (1). Oral analgesics are commonly

Uvod

Akutni dentalni bolovi mogu zahvatiti i tvrda i meka tkiva usne šupljine i mogu nastati iz osnovnih stanja ili zbog stomatoloških zahvata (1). Oralni analgetici obično se kori-

employed to manage this pain, with various medications and combinations available (2-4). Consistent with the American Dental Association guidelines, nonsteroidal anti-inflammatory drugs (NSAIDs) are the most effective in reducing pain and are thus recommended as the first-line therapy for managing acute oral pain (5-7). Nevertheless, the most effective NSAID/analgesic for the management of pain, swelling and trismus after various oral surgery scenarios has not yet been identified. Consequently, the present systematic review and meta-analysis aim to determine whether there is a difference in the mitigation of acute pain following oral surgery procedures within a hospital setting, such as extraction of lower and upper third molars, impacted teeth with osteotomy or odontosection, and other extractions; and regarding various medication analgesics schedules concerning medication compound, dosage and dosage regimen. Therefore, this meta-analysis aimed to establish a clinical consensus on the preemptive administration of NSAIDs in the postoperative oral procedures for pain, swelling and trismus.

Methods

Standardized criteria and study type

A thorough protocol was developed in accordance with the Cochrane Handbook guidelines and the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) criteria to accurately select and critically evaluate the clinical studies included in this systematic review (8-10).

Registry protocol

this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023420629).

Criteria for considering studies for this review

The present systematic review was established by the PICO index: Population - patients undergoing surgical oral procedures in hospital; Intervention - patients who used a NSAIDs medication; Comparison - patients who used other medication/placebo; Outcome - efficacy of mitigating acute pain, swelling and trismus.

Eligibility criteria

inclusion criteria

For inclusion, the studies were demanded to meet the following criteria: Randomized controlled trials (RCTs); General healthy individuals aged 12 years or older undergoing oral surgical procedures, such as the extraction of lower and upper impacted third molars with osteotomy and/or odontosection, as well as extractions of other teeth and receiving postoperative non-steroidal anti-inflammatory/analgesics drugs; Presence of a comparative non-steroidal anti-inflammatory/analgesics treatment group and placebo; Non-steroidal anti-inflammatory/analgesics treatment with the specification of non-steroidal anti-inflammatory/analgesic compound, dose, and duration.

Exclusion Criteria

The exclusion criteria were as follows: Controlled clinical trials (CCTs), case reports, systematic reviews, animal trials,

ste za kontrolu tih bolova, s različitim lijekovima i dostupnim kombinacijama (2 – 4). U skladu sa smjernicama Američkoga stomatološkog udruženja, nesteroidni protuupalni lijekovi (NSAID) najučinkovitije smanjuju bolove i zato se preporučuju kao prva linija terapije za liječenje akutnih oralnih bolova (5 – 7). Ipak, najučinkovitiji NSAID/analgetik za ublažavanje bolova, oteklina i trizmusa poslije različitih oralnokirurških zahvata još nije identificiran. Posljedično, svrha ovoga sustavnog pregleda i metaanalize jest ustanoviti postoji li razlika u ublažavanju akutnih bolova poslije oralno-kirurških zahvata u bolničkom okruženju, kao što je vađenje donjih i gornjih trećih kutnjaka, impaktiranih zuba s osteotomijom ili odontosekcijom i druge ekstrakcije; i u vezi s različitim rasporedom uzimanja lijekova protiv bolova koji se odnose na sastav lijeka, dozu i režim doziranja. Stoga je cilj ove metaanalize uspostaviti klinički konsenzus o preventivnoj primjeni NSAID-a u postoperativnim oralnim postupcima za ublažavanje bolova, oteklina i trizmusa.

Metode

Standardizirani kriteriji i vrsta studije

Razrađen je detaljni protokol u skladu sa smjernicama iz priručnika Cochrane i kriterijima Preferred Reporting Items for Systematic Review and Meta-Analysisa (PRISMA) za pravilan odabir i kritičku procjenu kliničkih istraživanja uvrštenih u ovaj sistematizirani pregled (8 – 10).

Registracija istraživanja

Ovaj sistematizirani pregled upisan je u Međunarodni prospektivni registar za sustavne pregledne radove (PROSPERO) (CRD42023420629).

Kriteriji za razmatranja istraživanja za ovaj pregled

Ovaj sustavni pregled usklađen je s indeksom PICO, što znači: populacijom – pacijentima podvrgnutima oralno-kirurškim zahvatima u bolnici; intervencijom – pacijentima koji su uzimali NSAID lijek; usporedbom – pacijentima koji su uzimali druge lijekove/placebo; ishodom – učinkovitosit ublažavanja akutnih bolova, oteklina i trizmusa.

Kriteriji prihvatljivosti

Kriteriji za uključivanje

Za uključivanje u istraživanja moralo je kao kriterij biti zadovoljeno sljedeće: randomizirana kontrolirana istraživanja; općenito zdravi pojedinci u dobi od 12 godina ili stariji koji se podvrgavaju oralno-kirurškim zahvatima, kao što je vađenje donjih i gornjih impaktiranih trećih kutnjaka s osteotomijom i/ili odontosekcijom, te vađenje drugih zuba i primaju postoperativno nesteroidne protuupalne lijekove/analgetike; usporedna skupina koja se liječi nesteroidnim protuupalnim lijekovima/analgeticima i placebom; liječenje nesteroidnim protuupalnim lijekovima/analgeticima sa specifikacijom (sastavom) da u sastavu nema nesteroidnoga protuupalnog/analgetika, doze i trajanja.

Kriteriji za isključivanje:

Kontrolirana klinička istraživanja, prikazi slučajeva, sustavni pregledi, ispitivanja na životinjama te laboratorijske

and *in vivo* and *in vitro* laboratory studies; Studies not published as full reports, such as conference abstracts or letters to editors; Studies with incomplete data; Studies involving children less than 12 years of age.

Types of intervention

Included studies has at least one treatment arm involving the use of analgesic and anti-inflammatory agents, with a comparison arm using either a placebo and/or a comparative analgesic and anti-inflammatory agents' treatment, for managing acute pain following oral surgery procedures.

The groups for comparison were as follows: NSAID versus placebo; NSAID versus paracetamol (acetaminophen); NSAID versus opioid; NSAID versus glucocorticoids; NSAID versus another NSAID.

Types of outocome measures

Primary outcomes

Pain

Our primary outcome measure was pain. Due to its subjective nature, there is no standardized method for reporting pain (11). As a result, different authors assessed pain using various approaches, typically employing categorical, visual analogue scales, or even qualitative scales, and at different time points (12). This means that the primary outcomes included the following: patient-reported pain outcomes (such as relief scale (PRS), pain intensity scale (PIS), visual analog scale (VAS), numeric rating scale (NRS), and verbal rating scale (VRS)), as well as the need for rescue analgesic and anti-inflammatory agents treatment (including the total number of doses, type of analgesic and anti-inflammatory agents, time to the first doses, and duration).

Secondary outcomes

Secondary outcomes included the following:

Swelling

We collected data on both subjectively reported and objectively measured swelling, which is considered a surrogate marker of inflammation. Both quantitative and qualitative data were gathered.

Trismus

Mouth opening ability or trismus is very common after oral surgery. Due to its objective nature a measurement in millimeters was used to compare pre and postoperative values.

Search methods for identification of studies

Electronic searches

The selected databases for the study's research included PubMed Medline, Cochrane, and Scopus between the years 2013 and 2023. Concepts and subject headings were combined for each of the database searches (Appendix 1).

Data collection and analysis

Selection of studies

Two authors independently reviewed all search results. Clearly ineligible studies based on title and abstract were directly excluded. For all remaining studies, full-text articles were independently analyzed by two authors to conduct the

studije *in vivo* i *in vitro*; istraživanja koje nisu objavljena kao cjelovita izvješća, kao što su sažetci s konferencija ili pisma urednicima; istraživanja s nepotpunim podatcima; istraživanja kojima su obuhvaćena djeca mlađa od 12 godina.

Vrsta intervencije

Uključena istraživanja imaju najmanje jednu terapijsku granu koja uključuje upotrebu analgetika i protuupalnih lijekova s usporednom granom koja se koristi ili placebom i/ili komparativnim liječenjem analgeticima i protuupalnim agensima za ublažavanje akutnih bolova poslije oralno-kirurških zahvata.

Skupine koje su se uspoređivale bile su: NSAID nasuprot placebu; NSAID nasuprot paracetamolu (acetaminofen); NSAID nasuprot opioidima; NSAID nasuprot glukokortikoidima; NSAID nasuprot drugim NSAID-ima.

Vrste ishoda

Primarni ishodi

Bolovi

Naš primarni ishod bili su bolovi. Zbog subjektivne prirode ne postoji standardizirana metoda za njihov opis (11). Kao rezultat toga, različiti su autori procjenjivali bol koristeći se različitim pristupima, obično kategoričkim, vizualno analognim ljestvicama ili čak kvalitativnim ljestvicama te u različitim vremenskim točkama (12). To znači da su primarni ishodi uključivali sljedeće: bolove koje su prijavili pacijenti (kao što su ljestvica ublažavanja (PRS), ljestvica intenziteta boli (PIS), vizualna analogna ljestvica (VAS), numerička ljestvica ocjenjivanja (NRS) i verbalna ljestvica ocjenjivanja (VRS), te potrebu za hitnim liječenjem analgeticima i protuupalnim sredstvima (uključujući ukupan broj doza, vrstu analgetika i protuupalnih sredstava, vrijeme do prve doze i trajanje).

Sekundarni ishodi

Sekundarni ishodi uključivali su otekline i trizmus.

Oteklina

Prikupili smo podatke o subjektivno prijavljenim i objektivno izmjerenim oteklinama koje se smatraju popratnim markerom/biljegom upale. Prikupljeni su i kvantitativni i kvalitativni podatci.

Trizmus

Ograničeno otvaranje usta ili trizmus vrlo je česta pojava poslije oralno-kirurških zahvata. Zbog svoje objektivne prirode mjerenje u milimetrima korišteno je za usporedbu prije i poslije postoperativnih vrijednosti.

Metode pretraživanja za identifikaciju istraživanja

Elektroničko pretraživanje

Odabrane baze podataka za pretraživanje istraživanja bile su PubMed Medline, Cochrane i Scopus između 2013. i 2023. Koncepti i naslovi predmeta kombinirani su za svako pretraživanje baze podataka (dodatak 1.).

Prikupljanje i analiza podataka

Odabir istraživanja

Dva autora neovisno su pregledala sve rezultate pretraživanja. Jasno neprihvatljiva istraživanja temeljena na naslovu i sažetku odmah su isključena. Za sva preostala istraživanja, radove s cijelim tekstom neovisno su analizirala dva autora

screening for inclusion. All disagreements were resolved by consensus with, whenever required, a third review by another author in case of uncertainty or if disagreements persisted.

Ultimately, the studies were chosen following a thorough evaluation of their full texts. The Cohen's Kappa index was applied to assess the concordance between the two primary reviewers in the risk of bias assessment of each included study (13).

Data extraction and management

Two review authors independently extracted the data using a standardized data collection form that was specifically designed for the present systematic review. Some of the collected information is provided in Table 1:

Methods: study design, total duration of study, details of any "run-in" period, study settings, withdrawals, and dates of the study.

Participants: sample dimension (n), mean age, age range, sex, inclusion criteria, exclusion criteria, type of intervention, severity of pain, severity of trismus, and severity of swelling.

Interventions: name, duration time, chemical structure, dosage, route of administration, and excluded medications.

