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Does Ketorolac reduce the intensity of postoperative pain after impacted third molars surgery in adults compared to the use of tramadol? A systematic review and meta-analysis

O cetorolaco reduz a intensidade da dor pós-operatória após cirurgia de terceiros molares retidos em adultos em comparação com o uso de tramadol? Uma revisão sistemática e meta-análise

¿Ketorolac reduce la intensidad del dolor posoperatorio después de la cirugía de terceros molares impactados en adultos en comparación con el uso de tramadol? Una revisión sistemática y un metanálisis

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Abstract

This systematic review and meta-analysis evaluated if ketorolac reduces the intensity of postoperative pain after impacted third molars surgery in adults compared to the use of tramadol. A comprehensive search was performed in the MEDLINE/PubMed, Scopus, Web of Science, LILACS, BBO, EMBASE, Cochrane Library, SIGLE and grey literature, in accordance with the PRISMA guidelines. The quality of the evidence was evaluated using the GRADE approach. Meta-analysis was performed on studies considered at low risk of bias. After duplicates removal, 4526 articles were identified, but only nine studies were included for qualitative analysis. After updating in 2021, four studies were added, totaling 13 studies included for qualitative analysis. Only two studies, classified at "low" risk of bias, were included in the meta-analysis of the primary outcome. The difference in means for pain intensity (moderate quality of evidence due to imprecision) was – 0.27 (95% CI = – 0.82 to 0.28; p = 0.34). Data from adverse effects (low quality of evidence due to very serious issues in imprecision) was just reported in one study at "low" risk of bias. Data was not heterogeneous (Chi2 test p = 0.14; I2 = 55%). It was not possible to evaluate any secondary outcomes (time to first rescue analgesic drug in h, total amount of analgesics consumed and adverse effects) due to low number of studies included. There is a lack of strong evidence to assure the superiority of ketorolac or tramadol in reducing the postoperative pain after extraction of impacted third molars.

Keywords: Ketorolac; Tramadol; Molar third; Surgery oral; Meta-analysis.

Resumo
Esta revisão sistemática e metanálise avaliou se o cetorolaco reduz a intensidade da dor pós-operatória após cirurgia de terceiros molares retidos em adultos em comparação ao uso de tramadol. Foi realizada uma busca abrangente no MEDLINE/PubMed, Scopus, Web of Science, LILACS, BBO, EMBASE, Biblioteca Cochrane, SIGLE e literatura cinza, de acordo com as diretrizes do PRISMA. A qualidade da evidência foi avaliada usando a abordagem GRADE. Meta-análise foi realizada em estudos considerados de baixo risco de viés. Após retirada das duplicatas, foram identificados 4.526 artigos, destes nove estudos foram incluídos para análise qualitativa. Após atualização em 2021, foram adicionados quatro estudos, totalizando 13 estudos incluídos para análise qualitativa. Apenas dois estudos, classificados como "baixo" risco de viés, foram incluídos na meta-análise do desfecho primário. A diferença nas médias para a intensidade da dor (qualidade moderada da evidência devido à imprecisão) foi - 0,27 (IC 95% = - 0,82 a 0,28; p = 0,34). Os dados de efeitos adversos (evidência de baixa qualidade devido a questões muito sérias na imprecisão) foram relatados em um estudo com risco "baixo" de viés. Os dados não eram heterogêneos (teste do Chi2 p = 0,14; I2 = 55%). Não foi possível avaliar nenhum desfecho secundário (tempo para o primeiro analgésico de resgate em horas, quantidade total de analgésicos consumidos e efeitos adversos) devido ao baixo número de estudos incluídos. Há uma forte falta de evidências para assegurar a superioridade do cetorolaco ou tramadol na redução da dor pós-operatória após a exodontia de terceiros molares retidos.
Palavras-chave: Cetorolaco; Tramadol; Terceiro molar; Cirurgia bucal; Metanálise.

Resumen
Esta revisión sistemática y metanálisis evaluó si el ketorolaco reduce la intensidad del dolor posoperatorio después de la cirugía de terceros molares impactados en adultos en comparación con el uso de tramadol. Se realizó una búsqueda integral (actualizada en julio de 2018 y enero de 2021) en MEDLINE/PubMed, Scopus, Web of Science, LILACS, BBO, EMBASE, Cochrane Library, SIGLE y literatura gris, de acuerdo con las guías PRISMA. La calidad de la evidencia se evaluó mediante el enfoque GRADE. Se realizó un metanálisis en estudios considerados de bajo riesgo de sesgo. Después de eliminar los duplicados, se identificaron 4526 artículos, pero solo se incluyeron nueve estudios para el análisis cualitativo. Después de la actualización en 2021, se agregaron cuatro estudios, totalizando 13 estudios incluidos para análisis cualitativo. En el metanálisis del resultado primario sólo se incluyeron dos estudios, clasificados como de "bajo" riesgo de sesgo. La diferencia en las medias para la intensidad del dolor (evidencia de calidad moderada debido a la imprecisión) fue -0,27 (IC del 95% = -0,82 a 0,28; p=0,34). Los datos de los efectos adversos (evidencia de baja calidad debido a problemas muy graves en la imprecisión) se informaron en un estudio con un riesgo de sesgo "bajo". Los datos no fueron heterogéneos (prueba de Chi2 p=0,14; I2=55%). No fue posible evaluar ningún resultado secundario (tiempo hasta el primer fármaco analgésico de rescate en horas, cantidad total de analgésicos consumidos y efectos adversos) debido al bajo número de estudios incluidos. Existe una falta de evidencia sólida que asegure la superioridad del ketorolaco o tramadol en la reducción del dolor posoperatorio después de la extracción de terceros molares impactados.
Palabras clave: Ketorolaco; Tramadol; Tercer molar; Cirugía bucal; Metaanálisis.

1. Introduction

A Pain is a major postoperative symptom after many dental procedures, particularly extraction of impacted third molars, which is the most frequent surgical intervention in dentistry (Isiordia-Espinoza, de Jesús Pozos-Guillén, & Aragon-Martinez, 2014). The intensity of the pain after extraction of third molars is usually moderate to severe. Pain occurs within the first 24 h after surgery, peaking between 6 h and 8 h when conventional anesthesia is performed (Isiordia-Espinoza, Pozos-Guillén, Martínez-Rider, Herrera-Abarca, & Pérez-Urizar, 2011; Seymour, Meechan, & Blair, 1985).

After the injury to the tissues, a cascade of inflammatory responses is initiated, and a sequence of physiological events takes place. The increase in vascular permeability and local vascularity (Laureano Filho, Maurette, Allais, Cotinho, & Fernandes, 2008; Moraschini, Hidalgo, & Porto Barboza, 2016), as well as the release of chemical mediators (prostaglandins, leukotrienes, bradykinin, serotonin and histamine) (Dray, 1997), activates and sensitizes nerve fiber receptors (Loeser & Melzack, 1999), leading to an undesirable risk of pain.

This situation can be managed with preemptive analgesia (Isiordia-Espinoza et al., 2011; Ong & Seymour, 2003) along with the use of postoperative drug therapy for inflammation control. There are numerous pharmacological options available for such an aim, including local anesthetics, nonsteroidal anti-inflammatory drugs (NSAIDs) and some opioids

(Esteller-Martínez, Paredes-García, Valmaseda-Castellón, Berini-Aytés, & Gay-Escoda, 2004; Isiordia-Espinoza, Pozos-Guillen, Martinez-Rider, & Perez-Urizar, 2016; López Carriches, Martínez González, & Donado Rodríguez, 2006; Singh et al., 2015).

Usually, dental-extraction-related pain is treated over 2 or 3 days with NSAIDs, such as diclofenac, dexketoprofen, meloxicam and ibuprofen (Bailey, Worthington, & Coulthard, 2014; Christensen et al., 2011; Eroglu, Ataoglu, Yildirim, & Kiresi, 2015; Isiordia-Espinoza, Sánchez-Prieto, Tobías-Azúa, & Reyes-García, 2012), and non-opioid analgesic drugs, such as paracetamol (acetaminophen), acetylsalicylic acid and dipyrone (Daniels, Reader, Berry, & Goulder, 2009; Happonen, Oksala, & Ylipaavalniemi, 1987; Noronha et al., 2009). Of the available NSAIDs, ketorolac has shown significant analgesic potency after oral and parenteral administration for treatment of mild to severe pain after a variety of surgical procedures (Barden, Edwards, McQuay, Wiffen, & Moore, 2004; Catapano, 1996; Mansuri, Mujeeb, Hussain, & Hussain, 2014).

The opioids are another option that can be used in multiple acute pain conditions when non-opioid analgesics fail to control pain. Among them, tramadol—a synthetic analogue of codeine—has been reported to show efficacy in some clinical trials for control of moderate to severe postsurgical pain (Eggers & Power, 1995; Isiordia-Espinoza et al., 2016; Scott & Perry, 2000; Tenglikar, 2014).

A large number of randomized clinical trials compared the analgesic efficacy of ketorolac and tramadol after third-molar surgery (Chethan, Ramamuthy, Patil, & Reddy, 2015; Dayashankara Rao et al., 2010; Gopalraju, Lalitha, Prasad, & Ranganath, 2014; Isiordia-Espinoza et al., 2016; Mishra & Khan, 2012; Ong & Tan, 2004; Shah, Arun Kumar, Rai, & Rajesh Kumar, 2013; Shaik, Kumar, Mobina, Satyanarayana, & Sunitha, 2010; Tenglikar, 2014). There are studies that reported the superiority of ketorolac in controlling postoperative pain (Gopalraju et al., 2014; Isiordia-Espinoza et al., 2016; Ong & Tan, 2004; Shah et al., 2013), while others showed that tramadol performed better (Chethan et al., 2015; Dayashankara Rao et al., 2010; Shaik et al., 2010; Tenglikar, 2014); another study described no differences between them (Mishra & Khan, 2012). These conflicting findings prevent clinicians from drawing a conclusion about which drug is more effective in controlling pain with fewer side effects.

Therefore, the aim of this systematic review and meta-analysis was to answer the following PICO question (P=Population, I=Intervention, C=Comparison, O=Outcome): Is ketorolac more effective than tramadol in reducing the intensity of postoperative pain after surgery of impacted third molars in adults?