Outcomes: outcomes, treatment group statistics (i.e. number of events, means, standard deviations, and number of participants per treatment group), and time points. If outcomes for time points outside pre-specified values were reported, the data corresponding to the time closest to one of the pre-specified time points was extracted to create as far as possible intention-to-treat samples for analysis.

Characteristics of the design of the trial for assessment of risk of bias, including sources of funding and conflicts of interest

The final extracted data were double checked by the same two reviewers as well as a third reviewer. Thus, following data collection, data extraction forms from each of the two independent reviewers were compared by the third reviewer to ensure the data extraction accuracy. We resolved any disagreement through consensus.

Assessment of risk of bias in included studies

To evaluate the potential bias in all full-text articles identified and gathered for this study, we employed the Joanna Briggs Institute Checklist for Prevalence Studies (14).

In order to qualify potentially included studies, the two primary reviewers conducted an independent analysis of these studies. The objective was to identify commonalities and discrepancies between them, thus mitigating the risk of selection bias. Each item was rated as "yes", "unclear", "no", or "not applicable/NA". Based on these ratings, each study was classified into one of the following three categories: low risk of bias, if the study received more than 70% "yes" ratings; moderate risk of bias, if "yes" ratings were between 50% and 69%; high risk of bias, if "yes" ratings were below 49%.

Furthermore, the quality of the generated evidence was assessed through the GRADE system (Grading of Recommendations, Assessment, Development, and Evaluations) to provide clinical practice recommendations (15).

kako bi obavili probir za uključivanje. Sva su neslaganja riješena konsenzusom uz, kad god je to bilo potrebno, treću recenziju drugog autora u slučaju nesigurnosti, ili ako su nesuglasice potrajale.

U konačnici, istraživanja su odabrana poslije temeljite evaluacije njihovih cjelovitih tekstova. Cohenov Kappa indeks primijenjen je za procjenu podudarnosti između dva primarna recenzenta u procjeni rizika od pristranosti svakoga uključenog istraživanja (13).

Ekstrakcija i upravljanje podatcima

Dva autora pregleda neovisno su izvukla podatke s pomoću standardiziranog obrasca/modela za prikupljanje podataka koji je posebno izrađen za ovaj sustavni pregled. Neki od prikupljenih podataka navedeni su u tablici 1. To su:

metode: studijski dizajn, ukupno trajanje istraživanja, pojedinosti o svakom „uhodnom" razdoblju, postavke istraživanja, odustajanja i datumi istraživanja

sudionici: veličina uzorka (n), srednja dob, raspon dobi, spol, kriteriji za uključivanje, kriteriji za isključivanje, vrsta intervencije, jakost boli, ozbiljnost trizmusa i ozbiljnost otekline

intervencije: naziv, trajanje, kemijska struktura, doziranje, način primjene i isključeni lijekovi.

ishodi: ishodi, statistika terapijske skupine (tj. broj događaja, srednje vrijednosti, standardne devijacije i broj sudionika po terapijskoj skupini) i vremenske točke; ako su prijavljeni ishodi za vremenske točke izvan unaprijed određenih vrijednosti, podatci koji odgovaraju vremenu najbližemu jednoj od unaprijed određenih vremenskih točaka izdvojeni su dao bi se stvorilo što je više moguće uzoraka s namjerom liječenja za analizu.

Karakteristike oblika ispitivanja za procjenu rizika od pristranosti, uključujući izvore financiranja i sukobe interesa.

Konačne izdvojene podatke dvostruko su provjerila dva ista recenzenta, kao i treći recenzent. Zato je, nakon prikupljanja podataka, treći recenzent usporedio obrasce za izdvajanje podataka iz svakoga od dva neovisna recenzenta kako bi se osigurala točnost ekstrakcije podataka. Sve nesuglasice rješavali smo konsenzusom.

Procjena rizika od pristrasnosti u uključenim studijama

Kako bismo procijenili potencijalnu pristranost u svim člancima s cjelovitim tekstom koji su identificirani i prikupljeni za ovo istraživanje, upotrijebili smo Kontrolni popis Instituta Joanna Briggsa za studije prevalencije (14).

Kako bi se kvalificirala potencijalno uključena istraživanja, dva primarna recenzenta obavila su neovisnu analizu tih istraživanja. Cilj je bio identificirati sličnosti i razlike među njima, čime se smanjuje rizik od pristranosti odabira. Svaka stavka ocijenjena je kao „da", „nejasno", „ne" ili „nije primjenjivo/NA". Na temelju tih ocjena svako je istraživanje klasificirano u jednu od triju kategorija: a) mali rizik od pristranosti, ako je istraživanje dobilo više od 70 % ocjena „da"; b) umjereni rizik od pristranosti, ako su ocjene „da" bile između 50 % i 69 %; c) visoki rizik od pristranosti, ako su ocjene „da" manje od 49 %.

Nadalje, kvaliteta generiranih dokaza procijenjena je s pomoću sustava GRADE (Grading of Recommendations,

Measures of treatment effect

Pain, swelling and trismus are time dependent, as are the effects of the interventions. 95% confidence intervals (CI) were performed.

Primary outcome

Pain

Some trials reported pain on a continuous scale, others used a categorical scale, and some used both. A homogeneous scale was found for all the studies that contained a quantitative scale. As a standard linear, 10-cm visual analogue scale (VAS-10) for acute pain has been shown to be a valid measurement tool. Regardless of the severity of pain, this was the preferred scale. Studies with qualitative scales were excluded for the pain meta-analysis.

There was a lack of consensus regarding the postoperative days for pain measurement. Therefore, the following time points were analyzed: First 24 hours; Days one to three; Day seven.

Secondary outcomes

Swelling

We intended to combine studies that reported swelling using an objective measure, such as circumference in cm or mm. If trials reported subjective reduction in swelling, these were also excluded from the meta-analysis.

We aimed to assess swelling at the following time points: First 48 hours; Day three; Day seven.

Trismus

We combined studies that reported trismus using an objective measure in mm. In order to calculate the real mouth opening ability, a baseline measurement, i.e. preoperative measurement, was necessary to compare both afterwards.

We aimed to assess trismus at the following time points: First 48 hours; Day three; Day seven.

Statistical analysis

A meta-analysis was attempted when studies evaluated the same intervention and reported comparable outcome measures. If there were insufficient data for statistical analysis, a narrative synthesis was planned instead. A meta-analysis was performed using the "meta" package in the statistical software R, version 4.2.2. To assess the variation in treatment effects, the Cochran's test for heterogeneity and I^2 statistics (16) were used, with heterogeneity considered statistically significant at a p-value lower than 0.05. Furthermore, the presence of heterogeneity between studies guided the choice of the applied model, i.e., between the application of the fixed effects model and the random effects model.

Assessment, Development, and Evaluations) kako bi se dale preporuke za kliničku praksu (15).

Mjere učinka liječenja

Bolovi, otekline i trizmusu ovise o vremenu, kao i učinci intervencija. Primijenjeni su 95-postotni intervali pouzdanosti (CI).

Primarni ishod

Bolovi

Autori nekih istraživanja izvijestili su o boli na kontinuiranoj ljestvici, drugi su se koristili kategoričkom ljestvicom, a neki objema. Pronađena je homogena ljestvica za sva istraživanja koja su sadržavala kvantitativnu ljestvicu. Budući da se standardna linearna 10-cm vizualna analogna ljestvica (VAS-10) za akutne bolove pokazala valjanim alatom za kvantifikaciju, bez obzira na jakost bolova, to je bila poželjna ljestvica. Istraživanja s kvalitativnim ljestvicama isključena su iz metaanalize bolova.

Nije bilo konsenzusa u vezi s brojem postoperativnih dana za mjerenje bolova. Zato su analizirane sljedeće vremenske točke: prva 24 sata; prvi do treći dan; sedmi dan.

Sekundarni ishodi

Oteklina

Namjeravali smo kombinirati istraživanja koja su izvještavala o oteklinima koristeći se objektivnom mjerom, kao što je obujam u centimetrima ili milimetrima. Ako su u ispitivanjima prijavljena subjektivna smanjenja oteklina, ona su također bila isključena iz metaanalize.

Namjeravali smo procijeniti oticanje u sljedećim vremenskim točkama: prva 24 sata; prvi do treći dan; sedmi dan.

Trizmus

Kombinirali smo istraživanja koja su izvještavala o trizmusu koristeći se objektivnom mjerom u milimetrima. Da bi se izračunala stvarna sposobnost otvaranja usta, osnovno mjerenje, tj. prijeoperacijsko mjerenje, bilo je potrebno za usporedbu nakon toga.

Namjeravali smo procijeniti trizmus u sljedećim vremenskim točkama: prva 24 sata; prvi do treći dan; sedmi dan.

Statistička analiza

Metaanaliza je provedena kada je u istraživanjima procijenjena ista intervencija i prijavljene usporedive mjere ishoda. Ako nije bilo dovoljno podataka za statističku analizu, planirana je narativna sinteza. Metaanaliza je obavljena korištenjem "meta" paketa u statističkom softveru R, verzija 4.2.2. Za procjenu varijacija u učincima liječenja korišteni su Cochranov test heterogenosti i I2 statistika (16), pri čemu se heterogenost smatra statistički značajnom pri p-vrijednosti nižoj od 0,05. Nadalje, prisutnost heterogenosti između istraživanja vodila je izbor primijenjenog modela, tj. između primjene modela fiksnih učinaka i modela slučajnih učinaka.

Results

Descrition of studies

292 studies were identified through the search strategy. After disregarding duplicates and articles without titles or authors, 281 unique studies remained. All titles and abstracts were screened, resulting in the selection of 60 articles for full-text review. Among these, three articles were not accessible in their entirety, leaving 57 articles for the detailed examination. After thorough analysis, 36 articles met the previously defined inclusion criteria and were included in this Systematic Review (17-52). Figure 1 presents, in a flowchart format, the outcomes of the database search, the selected studies, and the reasons for excluding the remaining ones.

Included studies

This study included 36 articles with a total of 5388 participants. Among these articles, 6 (16.6%) were retrospective, and 30 (83.4%) were prospective, with a higher proportion of women than men, at a ratio of 1.34:1, and an average age of 31.9 years. Of the 36 articles, four (involving 1015 participants) compared NSAIDs with a placebo, four (involving 287 participants) compared NSAIDs with glucocorticoids, ten compared NSAIDs with opioids (involving 757 participants), ten compared one NSAIDs with other NSAIDs (involving 833 participants), and eight compared the use of various NSAIDs in oral surgery situations without specifying individual active substances (involving 2496 participants).

Five main groups were established for the country groups, taking into account their cultural differences to ensure a more homogeneous comparison of results. The American countries include Brazil, Argentina, Mexico, and the United States, thus comprising eleven studies. Europe encompassed Denmark, Finland, Sweden, and the United Kingdom, with four studies. Asia comprised eighteen studies, with eleven in India, three in Iran, one in Taiwan, one in Vietnam, and two in Turkey. North Africa had one study in Tunisia. There was also one study in Australia and one in New Zealand.

If data were available, subgroup analyses were performed to explore differences in treatment effects for participants. The active substances were categorized based on their duration of action and chemical structure. NSAIDs are usually split into groups based on their chemical structure and selectivity: salicylic acids (aspirin, diflunisal), propionic acids (naproxen, ibuprofen), acetic acids (diclofenac, indomethacin, keterolac), enolic acids (meloxicam, piroxicam) anthranilic acids (meclofenamate, mefenamic acid) and selective COX-2 inhibitors (celecoxib, etoricoxib) (53,54). NSAIDs can also be classified into short-acting (plasma half-life less than 6 h) and long-acting (half-life approximately greater than 10 h) (54). However, for the meta-analysis, data were divided into 3 groups: less than 6 h (short acting), 6 to 10 h (medium acting) and more than 10 h (long acting).