2. Methodology

The description of the article followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009).

2.1 Protocol and registration

This study protocol was registered at the International Prospective Register of Systematic Reviews (#CRD42016036410). This study was accomplished from March to December of 2016 and updated July of 2018 and January of 2021.

2.2 Information sources and search strategy

The controlled vocabulary (MeSH terms) and free keywords in the search strategy were defined based on the following PICOS question, reported in the end of the introduction section. For each one of the concepts (population and intervention) medical subheadings (MESH) and free keyword were combined with the Boolean operator “OR” and the two

concepts combined with the Boolean operator "AND".

Pain intensity within the first 24 h was the primary outcome. Time to take the first rescue analgesic drug in hours, total amount of analgesics consumed in mg or in number of capsules and the total number of adverse effects were the secondary outcomes.

The electronic databases MEDLINE via PubMed, Scopus, Web of Science, Latin American and Caribbean Health Sciences Literature database (LILACS), Brazilian Library in Dentistry (BBO), EMBASE and Cochrane Library (Table 1) were searched for the primary studies. Their reference lists were hand searched for additional publications. The related articles links of each primary study in the PubMed database were another source of search. We did not implement restrictions on publication date or languages.

Table 1. Electronic database and search strategy.

Pubmed (03/June/2016; updated in 03/July/2018 and 15/Jan/2021)		
#1(Molar, Third[MeSH Terms]) OR Tooth, Unerupted[MeSH Terms]) OR Tooth, Impacted[MeSH Terms]) OR Tooth Extraction[MeSH Terms]) OR "Third Molar"[Title/Abstract]) OR "Third Molars"[Title/Abstract]) OR "Wisdom Tooth"[Title/Abstract]) OR "Wisdom Teeth"[Title/Abstract]) OR "Unerupted Tooth"[Title/Abstract]) OR "Unerupted Teeth"[Title/Abstract]) OR "Impacted tooth"[Title/Abstract]) OR "Impacted teeth"[Title/Abstract]) OR "Tooth Extraction"[Title/Abstract]	**#2** (Ketorolac[MeSH Terms]) OR Ketorolac Tromethamine[MeSH Terms]) OR Anti-Inflammatory Agents, Non-steroidal[MeSH Terms]) OR Cyclooxygenase Inhibitors[MeSH Terms]) OR Cyclooxygenase 2 Inhibitors[MeSH Terms]) OR Cyclooxygenase 2[MeSH Terms]) OR "Non-Steroidal Anti-inflammatory Agents"[Title/Abstract]) OR "Non Steroidal Anti-inflammatory Agents"[Title/Abstract]) OR "Nonsteroidal Anti Inflammatory Agents"[Title/Abstract]) OR "non-steroidal anti-inflammatory drugs"[Title/Abstract]) OR NSAIDs[Title/Abstract]) OR Preoperative[Title/Abstract]) OR Postoperative[Title/Abstract]) OR Pre-emptive[Title/Abstract]) OR Preemptive[Title/Abstract]) OR "Postoperative Analgesia"[Title/Abstract]) OR Ketorolac[Title/Abstract]) OR "Cyclooxygenase Inhibitors"[Title/Abstract]) OR "Cyclooxygenase 2 Inhibitors"[Title/Abstract]) OR "Cyclooxygenase 2"[Title/Abstract] OR "Cycloxygenase Inhibitors"[Title/Abstract] OR "Cycloxygenase 2"[Title/Abstract] OR "Cox 2"[Title/Abstract] OR (Tramadol[MeSH Terms]) OR Analgesics, opioid[MeSH Terms]) OR Analgesics[MeSH Terms]) OR Narcotics[MeSH Terms]) OR "Analgesic drug"[Title/Abstract]) OR Analgesic[Title/Abstract]) OR Narcotic[Title/Abstract]) OR "opioid combination"[Title/Abstract]) OR "opioids combination"[Title/Abstract]) OR Tramadol[Title/Abstract]	**#3** (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies as topic[mh] OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospective*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh]))
#1 AND #2 AND #3		
Scopus (03/June/2016 – updated in 03/July/2018 and 15/Jan/2021)		
#1 (TITLE-ABS-KEY ("Third Molar*") OR TITLE-ABS-KEY ("Wisdom Tooth") OR TITLE-ABS-KEY ("Unerupted Tooth") OR	**#2** (TITLE-ABS-KEY ("Non-Steroidal Anti-inflammatory Agents") OR TITLE-ABS-KEY ("non-steroidal anti-inflammatory drugs") OR TITLE-ABS-KEY (nsaids) OR TITLE-ABS-KEY (preoperative) OR TITLE-ABS-KEY (postoperative) OR TITLE-ABS-KEY (pre-emptive) OR TITLE-ABS-KEY ("Ketorolac Tromethamine") OR TITLE-ABS-KEY ("Postoperative Analgesia") OR TITLE-ABS-KEY (ketorolac) OR TITLE-ABS-KEY ("Cyclooxygenase	**#3** (LIMIT-TO (SUBJA REA , "DENT"