For each group, the parameters pain, swelling and trismus were assessed (Tables 2 - 7).

The principal attributes of the comprised studies are summarized in Table 4. The frequency of drugs prescribed, the active substances and the dosage are presented in Table 5.

Rezultati

Opis istraživanja

Na temelju strategije pretraživanja identificirana su 292 istraživanja. Nakon zanemarivanja duplikata i članaka bez naslova i autora ostalo je 281 jedinstveno istraživanje. Pregledani su svi naslovi i sažetci, što je rezultiralo izborom od 60 radova za pregled cjelovitoga teksta. Među njima tri rada nisu bila dostupna u cijelosti, pa je za detaljno pregledavanje ostalo 57 članaka. Poslije temeljite analize 36 radova zadovoljilo je prethodno definirane kriterije za uključivanje te je uvršteno u ovaj sustavni pregled (17 – 52). Slika 1. prikazuje, u obliku dijagrama, rezultate pretraživanja baze podataka, odabrana istraživanja i razloge za isključivanje preostalih.

Uključena istraživanja

Istraživanje je obuhvatilo 36 radova s ukupno 5388 sudionika. Među tim člancima šest (16,6 %) je bilo retrospektivno, a 30 (83,4 %) prospektivno, s većim udjelom žena nego muškaraca u omjeru 1,34 : 1 i prosječnom dobi od 31,9 godina. Od 36 radova, četiri (koja su uključivala 1015 sudionika) uspoređivala su NSAID s placebom, četiri (uključivala su 287 sudionika) uspoređivala su NSAID s glukokortikoidima, deset je uspoređivalo NSAID s opioidima (uključujući 757 sudionika), također deset uspoređivalo je jedan NSAID s drugim NSAID-om (uključujući 833 sudionika).), a osam je uspoređivalo upotrebu različitih NSAID-a poslije oralnokirurških zahvata bez navođenja pojedinačnih aktivnih tvari (uključujući 2496 sudionika).

Utvrđeno je pet glavnih skupina za skupine zemalja, uzimajući u obzir njihove kulturne razlike da bi se osigurala homogenija usporedba rezultata. Američke zemlje obuhvaćaju Brazil, Argentinu, Meksiko i Sjedinjene Države, koje se sastoje od jedanaest istraživanja. Europa obuhvaća Dansku, Finsku, Švedsku i Ujedinjeno Kraljevstvo s četirima istraživanjima. Azija obuhvaća osamnaest istraživanja, od kojih je jedanaest u Indiji, tri u Iranu, jedno u Tajvanu, jedno u Vijetnamu i dva u Turskoj. Sjeverna Afrika imala je jedno istraživanje u Tunisu. Postojalo je i jedno istraživanje u Australiji i jedno u Novom Zelandu.

Ako su podatci bili dostupni, provedena je analiza podskupina da bi se istražile razlike u učincima liječenja za sudionike. Aktivne tvari kategorizirane su na temelju trajanja djelovanja i kemijske strukture. NSAID se obično dijele u skupine prema njihovoj kemijskoj strukturi i selektivnosti. To su salicilne kiseline (aspirin, diflunisal), propionske kiseline (naproksen, ibuprofen), octene kiseline (diklofenak, indometacin, keterolak), enolne kiseline (meloksikam, piroksikam), antranilne kiseline (meklofenamat, mefenaminska kiselina) i selektivni COX-2 inhibitori (celekoksib, etorikoksib) (53, 54). NSAIL-i se također mogu podijeliti na kratkodjelujuće (poluvijek u plazmi manje od 6 sati) i dugodjelujuće (poluvijek približno dulje od 10 sati) (54). No za metaanalizu podatci su podijeljeni u tri skupine: manje od 6 sati (kratko djelovanje), od 6 do 10 sati (srednje djelovanje) i više od 10 sati (dugo djelovanje).

Za svaku skupinu procijenjeni su parametri boli, oteklina i trizmusa (tablice 2. - 7.).

Risk of bias in included studies

Fifteen articles had a low risk of bias, eighteen a moderate risk, and three a high risk of bias. Table 6 summarizes the risk of bias for the included studies (14, 15). The Cohen's Kappa concordance index values between the two reviewers in the assessed nine questions were between 0.546 and 1.

Meta-analysis

Regarding the pain classification, as per the results of meta-analysis, long-acting drugs exhibited a decrease in pain from the first day (5.5570 in a meta-analysis based on 3 studies) to the third day (2.3440 based on 2 studies) and a slight increase from the third to the seventh day (3.0969 based on 2 studies). Medium-duration action drugs all showed a decrease in pain over the days (day 1 – 2.5421 based on 6 studies, as shown in Figure 2; day 2 – 0.9315 based on 3 studies; day 3 – 0.4474 based on 3 studies; day 7 – 0.0892 based on 2 studies). Short-duration action drugs exhibited a similar pattern to long-acting drugs, with pain intensity decreasing from the first day (4.9705, based on 3 studies) to the third day (3.6611, based on 2 studies) and then increasing on the seventh postoperative day (4.04, based on 2 studies). On the second day of long-acting drugs, pain was 10.4226 (based on 2 studies); on the seventh day, it was 8.2158 (based on 2 studies), with a decrease in swelling. For medium-duration action drugs, there was a significant decrease in swelling from the second day (37.2787, based on 5 studies) to the third day (4.7695, based on 3 studies) and an increase from the third to the seventh day (6.7381, based on 4 studies).

It was not possible to perform a meta-analysis for the trismus classification due to the low number of studies assessing it. Moreover, high heterogeneity was observed in most meta-analyses, with a p-value less than 0.0001.

Regarding the classification based on chemical structure, opioids exhibited a pain intensity of 6.9168 (based on 3 studies) on the first postoperative day. The pain intensity decreased over all days in the group of drugs derived from propionic acid (day 1 – 3.8227 based on 5 studies; day 2 – 0.9661 based on 3 studies; day 3 – 0.4388 based on 3 studies; day 4 – 0.1270 based on 2 studies). As for drugs derived from acetic acid, pain decreased from the first day (3.6236, based on 5 studies) to the third day (2.1976, based on 3 studies), but it slightly increased on the seventh day (3.6321, based on 2 studies).

It was not possible to perform a meta-analysis for swelling in the opioid group. Also, it was not possible to assess postoperative trismus due to the low number of studies assessing it. Moreover, high heterogeneity was observed in most meta-analyses, with a p-value less than 0.0001.

On the second day, the swelling for drugs derived from propionic acid was 78.2472 mm, with no comparison to other days. Finally, the group of drugs derived from acetic acid exhibited an increase in swelling from the second day (12.1051, based on 3 studies) to the third day (18.1617, based

Glavni atributi obuhvaćenih istraživanja sažeti su u tablici 4. Učestalost propisanih lijekova, djelatne tvari i doziranje prikazani su u tablici 5.

Rizik od pristranosti u uključenim istraživanjima

Petnaest radova imalo je nizak rizik od pristranosti, osamnaest umjeren, a tri visok. U tablici 6. sažet je rizik od pristranosti za uključena istraživanja (14, 15). Vrijednosti Cohenova kappa indeksa podudarnosti između dva recenzenta u procijenjenih devet pitanja bile su između 0,546 i 1.

Metaanaliza

Što se tiče klasifikacije boli, prema rezultatima metaanalize, dugodjelujući lijekovi pokazali su smanjenje bolova od prvoga dana (5,5570 u metaanalizi na temelju triju istraživanja) do trećega dana (2,3440 na temelju dvaju istraživanja) i blagi porast od trećega do sedmoga dana (3,0969 na temelju dvaju istraživanja). Svi lijekovi srednjeg trajanja djelovanja pokazali su smanjenje bolova tijekom dana (1. dan – 2,5421 na temelju šest istraživanja, kao što je prikazano na slici 2; 2. dan – 0,9315 na temelju triju istraživanja; 3. dan – 0,4474 na temelju triju istraživanja; 7. dan – 0,0892 na temelju dvaju istraživanja). Lijekovi s kratkotrajnim djelovanjem pokazali su sličan obrazac kao i dugodjelujući lijekovi, s intenzitetom bolova koji se smanjivao od prvoga dana (4,9705, na temelju triju istraživanja) do trećega dana (3,6611, na temelju dvaju istraživanja), a zatim se povećavao sedmoga postoperativnoga dana (4,04, na temelju dvaju istraživanja). Drugoga dana dugodjelujućih lijekova, bol je bila 10,4226 (na temelju dvaju istraživanja); sedmoga dana iznosila je 8,2158 (na temelju dvaju istraživanja), uz smanjenje otekline. Kad je riječ o lijekovima srednjega trajanja djelovanja, oteklina se značajno smanjivala od drugoga dana (37,2787, na temelju pet istraživanja) do trećega dana (4,7695, na temelju triju istraživanja) i povećavala se od trećega do sedmoga dana (6,7381, na temelju četiriju istraživanja).

Metaanaliza za klasifikaciju trizmusa nije bila moguća zbog malog broja istraživanja u kojima se procjenjivao. Štoviše, uočena je visoka heterogenost u većini metaanaliza, s p-vrijednošću manjom od 0,0001.

Kad je riječ o klasifikaciji na temelju kemijske strukture, opioidi su pokazali intenzitet bola od 6,9168 (na temelju triju istraživanja) prvoga postoperativnog dana. Jakost bolova smanjivala se tijekom svih dana u skupini lijekova na temelju propionske kiseline (1. dan – 3,8227 na temelju pet istraživanja; 2. dan – 0,9661 na temelju triju istraživanja; 3. dan – 0,4388 na temelju triju istraživanja; 4. dan – 0,1270 na temelju triju istraživanja). U analizi lijekova dobivenih iz octene kiseline, bolovi su se smanjivali od prvoga dana (3,6236, na temelju pet istraživanja) do trećega dana (2,1976, na temelju triju istraživanja), ali su se neznatno povećali sedmoga dana (3,6321, na temelju dvaju istraživanja).

Metaanaliza za oticanje u opioidnoj skupini ili procjena postoperativnog trizmusa nije bila moguća zbog malog broja istraživanja u kojima se to procjenjivalo. Štoviše, uočena je visoka heterogenost u većini metaanaliza, s p-vrijednošću manjom od 0,0001.

Drugoga dana oteklina za lijekove dobivene od propionske kiseline bila je pri primjeni lijekova dobivenih od propi-

on 2 studies) and a decrease on the seventh day (10.2886, based on 4 studies).

Statistically, the first day recorded higher pain intensity for all action durations, with a 95% CI for long duration between 1.2473 and 9.8667. For medium duration, the 95% CI ranged from 1.5690 to 3.5152; for short duration, it ranged from 1.9395 to 8.0016. Additionally, the medium duration showed lower pain intensity compared to the other durations on the seventh day, corresponding to a 95% CI between 0.0299 and 0.1485. The second postoperative day showed higher swelling values, with a 95% CI between 7.1399 and 13.7054 for long duration and between 0 and 94.0589 for medium duration.

Among the divisions based on chemical structure, the drugs derived from propionic acid displayed a 95% CI on the seventh day between 0 and 0.3333, indicating lower pain intensity compared to other groups. In contrast, the drugs derived from acetic acid showed a 95% CI between 5.7669 and 14.8102 on the seventh day concerning swelling.

Discussion

The most frequently prescribed drug for decreasing the postoperative pain, swelling and trismus in this meta-analysis is ibuprofen, which is in line with findings from other authors (55-59). The recommended dose for adults is 400mg (60-63).

The comparison of postoperative pain and swelling was conducted by analyzing different groups based on factors such as the duration of action and chemical structure. Both ibuprofen and paracetamol fall within the category of medium duration of action. The values for post-operative pain in this group were the highest (55, 56, 58).

When evaluating the post-operative pain in the group of propionic acid derivatives, it showed lower values, thus having a greater analgesic and anti-inflammatory effect. According to the guidelines of the Portuguese Directorate-General of Health (DGS), ibuprofen, a propionic acid derivative, should be prescribed in combination with paracetamol when an inflammatory component is present (64).

Opioids exhibited higher postoperative pain values on the first day when compared to propionic and acetic acid derivatives. The opioid compared in this study was tramadol, which, according to the World Health Organization (WHO) pain ladder, should be prescribed in cases of moderate pain (64). Furthermore, the dosage of this active ingredient was 50mg, which is described in the study by the Portuguese Association of General Practitioners as equivalent to 10mg of oral morphine (65). This may suggest that these were cases of severe pain. Additionally, higher pain values associated with opioids can be explained by the fact that this drug was prescribed in the studies included in this meta-analysis during the extraction of impacted lower third molars. Such an extraction is a complex and traumatic surgery in the jaw, which, in turn, consists of denser bone. However, this relationship

onske kiseline oteklina je bila 78,2472 mm, bez usporedbe s drugim danima. Konačno, skupina lijekova proizvedenih na temelju octene kiseline pokazala je povećanje otekline od drugoga dana (12,1051, na temelju triju istraživanja) do trećega dana (18,1617, na temelju dvaju istraživanja) i smanjenje sedmoga dana (10,2886, na temelju četiriju istraživanja).

Statistički, prvi dan zabilježen je veći intenzitet bolova za sva trajanja djelovanja, s 95 % CI-ja za dugo trajanje između 1,2473 i 9,8667. Za srednje trajanje, 95 % CI-ja bilo je u rasponu od 1,5690 do 3,5152; za kratko trajanje kretalo se od 1,9395 do 8,0016. Dodatno, srednje trajanje pokazalo je manji intenzitet bolova u usporedbi s drugim trajanjima sedmoga dana, što odgovara 95 % CI-ja između 0,0299 i 0,1485. Drugi postoperativni dan pokazao je veće vrijednosti otekline, s 95 % CI-ja između 7,1399 i 13,7054 za dugo trajanje i između 0 i 94,0589 za srednje trajanje.

Među podjelama temeljenima na kemijskoj strukturi, lijekovi na bazi propionske kiseline pokazali su 95 % CI-ja sedmoga dana između 0 i 0,3333, što upućuje na manji intenzitet bolova u usporedbi s drugim skupinama. Suprotno tomu, lijekovi dobiveni iz octene kiseline imali su 95 % CI-ja između 5,7669 i 14,8102 sedmoga dana u vezi s oteklinama.

Rasprava

Ibuprofen je najčešće propisivani lijek za smanjenje postoperativnih bolova, oteklina i trizmusa u ovoj metaanalizi, što je u skladu s nalazima drugih autora (55 – 59). Preporučena doza za odrasle je 400 mg (60 – 63).

Usporedba postoperativnih bolova i oteklina provedena je analizom različitih skupina na temelju čimbenika kao što su trajanje djelovanja i kemijska struktura. I ibuprofen i paracetamol ubrajaju se u kategoriju srednje dugoga djelovanja. Vrijednosti postoperativnih bolova u ovoj su skupini bile najviše (55, 56, 58).

Pri procjeni postoperativnih bolova u skupini derivata propionske kiseline, zabilježene su niže vrijednosti, što upućuje na veći analgetski i protuupalni učinak. Prema smjernicama portugalskoga Glavnoga direktorata za zdravstvo (DGS), ibuprofen, derivat propionske kiseline, treba propisivati u kombinaciji s paracetamolom kada je je riječ o upalnoj komponenti (64).

Opioidi su pokazali veće vrijednosti postoperativnih bolova prvoga dana u usporedbi s derivatima propionske i octene kiseline. Opioid uspoređivan u ovom istraživanju bio je tramadol koji bi se, prema ljestvici boli Svjetske zdravstvene organizacije (WHO), trebao propisati u slučaju umjerenih bolova (64). Nadalje, doza ovoga aktivnog sastojka bila je 50 mg, što je u istraživanju portugalske Udruge liječnika opće prakse opisano kao ekvivalent 10 mg oralnoga morfija (65). To može sugerirati da su to bili slučajevi jakih bolova. Dodatno, veće vrijednosti bolova povezane s opioidima mogu se objasniti činjenicom da je taj lijek bio propisan u istraživanjima uključenima u ovu metaanalizu tijekom ekstrakcije impaktiranih donjih trećih kutnjaka. Riječ je o složenoj i traumatičnoj operaciji u čeljusti koja se sastoji od gušće kosti. No taj se odnos ne može dokazati jer nije bilo zapisa o početnim bolovima pojedinaca u dotičnim uzorcima (66).

cannot be proven, as there were no records of the initial pain of the individuals in the respective samples (66).

In this systematic review, it is evident that the pain level in individuals who received medication only in case of pain, when compared to regular use of the same medication, did not show a significant difference. However, the number of analgesic medications used in the group instructed to only take tablets if they felt pain was lower than in the group where medication was taken on a regular basis, and these results are in line with the existing literature (66-68).

Strengths and limitations of the study

This meta-analysis has a few limitations. Considering the included studies, different drugs were used, in different ways of administration for different durations. For this reason, it is possible to observe lower level of evidence, due to the heterogeneity in partially integrated data. Concerning the data analysis, all factors that could possibly affect the results were considered. The characteristics of the included studies, allowed the performance of subgroup analyses, including the type of pain, follow-up time, drug, dose, and duration. Also, the PRISMA statement was followed in this review and the procedures throughout the review process are rigorous and reproducible.

Conclusions

The quality of evidence was low to very low- certainty. The meta-analysis suggests that postoperative pain, swelling and trismus following oral surgery management may be effectively treated with the following drugs: NSAID medium-duration action drugs; propionic acid derivatives for lower pain levels and acetic acid derivatives for lower swelling measures; and Ibuprofen 400mg every 8h for 3 days or less.

Ibuprofen 400mg was the most prescribed drug after or before an oral surgery procedure. However, the evidence is indirect; hence it requires to be interpreted with caution.

Acknowledgments: This research is partially supported by FCT – Fundação para a Ciência e a Tecnologia under the project UIDB/00006/2020 (https://doi.org/10.54499/UIDB/00006/2020).

Conflict of Interest: The authors declare no conflicts of interest.

Author's Contribution: The authors conform contribution to the paper as follows: Study Conception and Design - **C. P. P.**; Data Collection – **M. M. T., A. R. F. A. C.**; Analysis and Interpretation of results - **R. S., M. F. B., C. P. P., F. S.**; Draft Manuscript preparation: **A. R., D. A., M. M. T.** All authors reviewed the results and approved the final version of the manuscript.

U ovom sistematiziranom pregledu vidljivo je da razina bolova kod osoba koje su uzimale lijek samo u slučaju bolova, u usporedbi s redovitom primjenom istoga lijeka, nije pokazala značajnu razliku. Međutim, broj analgetika korištenih u skupini koja je dobila uputu da uzima tablete samo ako osjete bol bio je manji nego u skupini u kojoj su lijekovi uzimani redovito, a ti su rezultati u skladu s postojećom literaturom (66 – 68).

Ograničenja istraživanja

Ova metaanaliza ima nekoliko ograničenja. S obzirom na uključena istraživanja, korišteni su različiti lijekovi uz različite načine primjene u različitom trajanju. Iz tog razloga niža je razina evidencije zbog heterogenosti u djelomično integriranim podatcima. Kad je riječ o analizi podataka, uzeti su u obzir svi čimbenici koji bi mogli utjecati na rezultate. Karakteristike uključenih istraživanja omogućile su analize podskupina, uključujući vrstu bolova, vrijeme praćenja, lijek, dozu i trajanje. Također, pravila PRISMA-e poštovana su u ovom pregledu, a postupci tijekom cijelog procesa pregledavanja bili su rigorozni i ponovljivi.

Zaključci

Kvaliteta dokaza bila je niske do vrlo niske pouzdanosti. Metaanaliza sugerira da se postoperativni bolovi, otekline i trizmusi poslije oralno-kirurških zahvata mogu učinkovito liječiti sljedećim lijekovima: NSAID-ima srednjeg trajanja, derivatima propionske kiseline za smanjenje razine bolova i derivatima octene kiseline za smanjenje otekline i ibuprofenom od 400 mg svakih 8 sati tijekom 3 dana ili manje.

Ibuprofen od 400 mg bio je najčešće propisivani lijek poslije ili prije oralno-kirurškoga zahvata. No dokazi su neizravni i treba ih tumačiti s oprezom.

Zahvala: Ovo istraživanje djelomično je financirao Fundação para a Ciência e a Tecnologia – FCT, u sklopu projekta UIDB/00006/2020 (https://doi.org/10.54499/UIDB/00006/2020).

Sukob interesa: Autori nisu bili u sukobu interesa.

Doprinos autora: Autori su usaglasili doprinos radu kako slijedi: Koncepcija i dizajn studije - **C. P. P.**; Prikupljanje podataka – **M. M. T., A. R. F. A. C.**; Analiza i interpretacija rezultata - **R. S., M. F. B., C. P. P., F. S.**; Priprema nacrta rukopisa: **A. R., D. A., M. M. T.** Svi su autori pregledali rezultate i odobrili konačnu verziju rukopisa.

Appendix I

Search protocol used in the systematic review.

Detailed search queries were as follows:

Pubmed, cochrane and scopus

Simple search (including all possible combinations)

Search term (or terms): ("anti-inflammatory drugs" OR "anti-inflammatory agents") AND ("oral surgery" OR "dental pain" OR "tooth extraction") AND "prescription" AND NOT "antibiotic*" AND NOT "opioid*"

Dodatak I.