TITLE-ABS-KEY ("Impacted tooth") OR TITLE-ABS-KEY ("Tooth Extraction"))	Inhibitors") OR TITLE-ABS-KEY ("Cox 2") nOR TITLE-ABS-KEY ("Cyclooxygenase 2")) OR (TITLE-ABS-KEY ("Analgesic drug") OR TITLE-ABS-KEY (analgesic*) OR TITLE-ABS-KEY (narcotic*) OR TITLE-ABS-KEY ("opioid combination") OR TITLE-ABS-KEY (tramadol) OR TITLE-ABS-KEY ("Analgesic opioid"))	))
#1 AND #2 AND #3		
Web of Science (03/June/2016; updated in 03/July/2018 and 15/Jan/2021)		
#1 TOPIC: ("Third Molar$") OR TOPIC: ("Wisdom Tooth") OR TOPIC: ("Unerupted Tooth") OR TOPIC: ("Impacted tooth") OR TOPIC: ("Tooth Extraction")	**#2** TOPIC: ("Non-Steroidal Anti-inflammatory Agents") OR TOPIC: (Ketorolac Tromethamine) OR TOPIC: (“non-steroidal anti-inflammatory drugs”) OR TOPIC: (NSAIDs) OR TOPIC: (Preoperative) OR TOPIC: (Postoperative) OR TOPIC: (Pre-emptive) OR TOPIC: ("Cox 2") OR TOPIC: (“Postoperative Analgesia”) OR TOPIC: (Ketorolac) OR TOPIC: ("Cyclooxygenase Inhibitors") OR TOPIC: ("Cyclooxygenase 2") OR TOPIC: ("Analgesic drug") OR TOPIC: (Analgesic$) OR TOPIC: (Narcotic$) OR TOPIC: ("opioid* combination") OR TOPIC: (Tramadol)	**#3** Research areas: (Dentistry oral surgery medicine)
#1 AND #2 AND #3		
Lilacs and BBO (03/June/2016; updated in 03/July/2018 and 15/Jan/2021)		
#1 (mh:(Molar, Third)) OR (mh:(Tooth, Unerupted)) OR (mh:(Tooth, Impacted)) OR (mh:(Tooth Extraction)) OR (tw:("Third Molar")) OR (tw:("Tercer molar")) OR (tw:("Terceiro molar")) OR (tw:("Dente serotino")) OR (tw:("Third Molars")) OR (tw:("terceros molares")) OR (tw:("Terceiros molares")) OR (tw:("dentes serotinos")) OR (tw:("Wisdom Tooth")) OR (tw:("muela del juicio")) OR (tw:("Dente do siso")) OR (tw:("dente do juízo")) OR (tw:("Wisdom Teeth")) OR (tw:("muelas del juicio")) OR (tw:("Dentes do juízo")) OR (tw:("dentes do siso")) OR (tw:("Unerupted Tooth")) OR (tw:("Diente no erupcionado")) OR (tw:("Dente não irrompido")) OR (tw:("Unerupted Teeth")) OR (tw:("Dientes no erupcionados")) OR (tw:("Dente não irrompido")) OR (tw:("Unerupted Teeth")) OR (tw:("Dientes no erupcionados")) OR (tw:("Dentes não irrompidos")) OR (tw:("Impacted tooth")) OR (tw:("Diente impactado")) OR	**#2** (mh:(Ketorolac)) OR (mh:(Ketorolac Tromethamine)) OR (mh:(Anti-Inflammatory Agents, Non-steroidal)) OR (mh:(Cyclooxygenase Inhibitors)) OR (mh:(Cyclooxygenase 2 Inhibitors)) OR (mh:(Cyclooxygenase 2)) OR (mh:("Non-Steroidal Anti-inflammatory Agents")) OR (tw:(“Agente Antiinflamatorio no steroidal”)) OR (tw:("Non Steroidal Anti-inflammatory Agents")) OR (tw:(“Agentes antiinfamatorios no esteroidales”)) OR (tw:(“Agente anti-inflamatório não esteroidal”)) OR (tw:(“Agente antiinflamatório não esteroidal”)) OR (tw:("Nonsteroidal Anti Inflammatory Agents")) OR (tw:(“Agentes antiinfamatorios no esteroidales”)) OR (tw:(“Agentes anti-inflamatórios não esteroidais”)) OR (tw:(“Agentes antiinflamatórios não esteroidais”)) OR (tw:(“non-steroidal anti-inflammatory drugs”)) OR (tw:(“Medicamentos antiinflamatorios no esteroidales”)) OR (tw:(“Drogas anti-inflamatória não esteroidal”)) OR (tw:(“Drogas antiinflamatória não esteroidal”)) OR (tw:(NSAIDs)) OR (tw:(AINEs)) OR (tw:(Preoperative)) OR (tw:(Pre-operatorio)) OR (tw:(Pré-operatória)) OR (tw:(Postoperative)) OR (tw:(Pos-operatorio)) OR (tw:(Post-operatorio)) OR (tw:(Posoperatorio)) OR (tw:(postoperatorio)) OR (tw:(Pós-operatória)) OR (tw:(Pre-emptive)) OR (tw:(Preemptive)) OR (tw:(Preemptiva)) OR (tw:(“Postoperative Analgesia”)) OR (tw:(“Analgesia post-operatoria”)) OR (tw:(“Analgesia pós-operatória”)) OR (tw:(Ketorolac)) OR (tw:(ketorolaco)) OR (tw:(Cetorolaco)) OR (tw:("Cyclooxygenase Inhibitors")) OR (tw:(“Inhibidor de ciclooxigenasa”)) OR (tw:(“Inhibidor de cicloxigenasa”)) OR (tw:(“Inibidor de Cicloxigenase”)) OR (tw:(“Inibidor de ciclooxigenase”)) OR (tw:(“Cox 2”)) OR (tw:("Cyclooxygenase 2")) OR (tw:(“Ciclooxigenasa 2”)) OR (tw:(“Cicloxigenasa 2”)) OR (tw:(“Cicloxigenase 2”)) OR (tw:(“ciclooxigenase 2”)) OR (mh:(Tramadol)) OR (mh:(Analgesics, opioid)) OR (mh:(Analgesics)) OR (mh:(Narcotics)) OR	**#3** (instance:" regional") AND (db: ("LILACS " OR "BBO") AND jd:("ODONTOLOGIA")

(tw:("Dente impactado")) OR (tw:("Impacted teeth")) OR (tw:("Dientes impactados")) OR (tw:("Dentes impactados")) OR (tw:("Tooth Extraction")) OR (tw:("Extracción del diente")) OR (tw:("Extracción dental")) OR (tw:("Extração dental"))	(tw:("Analgesic drug")) OR (tw:("Medicamento analgesico")) OR (tw:("Droga analgésica")) OR (tw:(Analgesic)) OR (tw:(analgésico)) OR (tw:(Narcotic)) OR (tw:(narcótico)) OR (tw:("opioid combination")) OR (tw:("Combinación de opioide")) OR (tw:("Combinação de opióide")) OR (tw:("Associação de opióide")) OR (tw:("opioids combination")) OR (tw:("Combinación de opioides")) OR (tw:("Combinações de opióide")) OR (tw:("Associações de opióides")) OR (tw:(Tramadol))	
#1 AND #2 AND #3		
Cochrane Library (03/June/2016; updated in 03/July/2018 and 15/Jan/2021)		
#1 Molar, Third #2 Tooth, Unerupted #3 Tooth, Impacted #4 Tooth Extraction #5 third next molar*:ti,ab,kw (Word variations have been searched) #6 wisdom next t*th:ti,ab,kw (Word variations have been searched) #7 Unerupted next t*th:ti,ab,kw (Word variations have been searched) #8 Impacted next t*th:ti,ab,kw (Word variations have been searched) #9 t*th next extraction:ti,ab,kw (Word variations have been searched) #10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 #11 Ketorolac #12 Ketorolac Tromethamine	#13 Anti-Inflammatory Agents, Non-steroidal #14 Cyclooxygenase Inhibitors #15 Cyclooxygenase 2 Inhibitors #16 Cyclooxygenase 2 #17 "Non-Steroidal Anti-inflammatory Agents":ti,ab,kw (Word variations have been searched) #18 "Non Steroidal Anti-inflammatory Agents":ti,ab,kw (Word variations have been searched) #19 "Nonsteroidal Anti Inflammatory Agents":ti,ab,kw (Word variations have been searched) #20 "non-steroidal anti-inflammatory drugs":ti,ab,kw (Word variations have been searched) #21 NSAIDs:ti,ab,kw (Word variations have been searched) #22 Preoperative:ti,ab,kw (Word variations have been searched) #23 Postoperative:ti,ab,kw (Word variations have been searched) #24 Pre-emptive:ti,ab,kw (Word variations have been searched) #25 Preemptive:ti,ab,kw (Word variations have been searched) #26 "Postoperative Analgesia":ti,ab,kw (Word variations have been searched) #27 Ketorolac:ti,ab,kw (Word variations have	#30 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 #31 Tramadol #32 Analgesics, opioid #33 Analgesics #34 Narcotics #35 Analgesic*:ti,ab,kw (Word variations have been searched) #36 Narcotic*:ti,ab,kw (Word variations have been searched) #37 Opioid* next combination:ti,ab,kw (Word variations have been searched) #38 tramadol:ti,ab,kw (Word variations have been searched) #39 #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 #40 "cox 2":ti,ab,kw (Word variations have been searched) #41 #30 or #40 #42 #39 or #41 #43 #10 and #42	