Protokol pretraživanja korišten u sustavnom pregledu

Detaljni upiti za pretraživanje bili su sljedeći:

Pubmed, cochrane i scopus

Jednostavno pretraživanje (uključujući sve moguće kombinacije)

Pojam (ili pojmovi): ("protuupalni lijekovi" ILI "protuupalni agensi") I ("oralna kirurgija" ILI "stomatološka bol" ILI "vađenje zuba") I "recept", A NE "antibiotik*," A NE "opioid*"

Table 1 Data extraction
Tablica 1. Ekstrakcija podataka

Study	Authors	Year	Study type	Country	n[a]	Male[b]	Female[c]	Male pro[d]	Age	
									Mean age	SD[e]
1	Akbulut N. Et al	2014	P	Turkey	42	14	28	0,33	20,8	4,1
2	Atkinson H. et al	2015	P	New Zealand	159	69	90	0,43	23,7	
3	Berhouma L. et al	2021	R	Tunisia	200	60	140	0,3	35	9
4	Bryant C. et al	2013	P	England	131	52	79	0,39	28,33	
5	Camargo I. et al	2015	P	Brasil	94				32,68	7,97
6	Chethan R. et al	2015	P	Índia	40					
7	Cooper S. et al	2019	P	USA	387	191	194	0,49	19	2,8
8	Eroglu C-N. Et al	2015	P	Turkey	36	13	23	0,36	21,83	
9	Gopalraju P. et al	2013	P	India	40	25	15	0,625	25,675	
10	Gorecki P. et al	2017	P	England	75	28	47	0,37	28,6	
11	Hong B. et al	2016	R	England	106	23	83	0,22	38,7	
12	Isiordia-Espinoza M-A. Et al	2016	P	Mexico	30	11	19	0,37	32,5	
13	Kellstein D. et al	2020	P	USA	394	195	199	0,49	18,12	
14	Kofina V. et al	2022	R	USA	75	36	39	0,48	51,7	2,3
15	Kumar SS et al	2023	P	India	301	142	159	0,47	48,28	
16	Le SH. Et al	2021	P	Vietnam	59	27	32	0,46	22,12	2,63
17	Mangalgi A. et al	2018	P	India	40				24,6	
18	Mei C-C. Et al	2016	P	Taiwan	330				47,7	13,3
19	Fernando I. et al	2017	P	Argentina	29	10	19	0,34	65,42	
20	Mishra H. et al	2012	P	India	74	36	38	0,49	31,57	
21	Mishriky J. et al	2019	R	Australia	113	37	76	0,33	35,62	
22	Monisha M. et al	2019	R	India	100					

	Active substance				Duration of action			Chemical structure		
	Type	SD[e]	n[a]	Dose	Type	SD[e]	n[a]	Type	SD[e]	n[a]
	Etodolac		14		long	1	42	acetic acid derivative	0,67	28
	Naproxen		14					propionic acid derivative	0,33	14
	Diclofenac		14							
	Acetaminophen + Ibuprofen		110		medium	0,69	110	p-aminophenol + propionic acid derivative	0,69	110
	Ibuprofen		164		medium	0,82	164	propionic acid derivative	0,82	164
	Dexamethasone		136					glucocorticoid	0,68	136
	Ibuprofen	0,64	84	400	medium	1	131	propionic acid derivative	1	131
	Ketorolac	0,5	20	10	short	0,5	20	acetic acid derivative	0,5	20
	Tramadol	0,5	20	50				opioid	0,5	20
	Naproxen		166		medium	0,43	165	propionic acid derivative	0,86	331
	Ibuprofen		166		long	0,43	166			
	Acetaminophen		12		short	0,33	12	p-aminophenol	0,33	12
	Methylprednisolone + Acetaminophen		12		medium	0,33	12	propionic acid derivative	0,33	12
	Dexketoprofen trometamol		12					glucocorticoid + p-aminophenol	0,33	12
	Ketorolac		20		short	0,5	20	acetic acid derivative	0,5	20
	Tramadol	0,5	20	50				opioid	0,5	20
	HPβCD-diclofenac				medium	0,79	59	acetic acid derivative	0,79	59
	Ketorolac	0,5	15	10	short	0,5	15	acetic acid derivative	0,5	15
	Tramadol	0,5	15	50				opioid	0,5	15
	Ibuprofen	0,23	92	400	medium	0,92	364	propionic acid derivative	0,23	92
	Acetaminophen + Ibuprofen		272					p-aminophenol + propionic acid derivative		272
	Ibuprofen			400	medium			propionic acid derivative		
	Ketorolac		20		short	0,5	20	acetic acid derivative	0,5	20
	Tramadol	0,5	20	50				opioid	0,5	20
	Ibuprofen	0,78	256	400	medium	1	330	propionic acid derivative		
	Acetaminophen		74					p-aminophenol		
	Ketorolac	0,48	14	10	short	1	29	acetic acid derivative	0,48	14
	Ketorolac + Betamethasone		15					acetic acid derivative + glucocorticoid	0,52	15
	Ketorolac		25		short	0,34	25	acetic acid derivative	0,34	25
	Tramadol		25					opioid	0,34	25
	Diclofenac		50		medium	0,4	40	acetic acid derivative	0,5	50
	Ibuprofen		31		long	0,5	50	propionic acid derivative	0,31	31
	Acetaminophen + codeine		9					p-aminophenol + opioid	0,09	9

23	Moura C et al	2014	P	Brasil	92	25	67	0,27	22	1,54
24	Oliveira E. et al	2021	P	USA	22	15	7	0,68	23,05	3,78
25	Orozco-Solís M. et al	2016	P	Mexico	36	18	18	0,5	22,5	
26	Parirokh M. et al	2014	P	Iran	58	25	33	0,43	31,41	10,7
27	Passi D. et al	2018	P	India	100	64	36	0,64	32	
28	Pathi J. et al	2020	P	India	200	63	137	0,315	26	
29	Pouchain E. et al	2015	P	Brasil	18	2	16	0,11	19	4,4
30	Rajaraman V. et al	2018	P	India	100					
31	Samieirad S. et al	2017	P	Iran	76	38	38	0,5	41,5	5,3
32	Sengupta K. et al	2019	R	Denmark, Finland, Sweden	1615	674	941	0,42	48,41	
33	Shenoi B. et al	2021	P	India	39	19	20	0,49	33,2	3,3
34	Singh P. et al	2015	P	India	57	33	24	0,58		
35	Velásquez G. et al	2014	P	Mexico	40	16	24	0,4	35,55	
36	Zadsirjan S. et al	2022	P	Iran	80	40	40	0,5	35,1	

Legend: a - sample size; b - number of males; c- number of females; d - proportion of males; e- standard deviation; P – Prospective study; R – Retrospective study

Table 2 Duration of action with pain level
Tablica 2. Trajanje djelovanja s razinom boli

Study	Duration of action			Pain											
	Type	SD[a]	n[b]	Day 1			Day 2			Day 3			Day 7		
				Mean	SD[a]	n[b]	Mean	SD[a]	n[b]	Mean	SD[a]	n[b]	Mean	SD[a]	n[b]
1	long	1	42	1,2367	1,1970	42	0,4733	0,8418	42	0,2833	0,7892	42	0,0467	0,3059	42
2	medium	0,692	110	1,9797	3,2059	110									
6	short	0,5	20	4,3		20									
7	medium	0,43	165	4,857	5,058	165									
	long	0,43	166	8,33	5,058	166									
9	short	0,5	20	3,29	8,18	20									
10	medium	0,79	59	2,7605	1,9617	59									
12	short	0,5	15	0,1		15									
13	medium	0,92	364	7,9224		364									
17	short	0,5	20	2,305		20									
19	short	1	29							2,1031	1,8318	29	0,8596	1,7107	29
20	short	0,34	25	2,884		25									
27	short	0,5	50	2,12		50									
28	short	0,5	100	3,356	6,98	100									
29	medium	1	18	1,4725	2,2202	18	1,5275	2,6718	18	0,9166	1,8688	18	0,1666	0,5659	18
31	medium	1	76	2,665	0,8988	76	0,86	0,8754	76	0,475	0,6329	76	0,085	0,2708	76
34	long	0,37	21	7,14	1,79	21				4,42	1,25	20	6,16	1,27	20
	short	0,35	20	7,66	2,31	20				5,22	1,54	20	7,24	2,13	20
36	medium	1	80	1,5375	1,1689	80	1	0,9906	80	0,4125	0,6039	80			

Legend: a- standard deviation; b - sample size

Dexamethasone		22					glucocorticoid	1	22
Diclofenac		18		medium	0,5	18	acetic acid derivative	0,5	18
Meloxicam		18		long	0,5	18	enolic acids	0,5	18
Ibuprofen	1	58	400	medium	1	58	propionic acid derivative	1	58
Ketorolac	0,5	50	10	short	0,5	50	acetic acid derivative	0,5	50
Tramadol	0,5	50	50				opioid	0,5	50
Ketorolac		100		short	0,5	100	acetic acid derivative	0,5	100
Tramadol	0,5	100	50				opioid	0,5	100
Ketoprofen		9		medium	1	18	propionic acid derivative	0,5	9
Nimesulide		9					sulfanilamide derivative	0,5	9
Acetaminophen + codeine		38		medium	1	76	p-aminophenol + opioid	0,5	38
Acetaminophen + caffeine		38					p-aminophenol + xanthine	0,5	38
Diclofenac + Acetaminophen		39		medium	1	39	acetic acid derivative + p-aminophenol	1	39
Ketorolac	0,35	20	10	long	0,37	21	acetic acid derivative	0,72	41
Tramadol	0,28	16	50	short	0,35	20	opioid	0,28	16
Diclofenac		21							
Ketoprofen		20		medium	0,5	20	acetic acid derivative	0,5	20
Diclofenac		20		long	0,5	20	propionic acid derivative	0,5	20
Ibuprofen	0,5	40	400	medium	1	80	propionic acid derivative	1	80
Ibuprofen lysine		40							

Table 3 Duration of action with swelling measures
Tablica 3 Trajanje djelovanja s veličinom otekline

Study	Duration of action			Swelling								
				Day 2			Day 3			Day 7		
	Type	SD[a]	n[b]	Mean	SD[a]	n[b]	Mean	SD[a]	n[b]	Mean	SD[a]	n[b]
1	long	1	42	8,73	2,7815	42				4,64	1,6708	42
8	short	0,3333	12	4,58	2,33	12						
	medium	0,3333	12	3,73	4,81	12						
10	medium	0,7867	59	15,3227	0,8758	59				15,1471	0,9299	59
16	medium			152,76	8,67	59						
18	medium	1	330	36		253						
19	short	1	29				24,8255	15,5206	29	9,6548	12,2687	29
25	medium	0,5	18	12,21	0,76	18	12,15	0,86	18	11,57	0,81	18
	long	0,5	18	12,08	1,09	18	11,9	0,91	18	11,81	1,89	18
29	medium	1	18				0,025	0,1275	18	0,02	0,1202	18
31	medium	1	76	2,39	0,6762	76	2,14	0,7971	76	0,22	0,3613	76

Legend: a- standard deviation; b - sample size

Table 4 Duration of action with trismus measures
Tablica 4 Trajanje djelovanja s jačinom trizmusa

Study	Duration of action			Trismus								
				Day 2			Day 3			Day 7		
	Type	SD[a]	n[b]	Mean	SD[a]	n[b]	Mean	SD[a]	n[b]	Mean	SD[a]	n[b]
1	long	1	42	32,69	6,0138	42				40,9367	6,8605	42
16	medium			152,76	8,67	59						
29	medium	1	18				36,915	7,3062	18	40,5	6,3008	18