	been searched) #28 Cycl*xygenase next Inhibitor*:ti,ab,kw (Word variations have been searched) #29 Cycl*xygenase 2:ti,ab,kw (Word variations have been searched)	
Embase (03/June/2016; updated in 03/July/2018 and 15/Jan/2021)		
#1 'molar tooth'/exp OR 'tooth extraction'/exp OR 'tooth disease'/exp OR 'third molar*':ab,ti OR 'wisdom tooth':ab,ti OR 'wisdom teeth':ab,ti OR 'unerupted teeth':ab,ti OR 'unerupted tooth':ab,ti OR 'impacted tooth':ab,ti OR 'impacted teeth':ab,ti OR 'tooth extraction':ab,ti AND [embase]/lim	**#2** 'ketorolac'/exp OR 'ketorolac trometamol'/exp OR 'nonsteroid antiinflammatory agent'/exp OR 'prostaglandin synthase inhibitor'/exp OR 'cyclooxygenase 2 inhibitor'/exp OR 'postoperative analgesia'/exp OR 'postoperative pain'/exp OR 'non-steroidal anti-inflammatory agents':ab,ti OR 'nonsteroidal anti inflammatory agents':ab,ti OR 'non-steroidal anti-inflammatory drugs':ab,ti OR nsaids:ab,ti OR preoperative:ab,ti OR postoperative:ab,ti OR 'pre emptive':ab,ti OR preemptive:ab,ti OR ketorolac:ab,ti OR 'cyclooxygenase inhibitors':ab,ti OR 'cox 2':ab,ti OR 'cyclooxygenase 2':ab,ti AND [embase]/lim OR 'tramadol'/exp OR 'narcotic analgesic agent'/exp OR 'analgesic activity'/exp OR analgesic*:ab,ti OR narcotic*:ab,ti OR 'opioid* combination':ab,ti OR analgesia:ab,ti OR tramadol:ab,ti AND [embase]/lim	**#3** [randomized controlled trial]/lim AND [embase]/lim
#1 AND #2 AND #3		

Source: Authors.

We searched grey literature through the System for Information on Grey Literature in Europe (SIGLE); dissertations and theses were searched using the ProQuest Dissertations and Theses Full Text, Periodicos Capes Theses database and Google Scholar. Trial registries were also searched for unpublished articles: Current Controlled Trials (www.controlled-trials.com), the International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), ClinicalTrials.gov (www.clinicaltrials.gov), Rebec (www.rebec.gov.br) and the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu).

2.3 Eligibility criteria

We included randomized controlled trials that compared ketorolac vs. tramadol for treatment and prevention of postoperative pain after surgery of impacted third molars. Studies with parallel or crossover designs in humans were included.

RCTs were excluded if they (1) evaluated only one of the drugs (ketorolac or tramadol), (2) associated the ketorolac with tramadol for treatment and prevention of postoperative pain or (3) compared ketorolac vs. tramadol for treatment and prevention of postoperative pain for maxillofacial surgery or extraction of all four third molars in a single session.

2.4 Study selection and data collection process

Initially, the articles were selected by title and abstracts. Duplicate articles were removed. Full-text articles were obtained when the title and abstract presented insufficient information to make a clear decision. Subsequently, two reviewers

(L.D.M. and M.R.) classified those that met the inclusion criteria. Each study received a study ID combining the first author and year of publication. Any disagreement between the reviewers over the eligibility of particular studies was resolved through discussion with a third reviewer (A.R.).

Relevant information about the study design, participants, interventions and outcomes was extracted using customized extraction forms. Two reviewers (L.D.M. and M.R.), independently and in duplicate, extracted the data. If there were any disagreements between the reviewers, a third reviewer was consulted (A.R.). When data were not reported in the studies, the authors were contacted by email at least twice to request the missing information.

2.5 Data extraction and management

Two review authors, independently and in duplicate, extracted data using a data extraction form. Any disagreement was discussed, and a third review author was consulted when necessary.

2.6 Risk of bias in individual studies

The quality of the selected trials was assessed using the Cochrane Collaboration tool for assessing the risk of bias. For each aspect of the quality assessment, the risk of bias was scored following recommendations of the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (http://handbook.cochrane.org).

The assessment criteria included six items: sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting and other possible sources of bias. For this systematic review, with the patient-centered outcome of pain intensity, the key domains were sequence generation, allocation concealment, and patient blinding.

For each aspect of the quality assessment, the risk of bias was scored following recommendations of the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (http://handbook.cochrane.org). At the domain level, the judgment for each entry involved recording “yes” to indicate a low risk of bias, “no” for a high risk of bias or “unclear,” indicating either lack of information or uncertainty over the potential for bias.

At the study level, the paper was considered to be at “low” risk of bias if all key domains for each outcome were at low risk of bias. If one or more key domains were judged as “unclear” or at “high” risk of bias, the study was considered at “high” risk of bias. When the study was judged as “unclear” in its key domains, the authors were contacted to obtain more information, which allowed a definitive “yes” or “no” judgment. The whole process of quality assessment was done by two independent reviewers (L.D.M. and M.R.) and disagreements solved through discussion and by consulting a third reviewer (A.R.).

2.7 Summary measures and synthesis of the results

Data were analyzed using RevMan 5 (Review Manager Version 5.3, the Cochrane Collaboration, Copenhagen, Denmark). Only studies classified at “low” risk of bias in the key domains were entered into the meta-analysis. The calculation of the standardized mean difference for the continuous data (pain intensity) and the risk ratio for dichotomous data allowed us to summarize the outcomes.

Depending on the number of included studies, subgroup analysis would be performed to evaluate (1) whether or not the outcomes differ if the drug was administered pre- or postoperatively, (2) whether or not the outcomes differ depending on the type of administration of ketorolac (sublingual, intramuscular or intravenous) and (3) whether or not the outcomes differ depending on the dosage of the medicines (low and high dosages).

Random-effects models were used. Heterogeneity was assessed using the Cochran Q test and I2 statistics. Sensitivity analyses were also conducted to investigate the reasons for high heterogeneity whenever detected.

2.8 Assessment of the quality of evidence using GRADE

We graded the quality of the evidence for each outcome across studies (body of evidence) using the Grading of Recommendations: Assessment, Development and Evaluation (GRADE) (http://www.gradeworkinggroup.org/). This technique allows one to determine the overall strength of evidence for each meta-analysis (Guyatt, Oxman, Schünemann, Tugwell, & Knottnerus, 2011). The GRADE approach grades the evidence in four levels: very low, low, moderate, high. The "high quality" suggests that we are very confident that the true effect lies close to the estimate of the effect. On the other extreme "very low quality" suggests that we have very little confidence in the effect estimate and the estimate reported can be substantially different from what it was measured.

For randomized clinical trials, the GRADE approach addresses five reasons (risk of bias, imprecision, inconsistency, indirectness of evidence and publication bias) to possibly rate down the quality of the evidence in 1 or 2 levels (Guyatt et al., 2011). Each domain was assessed as "no limitation" (0); "serious limitations" (1 level downgraded) and "very serious limitations" (2 levels downgraded). The GRADEpro Guideline Development Tool, available online (www.gradepro.org), was used to create Summary of findings table as suggested in the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann et al., 2008).

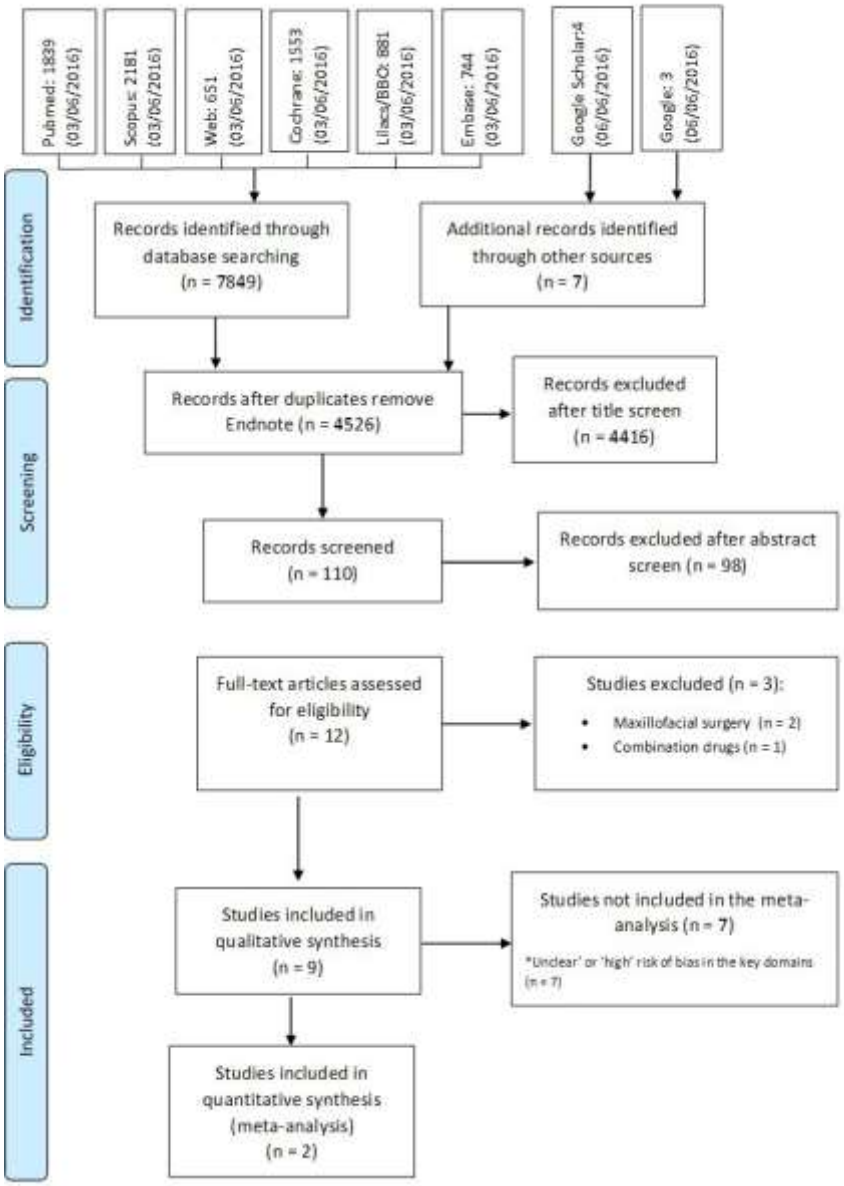
3. Results

Some studies did not contain all the information needed; thus, emails were sent to seven authors to request further information (Chethan et al., 2015; Dayashankara Rao, 2010; Gopalraju et al., 2014; Isiordia-Espinoza et al., 2016; Shah et al., 2013; Shaik et al., 2010; Tenglikar, 2014), and five of them did not answer (Chethan et al., 2015; Dayashankara Rao, 2010; Gopalraju et al., 2014; Isiordia-Espinoza et al., 2016; Shaik et al., 2010).