Legend: a- standard deviation; b - sample size

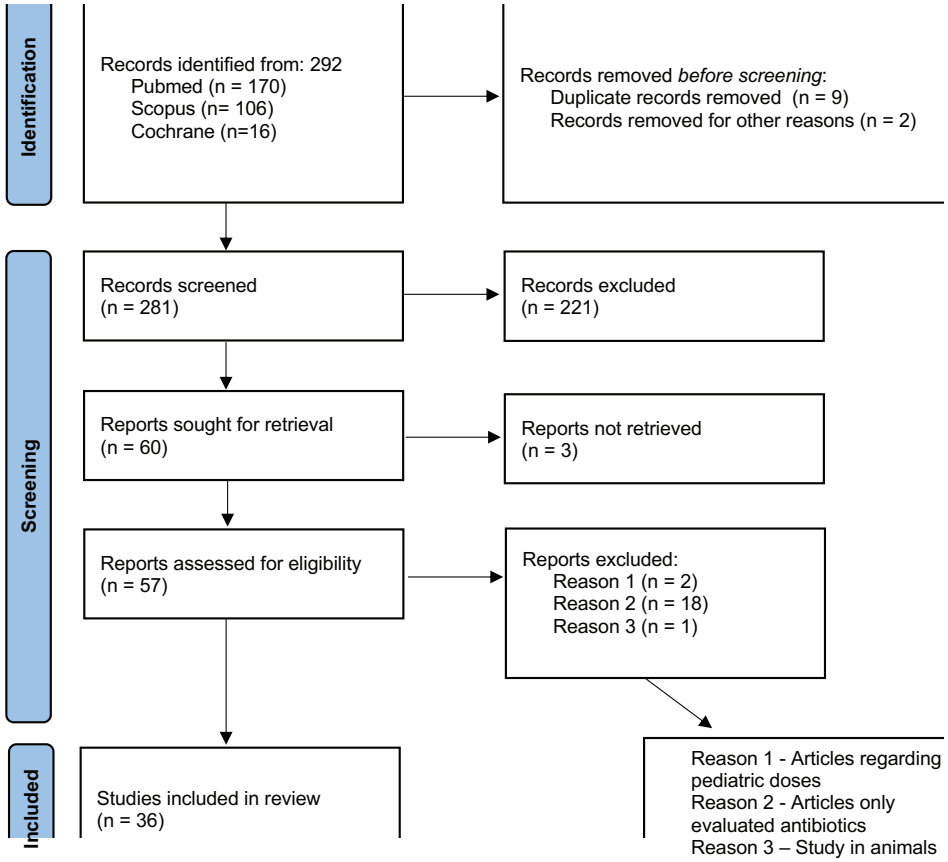

Figure 1 Identification of studies via datebases and registers
Slika 1. Identifikacija podataka putem baza podataka i registara

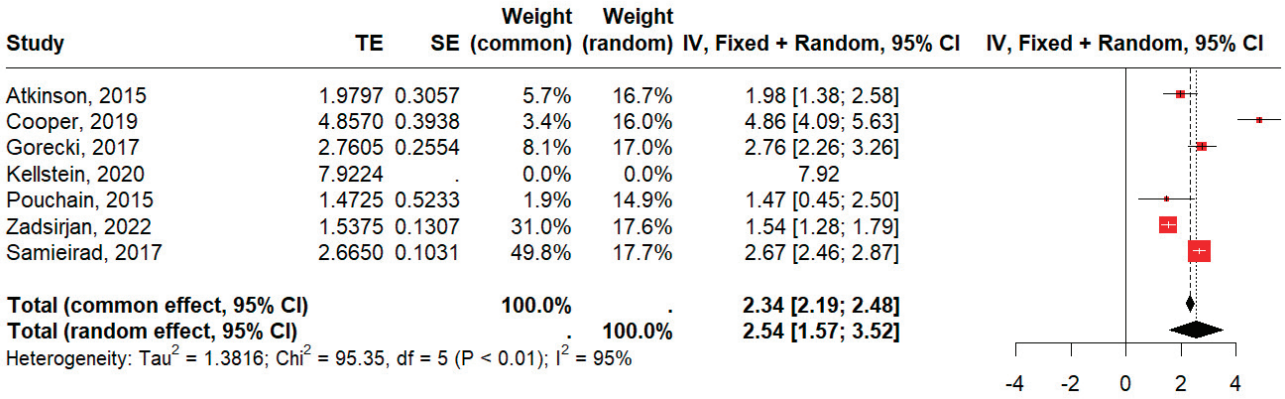

Figure 2 Forest plot for medium duration drugs for pain on day 1
Slika 2. Forest plot za srednje dugotrajne lijekove protiv bolova 1. dana

Table 5 Chemical structure with pain level
Tablica 5 Kemijska struktura s razinom boli

Study	Chemical structure			Pain											
	Type	SD[a]	n[b]	Day 1			Day 2			Day 3			Day 7		
				Mean	SD[a]	n[b]	Mean	SD[a]	n[b]	Mean	SD[a]	n[b]	Mean	SD[a]	n[b]
1	AAD	0,6667	28	1,21	1,1643	28	0,355	0,7569	28	0,07	0,3748	28	0	0	28
	PAD	0,3333	14	1,29	1,26	14	0,71	0,99	14	0,71	1,26	14	0,14	0,53	14
2	PA + PAD	0,6918	110	1,9797	3,2059	110									
6	AAD	0,5	20	4,3		20									
	OPI	0,5	20	2,2		20									
7	PAD	0,8579	331	6,5987	5,058	331									
9	AAD	0,5	20	3,29	8,18	20									
	OPI	0,5	20	5,46	7,1	20									
10	AAD	0,7867	59	2,7605	1,9617	59									
12	AAD	0,5	15	0,1		15									
	OPI	0,5	15	7,34		15									
13	PAD	0,2335	92	7,9		92									
	PA + PAD		272	7,93		272									
17	AAD	0,5	20	2,305		20									
	OPI	0,5	20	2,785		20									
19	AAD	0,4828	14							1,71	1,49	14	0,57	0,76	14
	AAD + GC	0,5172	15							2,47	2,1	15	1,13	2,26	15
20	AAD	0,3378	25	2,884		25									
	OPI	0,3378	25	2,132		25									
27	AAD	0,5	50	2,12		50									
	OPI	0,5	50	2,42		50									
28	AAD	0,5	100	3,356	6,98	100									
	OPI	0,5	100	5,323	4,49	100									
29	PAD	0,5	9	1,667	2,249	9	1,611	2,547	9	0,9444	1,798	9	0,1111	0,4714	9
	SuD	0,5	9	1,278	2,191	9	1,444	2,791	9	0,8889	1,937	9	0,2222	0,6468	9
31	PA + OPI	0,5	38	2,39	1,037	38	0,78	1,166	38	0,28	0,575	38	0	0	38
	PA + XAN	0,5	38	2,94	0,735	38	0,94	0,416	38	0,67	0,686	38	0,17	0,383	38
34	AAD	0,7193	41	7,3937	2,0598	41				4,82	1,4025	40	6,7	1,7535	40
	OPI	0,2807	16	10,08	4,73	16				5,21	1,74	16	6,8	1,97	16
36	PAD	1	80	1,5375	1,1689	80	1	0,9906	80	0,4125	0,6039	80			

Legend: a- standard deviation; b - sample size; AAD- acetic acid derivative; PAD- propionic acid derivative; PA- p-aminophenol; OPI- opioid; GC- glucocorticoid; SuD- sulfanilamide derivative; XAN- xanthine.

Table 6 Chemical structure with swelling measures
Tablica 6. Kemijska struktura s veličinom otekline

Study	Chemical structure			Swelling								
	Type	SD[a]	n[b]	Day 2			Day 3			Day 7		
				Mean	SD[a]	n[b]	Mean	SD[a]	n[b]	Mean	SD[a]	n[b]
1	AAD	0,6667	28	8,45	2,9034	28				4,435	1,3377	28
	PAD	0,3333	14	9,29	2,52	14				5,05	2,19	14
8	PA	0,3333	12	3,73	4,81	12						
	PAD	0,3333	12	4,58	2,33	12						
	GC + PA	0,3333	12	2,34	2,1	12						
10	AAD	0,7867	59	15,3275		59				15,1525		59
16	PAD			152,76		59						
18	PAD			36		253						
	PA											
19	AAD	0,4828	14				25,71	17,42	14	10,71	14,39	14
	AAD + GC	0,5172	15				24	13,52	15	8,67	13,52	15
25	AAD	0,5	18	12,08	1,09	18	11,9	0,91	18	11,81	1,89	18
	EA	0,5	18	12,21	0,76	18	12,15	0,86	18	11,57	0,81	18
29	PAD	0,5	9				0,04	0,15	9	0,02	0,15	9
	SuD	0,5	9				0,01	0,1	9	0,02	0,08	9
31	PA + OPI	0,5	38	1,89	0,758	38	1,78	0,808	38	0	0	38
	PA + XAN	0,5	38	2,89	0,583	38	2,5	0,786	38	0,44	0,511	38

Legend: a- standard deviation; b - sample size; AAD- acetic acid derivative; PAD- propionic acid derivative; PA- p-aminophenol; OPI- opioid; GC- glucocorticoid; SuD- sulfanilamide derivative; XAN- xanthine; EA- enolic acids.

Table 7 Chemical structure with trismus measures
Tablica 7. Kemijska struktura s jačinom trizmusa

Study	Chemical structure			Trismus								
	Type	SD[a]	n[b]	Day 2			Day 3			Day 7		
				Mean	SD[a]	n[b]	Mean	SD[a]	n[b]	Mean	SD[a]	n[b]
1	AAD	0,6667	28	32,285	5,3493	28				40,8	7,5586	28
	PAD	0,3333	14	33,5	7,16	14				41,21	5,19	14
16	PAD			152,76	8,67	59						
29	PAD	0,5	9				36,47	7	9	40,39	6,2	9
	SuD	0,5	9				37,36	7,6	9	40,61	6,4	9

Legend: a- standard deviation; b - sample size; AAD- acetic acid derivative; PAD- propionic acid derivative; SuD- sulfanilamide derivative.

Table 8 Characteristics of the included studies
Tablica 8. Karakteristike uključenih studija

Study	Participants and intervention	Results
Akbulut et al, randomized, double-blind, crossover	42 patients who underwent impacted lower third molar extractions (28 (33.3%) men with a mean age of 20.8 ± 4.1 years) were compared for their anti-inflammatory action and analgesic effect between etodolac, naproxen, and diclofenac.	For acetic acid derivatives: Pain – day 1: 1.21 ± 1.16; day 2: 0.355 ± 0.75; day 3: 0.07 ± 0.37; day 7: 0 ± 0. Swelling – day 2: 8.45 ± 2.9; day 7: 4.435 ± 1.34. Trismus – day 2: 32.28 ± 5.35; day 7: 40.8 ± 7.56. For propionic acid derivatives: Pain – day 1: 1.29 ± 1.26; day 2: 0.71 ± 0.99; day 3: 0.71 ± 1.26; day 7: 0.14 ± 0.53. Swelling – day 2: 9.29 ± 2.52; day 7: 5.05 ± 2.19; Trismus – day 2: 33.5 ± 7.16; day 7: 41.21 ± 5.19.
Atkinson et al, randomized, controlled by placebo, double-blind with multiple doses	159 patients who underwent impacted lower third molar extractions along with others (69 (43.4%) men with a mean age of 23.7 years) were compared for the analgesic effect between paracetamol + ibuprofen and a placebo.	Para-aminophenol + propionic acid derivative pain: day 1 – 1.97 ± 3.20. Placebo pain: day 1 – 6.63 ± 2.83.
Berhouma et al, cross-over	200 participants (60 (30%) men with an average age of 35 ± 9 years) were prescribed either ibuprofen or dexamethasone.	60% rarely prescribe anti-inflammatory medications. Prescription percentages: Ibuprofen – 82% and Dexamethasone – 68%. 65% prescribed NSAIDs to treat postoperative pain. 61% prescribed NSAIDs for a period of time equal to or less than 3 days. Adverse effects included gastric irritation (69%), renal insufficiency (16%), allergic reactions (10%), and liver insufficiency (6.5%).
Bryant et al, cross-over	131 participants who underwent impacted lower third molar extractions (52 (39.7%) men with a mean age of 28.33 years) with a prescription for 400 mg.	Prescribing based on 600 mg of ibuprofen, both pre and postoperatively, along with clear written instructions, resulted in a significant reduction in postoperative pain.
Camargo et al, cross-over	94 participants who underwent third molar extractions (mean age 32.68 ± 7.97 years) were prescribed NSAIDs.	Nimesulide, when administered before patients experienced postoperative pain, was more effective than other NSAIDs in reducing pain severity, delaying the peak intensity of pain, providing pain relief, and prolonging the duration of analgesic effect.
Chethan et al, controlled, randomized and double-blind	40 patients who underwent lower third molar extractions (18-25 years) were prescribed 10 mg of ketorolac and 50 mg of tramadol.	For acetic acid derivatives: Pain – day 1: 4.3. Opioids pain: day 1: 2.2. Compared to ketorolac, tramadol is a more effective analgesic for post-extraction pain relief, with a longer duration of action and fewer associated side effects.
Cooper et al, controlled by placebo, randomized and double-blind	387 patients who underwent lower third molar extractions (191 (49.4%) men with a mean age of 19 ± 2.8 years) were prescribed ibuprofen, naproxen, or a placebo.	For propionic acid derivatives: Pain – day 1: 6.6 ± 5.06. Analgesic efficacy is significantly greater with naproxen 440 mg than with ibuprofen 400 mg in dental post-surgical pain. Although NSAIDs have similar analgesic efficacy in the first 6-7 hours and a similar maximum level of analgesia, pain relief was sustained for a longer period with naproxen.
Eroglu et al, randomized and double-blind	36 patients who underwent impacted lower third molar extractions (13 (36.1%) men with a mean age of 21.83 years) were compared for postoperative inflammation between paracetamol, methylprednisolone + paracetamol, and dexketoprofen trometamol.	For para-aminophenol swelling: day 2 – 3.73 ± 4.81. For propionic acid derivatives swelling: day 2 – 4.58 ± 2.33. For glucocorticoid and para-aminophenol swelling: day 2 – 2.34 ± 2.1. The combination of preoperative methylprednisolone and postoperative paracetamol was clinically effective in controlling swelling without side effects.
Gopalraju et al, controlled and randomized	40 patients who underwent lower third molar extractions (25 (62.5%) men with a mean age of 25.7 years) were prescribed ketorolac or tramadol.	For acetic acid derivatives: Pain – day 1: 3.29 ± 8.18. Opioids pain: day 1: 5.46 ± 7.1. Preoperative IV ketorolac intake has advantages in terms of delaying the onset of postoperative pain and increasing the pain threshold compared to IV tramadol.
Gorecki et al, controlled by placebo, randomized and double-blind	75 patients who underwent lower third molar extractions (28 (37.3%) men with a mean age of 28.6 years) were compared for four different doses of hydroxypropyl beta-cyclodextrin diclofenac (5, 12.5, 25, and 50 mg) or a placebo.	For acetic acid derivatives: Pain – day 1: 2.76 ± 1.96. Swelling – day 2: 15.3. Trismus – day 2: 15.15. Furthermore, low doses (5 mg) are as effective as higher doses for postoperative pain, swelling, and trismus.
Hong et al, retrospective and cross-over	106 participants who underwent third molar extractions under general anesthesia (23 (21.7%) men with a mean age of 38.7 years).	A significant proportion of the prescriptions for Dental General Anesthesia (DGA) were driven by patient request rather than clinical necessity.
Isiordia-Espinoza et al, parallel, controlled by placebo, randomized and double-blind	30 patients who underwent impacted lower third molar extractions (11 (36.7%) men with a mean age of 32.5 years) were compared for analgesic efficacy between 10 mg of ketorolac or 50 mg of tramadol.	For acetic acid derivatives: Pain – day 1: 0.1. Opioids pain: day 1: 7.34. The administration of 10 mg of oral ketorolac provided superior analgesic effects compared to 50 mg of tramadol when administered before mandibular third molar surgery.

Kellstein et al, controlled by placebo, randomized, parallel and double-blind	394 patients (195 (49.5%) men with a mean age of 18.12 years) who underwent the extraction of at least 2 impacted or partially impacted third molars were prescribed ibuprofen, three different combinations of ibuprofen + paracetamol or a placebo.	Propionic acid derivatives pain: day 1 – 7.9. Para-aminophenol + propionic acid derivatives pain: day 1 – 7.93. Each of the ibuprofen + paracetamol medication combinations had a faster onset of action and comparable analgesic efficacy to 400 mg of ibuprofen.
Kofina et al, restrospective, cross-over	75 participants who underwent dental extractions (36 (48%) men with an average age of 51.7 ± 2.3 years).	Postoperative emergency calls are rare and not related to the operator's experience, generally triggered by pain and rarely leading to referrals to the hospital emergency service.
Kumar et al, transversal	301 participants who underwent dental extractions (142 (47.2%) men with an average age of 48.28 years) to investigate the relationship between amplified emotional components and postoperative pain.	Post-extraction pain is a multifaceted condition in which pain expectations, pre-operative anxiety, depression, and treatment outcome expectations should be assessed before the extraction procedure.
Le et al, prospective, cross-over	59 participants who underwent impacted lower third molar extractions (27 (45.8%) men with an average age of 22.12 ± 2.63 years) to evaluate the association between pre-operative anxiety and the prescription of 400 mg of ibuprofen with the postoperative condition.	Propionic acid derivatives swelling/trismus: day 2 – 152.76 ± 8.67. The higher an individual's anxiety, the more severe the swelling and trismus. Additionally, the extent of surgery was found to be a significant predictor of postoperative reactions.
Mangalgi et al, randomized	40 participants who underwent impacted lower third molar extractions (average age of 24.6 years) were compared for analgesic effects between ketorolac and tramadol.	Acetic acid derivatives pain: day 1 – 2.305. Opioids pain: day 1 – 2.785. Ketorolac was superior to tramadol in terms of pain relief, total postoperative analgesic consumption, pain intensity values, and overall patient assessment.
Mei et al, retrospective, cross-over	330 participants who underwent simple or complex oral surgery situations (average age of 47.7 ± 13.3 years) were prescribed ibuprofen or paracetamol.	Propionic acid derivatives swelling: day 2 – 36. Most patients experienced either no pain or moderate pain, depending on the complexity of the surgical procedure. The extent of surgery and the amount of anesthesia used were associated with moderate to severe post-surgical pain.
Meta et al, duplo-cego, controlled and randomized	29 patients who underwent implant surgery (10 (34.5%) men with an average age of 65.42 years) were prescribed ketorolac or ketorolac + betamethasone.	Acetic acid derivatives pain: day 3 – 1.71 ± 1.49; day 7 – 0.57 ± 0.76; swelling: day 3 – 25.71 ± 17.42; day 7 – 10.71 ± 14.39. Acetic acid derivatives and glucocorticoid pain: day 3 – 2.47 ± 2.1; day 7 – 1.13 ± 2.26; swelling: day 3 – 24 ± 13.52; day 7 – 8.67 ± 13.52. Therefore, there is no significant difference in the use of ketorolac + betamethasone and isolated ketorolac for controlling postoperative pain and swelling.
Mishra et al, prospective, controlled by placebo, randomized and double-blind	74 patients who underwent third molar extractions (36 (48.6%) men with an average age of 31.57 years) were prescribed ketorolac or tramadol.	Acetic acid derivatives pain: day 1 – 2.884. Opioids pain: day 1 – 2.132. Postoperative tramadol administration is equally effective as traditional NSAIDs in relieving pain in the first 6 hours after dental extraction.
Mishriky et al, retrospective, cross-over	113 participants who completed a questionnaire (37 (32.7%) men with an average age of 35.62 years) about the availability of NSAIDs in Australian pharmacies.	Paracetamol was the preferred medication for fever, mild headaches, and mild to moderate pain. The combination of paracetamol and ibuprofen was preferred only for more severe cases. Aspirin was favored for mild to moderate migraines. The prescription of diclofenac increased as the severity of the condition increased.
Monisha et al, retrospective, cross-over	100 participants who underwent endodontic treatment and were prescribed diclofenac, ibuprofen, or paracetamol + codeine.	Aceclofenac is effective in treating postoperative pain. Paracetamol is the safest among NSAIDs for clinical conditions such as coagulation problems, gastric irritation, chronic kidney disease, and during pregnancy.
Moura et al, retrospective, cross-over	92 dental students from the 4th to the 10th semester (25 (27.1%) men with an average age of 22 ± 1.54 years) self-evaluated their knowledge of drug prescription and filled out a clinical case for paracetamol medication after dental extraction.	The quality of prescriptions improved between 2nd-year students (2.0) and 4th-year students (3.2); 4th and 5th-year students (3.6) had similar performance. Lack of information about pharmacological treatment, side effects, and administration route were the main deficiencies observed.
Oliveira et al, randomized	22 patients who underwent lower third molar extraction (15 (68.2%) men with an average age of 23.05 ± 3.78 years) were prescribed 4mg of dexamethasone.	The administration of dexamethasone reduced the average consumption of analgesic medication by 5 times. The facial swelling on the treated side was less compared to the control side after 72 hours of surgery. No significant difference in trismus was found.
Orozco-Solís et al, randomized and double-blind	36 patients who underwent partially impacted lower third molar extraction (18 (50%) men with an average age of 22.5 years) were prescribed diclofenac or meloxicam.	Acetic acid derivatives swelling: day 2 – 12.08 ± 1.09; day 3: 11.9 ± 0.91; day 7: 11.81 ± 1.89. Enolic acids swelling: day 2 – 12.21 ± 0.76; day 3: 12.15 ± 0.86; day 7: 11.57 ± 0.81. Therefore, preoperative meloxicam provided better postoperative analgesia and trismus control compared to diclofenac.

Parirokh et al, randomized, prospective	58 patients who underwent endodontic treatment (25 (43.1%) men with an average age of 31.41 ± 10.72 years) were prescribed ibuprofen 400mg either in case of pain or at regular intervals of 6/6 hours up to 48 hours.	Taking medication at regular intervals increased the amount of medication compared to taking it only when in pain.
Passi et al, randomized and double-blind	100 patients who underwent partially impacted lower third molar extraction (64 (64%) men with an average age of 32 years) were prescribed 10mg of ketorolac or 50mg of tramadol.	Acetic acid derivatives pain: day 1 – 2.12. Opioids pain: day 1 – 2.42. Acute pain relief was observed within 30 minutes, with a minimum VAS scale score of 2.68 for ketorolac, lasting for 4-5 hours. The minimum pain intensity was 1.65, and the duration of analgesia was 8-10 hours for tramadol. Nausea/vomiting (8%) and drowsiness/sedation (6%) were more frequent with tramadol, while pain/gastric acidity (8%) was more common in the ketorolac group.
Pathi et al, randomized and triple-blind	200 patients who underwent third molar extraction (63 (31.5%) men with an average age of 26 years) were prescribed ketorolac or tramadol.	Acetic acid derivatives pain: day 1 – 3.36 ± 6.98. Opioids pain: day 1 – 5.32 ± 4.49. Ketorolac showed lower pain intensity, longer duration of action, lower consumption of postoperative analgesics, and a better overall assessment compared to tramadol.
Pouchain et al, prospective, randomized and double-blind	18 participants who underwent lower third molar extraction (2 (11.1%) men with an average age of 19 ± 4.4 years) were prescribed ketoprofen or nimesulide.	Propionic acid derivatives pain: day 1 – 1.67 ± 2.249; day 2: 1.61 ± 2.547; day 3: 0.94 ± 1.798; day 7: 0.11 ± 0.4714. Swelling: day 3: 0.04 ± 0.15; day 7: 0.02 ± 0.15. Trismus: day 3: 36.47 ± 7; day 7: 40.39 ± 6.2. Sulfonamide derivatives pain: day 1 – 1.28 ± 2.191; day 2: 1.44 ± 2.79; day 3: 0.89 ± 1.937; day 7: 0.22 ± 0.65. Swelling: day 3: 0.01 ± 0.1; day 7: 0.02 ± 0.08. Trismus: day 3: 37.36 ± 7.6; day 7: 40.61 ± 6.4. Therefore, taking ketoprofen and nimesulide provided good control of pain, swelling and trismus.
Rajaraman et al, retrospective, cross-over	100 participants who underwent implant surgery.	96% of dentists prescribe NSAIDs for analgesic purposes after implant placement. 86% prescribe oral NSAIDs twice a day (71%) for nearly a week (60%). 66% prescribe combined analgesics. Steroid combination prescriptions were made by 47%.
Samieirad et al, randomized and triple-blind	76 patients who underwent implant surgery (38 (50%) men with an average age of 41.5 ± 5.3 years) were prescribed a combination of paracetamol with codeine or caffeine.	Para-aminophenol and opioid analgesic pain: day 1: 2.39 ± 1.04; day 2: 0.78 ± 1.166; day 3: 0.28 ± 0.575; day 7: 0 ± 0. Swelling: day 2: 1.89 ± 0.758; day 3: 1.78 ± 0.808; day 7: 0 ± 0. Para-aminophenol and xanthine pain: day 1: 2.94 ± 0.735; day 2: 0.94 ± 0.416; day 3: 0.67 ± 0.686; day 7: 0.17 ± 0.383. Therefore, analgesics with caffeine are effective in reducing postoperative pain and swelling.
Sengupta et al, based on population	1615 participants prescribed etoricoxib (674 (41.7%) men with an average age of 48.41 years) compared in different European populations.	The use of etoricoxib for dental pain was low (1615 prescriptions: Finland, 907; Sweden, 359; Norway, 337; Denmark, 12). 70% of the prescriptions were not associated with a dental procedure. Furthermore, 58%, 55%, 10%, and 58% of the prescriptions in Denmark, Finland, Sweden, and Norway, respectively, were for doses higher than 90mg/day.
Shenoi et al, randomized and double-blind	39 patients who underwent impacted lower third molar extraction (19 (48.7%) men with an average age of 33.2 ± 3.3 years) were prescribed diclofenac + paracetamol.	Verbal instructions are inadequate due to difficulties in retention. Therefore, a pictorial way of providing postoperative instructions increases information retention, significantly improving pain relief without increasing the use of analgesics.
Singh et al, prospective, randomized and double-blind	57 patients who underwent lower third molar extraction (33 (57.9%) men and an age equal to or greater than 18 years) were prescribed 10 mg of ketorolac, 50 mg of tramadol, or diclofenac.	Acetic acid derivatives pain: day 1 – 7.39 ± 2.06; day 3: 4.82 ± 1.4; day 7: 6.7 ± 1.75. Opioids pain: day 1 – 10.08 ± 4.73; day 3: 5.21 ± 1.74; day 7: 6.8 ± 1.97. After 7 days, tramadol and ketorolac showed similarities in suppressing the expression of IL-6, which was lower compared to the diclofenac group.
Velasquez et al, randomized and double-blind	40 patients who underwent impacted lower third molar extraction (16 (40%) men with an average age of 35.5 years) were prescribed ketoprofen or diclofenac.	The duration of analgesia was longer in the ketoprofen group than in the diclofenac group. Fewer patients in the ketoprofen group needed the first rescue analgesic after 6 hours. Patients who received ketoprofen had lower pain intensity compared to those who received diclofenac.
Zadsirjan et al, randomized	80 patients who underwent endodontic treatment (40 (50%) men with an average age of 35.1 years) were recommended to take ibuprofen or ibuprofen lysine at various dosages (regular intervals or "as needed").	Propionic acid derivatives pain: day 1 – 1.54 ± 1.16; day 2: 1 ± 0.99; day 3: 0.41 ± 0.60. There was no significant difference in pain intensity between ibuprofen and ibuprofen lysine, nor in the degree of pain between the on-demand and regular dosing groups. Patients who took medication on-demand required a lower number of medications.

Table 9 Active substances prescribed
Tablica 9. Propisane djelatne tvari

Active substance	n[a] of active substance	Dosage	n[a] of dose
Ketoprofen	29	100mg	29
Ketorolac	285	10mg	120
		20mg	25
		30mg	140
Ketorolac + Betamethasone	15	10mg + 2 mL	15
Ibuprofen	938	400mg	530
		600mg	47
		200mg	166
		Dosage not mentioned	195
Dexamethasone	158	4mg	22
		Dosage not mentioned	136
Dexketoprofen trometamol	12	12,5mg	12
Diclofenac	182	50mg	35
		75mg	20
		100mg	18
		Dosage not mentioned	50
		5mg/1mL	15
		12.5mg/1mL	15
		25mg/1mL	15
		50mg/1mL	14
Diclofenac + Acetaminophen	39	Dosage not mentioned	39
Etodolac	14	200mg	14
Meloxicam	18	15mg	18
Methylprednisolone + Acetaminophen	12	20mg + 300mg	12
Naproxen	180	275mg	14
		440mg	166
Nimesulide	9	100mg	9
Acetaminophen	86	500mg	74
		300mg	12
Acetaminophen + caffeine	38	20mg	38
Acetaminophen + codeine	47	300mg + 20mg	38
		Dosage not mentioned	9
Ibuprofen + Acetaminophen	382	300mg + 1000mg	30
		300mg + 500mg	89
		250mg + 500mg	93
		200mg + 500mg	90
		150mg + 500mg	34
		75mg + 250mg	46
Tramadol	266	100mg	25
		50mg	241

Legend: a- sample size; mg – milligrams; mL – milliliters

Table 10 JBI checklist and GRADE
Tablica 10 JBI kontrolni popis i OCJENA

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Risk of bias	GRADE
1	yes	yes	unclear	yes	yes	yes	yes	yes	yes	low	moderate
2	yes	yes	yes	yes	yes	yes	yes	yes	yes	low	moderate
3	yes	yes	unclear	yes	yes	NA	NA	yes	unclear	moderate	moderate
4	yes	yes	no	yes	yes	yes	no	no	unclear	high	low
5	yes	no	no	yes	yes	unclear	unclear	yes	no	high	very low
6	unclear	yes	yes	yes	yes	yes	yes	yes	NA	low	high
7	yes	yes	yes	yes	yes	yes	yes	yes	NA	low	moderate
8	yes	NA	unclear	yes	yes	yes	unclear	yes	NA	moderate	low
9	yes	yes	unclear	yes	yes	yes	yes	yes	NA	low	moderate
10	yes	NA	yes	yes	yes	yes	yes	yes	NA	moderate	moderate
11	yes	yes	no	yes	yes	yes	yes	yes	no	moderate	moderate
12	yes	yes	unclear	yes	yes	yes	yes	yes	NA	moderate	moderate
13	yes	yes	unclear	yes	yes	NA	NA	yes	unclear	moderate	low
14	unclear	yes	unclear	yes	yes	unclear	unclear	yes	unclear	high	low
15	yes	yes	yes	yes	yes	NA	NA	yes	NA	moderate	low
16	yes	yes	yes	yes	yes	yes	yes	yes	yes	low	low
17	yes	yes	unclear	yes	yes	yes	yes	yes	yes	moderate	moderate
18	unclear	yes	yes	yes	yes	yes	yes	yes	NA	moderate	moderate
19	yes	yes	unclear	yes	yes	yes	yes	yes	yes	low	high
20	yes	unclear	no	no	yes	yes	unclear	yes	unclear	moderate	low
21	yes	NA	yes	yes	yes	yes	yes	yes	NA	low	high
22	yes	yes	unclear	yes	yes	yes	yes	yes	yes	moderate	low
23	yes	yes	unclear	yes	yes	yes	yes	yes	unclear	moderate	moderate
24	yes	yes	yes	yes	yes	yes	yes	yes	yes	low	moderate
25	yes	yes	yes	yes	yes	yes	yes	yes	NA	low	moderate
26	yes	yes	yes	yes	yes	yes	yes	yes	NA	low	moderate
27	unclear	yes	yes	yes	yes	yes	yes	yes	NA	moderate	low
28	yes	yes	yes	yes	yes	unclear	unclear	yes	NA	moderate	low
29	yes	yes	yes	yes	yes	yes	yes	yes	unclear	low	moderate
30	unclear	yes	unclear	yes	yes	yes	yes	yes	unclear	moderate	moderate
31	unclear	yes	yes	yes	yes	yes	yes	yes	yes	low	high
32	yes	yes	yes	yes	yes	unclear	yes	yes	unclear	moderate	low
33	yes	yes	yes	yes	yes	yes	yes	yes	yes	low	moderate
34	yes	yes	yes	yes	unclear	yes	yes	unclear	NA	moderate	moderate
35	yes	yes	yes	yes	yes	yes	yes	yes	NA	low	moderate
36	yes	yes	unclear	yes	yes	yes	yes	unclear	NA	moderate	moderate

Legend: NA - Not Applicable
Q1. Was the sample frame appropriate to address the target population?
Q2. Were study participants recruited in an appropriate way?
Q3. Was the sample size adequate?
Q4. Were the study subjects and setting described in detail?
Q5. Was data analysis conducted with sufficient coverage of the identified sample?
Q6. Were valid methods used for the identification of the condition?
Q7. Was the condition measured in a standard, reliable way for all participants?
Q8. Was there appropriate statistical analysis?
Q9. Was the response rate adequate, and if not, was the low response rate managed appropriately?
References: 12, 13

Sažetak

Svrha istraživanja: Ispitivalo se postoje li razlike u ublažavanju akutnih bolova poslije oralno-kirurških zahvata u bolničkome okružju i u odnosu prema različitim režimima uzimanja lijekova. **Materijali i metode:** Sustavno pretraživanje literature provedeno je između 2013. i 2023., a uključene su baze podataka PUBMED, Cochrane i Scopus kako bi se identificirala klinička istraživanja u kojima se ispituje propisivanje nesteroidnih (NSAID) protuupalnih lijekova prije ili poslije oralno-kirurških zahvata. Metaanaliza s metaregresijskim modelom korištena je na primarnim i sekundarnim ishodima, kao što su bol, oteklina i trizmus. **Rezultati:** Uključeno je 36 radova – 6 retrospektivnih i 30 prospektivnih istraživanja, s većim udjelom žena nego muškaraca, u omjeru 1,34 : 1 i prosječne dobi od 31,9 godina. Lijekovi srednjeg trajanja pokazali su niže vrijednosti kad je riječ o bolovima i oteklinama. Što se tiče parametara bol i oteklina, derivatima propionske kiseline i derivatima octene kiseline postignute su niže vrijednosti. **Zaključci:** Kvaliteta dokaza bila je niske do vrlo niske sigurnosti. Metaanaliza sugerira da se postoperativni bolovi, otekline i trizmusi poslije oralno-kirurških zahvata mogu učinkovito liječiti sljedećim lijekovima: NSAID-ima srednjeg trajanja, derivatima propionske kiseline za smanjenje razine bolova i derivatima octene kiseline za smanjenje oteklina i ibuprofenom od 400 mg svakih 8 sati tijekom tri dana ili manje. **Kliničko značenje:** Protuupalni lijekovi i analgetici propisuju se za sprječavanje ili liječenje zubobolje. Ibuprofen od 400 mg bio je najčešće propisivani lijek poslije ili prije oralno-kirurških zahvata. No dokazi su neizravni i treba ih tumačiti s oprezom.

Zaprimljen: 9. lipnja 2024.
Prihvaćen: 2. rujna 2024.

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MeSH pojmovi: akutna bol; analgetici; poslijeoperativna bol; protuupalna sredstva
Autorske ključne riječi: protuupalni lijekovi, analgetici, oralna kirurgija, postoperativni bolovi

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