3.1 Study selection

The search strategy was realized on 03/06/2016 and updated twice (in 01/07/2018 and 15/01/2021). After the database screening and removal of duplicates, 4526 studies were identified (Figure 1). After title screening, 110 studies remained. This number was reduced to 12 after the abstracts were read and their full texts were assessed to check eligibility. Of these, three were excluded. The reasons for exclusion were (1) two studies evaluated postoperative pain after maxillofacial surgery (Shankariah, Mishra, & Kamath, 2012; Zackova, Taddei, Calò, Bellocchio, & Zanello, 2001) and (2) one study combined both drugs for treatment (Isiordia-Espinoza et al., 2011).

Figure 1. Flow diagram of study identification.



Source: Authors.

3.2 Characteristics of included articles

The characteristics of the thirteen included studies are listed in Tables 2 and 3. The parallel study design prevailed (Chethan et al., 2015; Dayashankara Rao, 2010; Gopalraju et al., 2014; Isiordia-Espinoza et al., 2016; Mangalgi, Shah, Sajjanshetty, Patil, & Halkai, 2018; Mishra & Khan, 2012; Nasyam, 2020; Ong & Tan, 2004; Passi et al., 2018; Pathi, Vidya, & Sangamesh, 2020; Shaik et al., 2010; Tenglikar, 2014) except in one study that used the crossover design (Shah et al., 2013). The majority of them were carried out in a university environment, except three, which were conducted in a partnership between a hospital and university (Dayashankara Rao et al., 2010; Shah et al., 2013; Shaik et al., 2010).

Table 2. Summary of the studies selected for this systematic review (only data from tramadol and ketorolac groups).

Study ID	Study design [Setting]	Drug Management	Subjects' age mean±SD [range] (yrs)	No. of subjects Male[%]	No. of surgeons	Antibiotic prophylaxis	Type of anesthesia used [anesthetic name]	Drug protocol [route of administration]	No. patients [drop-outs]
R. Chethan, T. Ramamuthy, S. Patil, and S. J. J. o. R. i. D. Reddy (2015)	Parallel [university]	Postoperative	TR: n.r. ± n.r. [n.r.] KE: n.r. ± n.r. [n.r.] Overall [18-25]	n.r.	1	n.r.	Local [2% lignocaine]	TR: 50 mg after the extraction and dose repeated after 6 h [PO][a] KE: 10 mg after the extraction and dose was repeated after 6 h [PO][a]	40 [n.r.]
Dayashankara Rao JK (2010)	Parallel [university - hospital]	Postoperative	TR: 24.5 ±5.4. [n.r.] KE: 24.3 ±6.5 [n.r.]	28 [70%]	n.r.	No	n.r.	TR: 50 mg 3 x day per 3 days [PO][a] KE: 10 mg 3 x day per 3 days [PO][a]	40 [n.r]
Gopalraju et al. (2014)	Parallel [university]	Preoperative	TR: 25.4 ± n.r. [n.r.] KE: 25.95 ± n.r. [n.r.] Overall [18-35]	25 [62%]	1	Amoxicillin[a] 1 g was given orally 1 h prior to surgery	Local [2% xylocaine comprising of lignocaine hydrochloride with 1:200,000 epinephrine]	TR: 50 mg 10 min prior to surgery [IV][a] KE: 30 mg 10 min prior to surgery [IV][a]	40 [0]
Isiordia-Espinoza et al. (2016)	Parallel [university]	Preoperative	TR: 23 ± n.r. [19-27] KE: 21 ± n.r. [18-23]	11 [36.6%]	1	n.r.	Local [2% lidocaine containing 1:100,000 epinephrine]	TR: placebo [PO][a] plus tramadol 50 mg [IM][a] 30 min prior to surgery KE: 10 mg Ketorolac [PO][a] plus placebo [IM][c] 30 min prior to surgery	30 [0]
Mangalgi et al. (2018)	Parallel [university]	Postoperative	TR: 24.95 ± n.r. [n.r.] KE: 24.2 ± n.r. [n.r.] Overall [16-40]	n.r.	n.r.	n.r.	Local [n.r.]	TR: tramadol 50 mg post - operatively [IM][a] KE: ketorolac 30 mg [IM] [a]	40 [n.r]
Mishra and Khan (2012)	Parallel [university]	Preoperative and postoperative	Overall 31.57 ± n.r. [18-65]	36 [49%]	n.r.	Not specified	Local [2% lignocaine]	TR: 100 mg pre and postoperative; 30 min prior to and 30 min after extraction [PO][a] KE: 20 mg pre and postoperative; 30 min prior to and 30 min after extraction [PO][a]	74 [n.r.]
Nasyam (2020)	Parallel [university]	Preoperative	TR: n.r ± 4.4 [18-25] KE: n.r ± n.r [18-24]	38 [63%]	1	n.r.	Local [2% lidocaine containing 1:100,000 epinephrine]	TR: placebo [PO][a] and tramadol 50 mg [IM] [a] KE: ketorolac 10	60 [n.r.]

			Median TR: 23 KE: 22					mg [PO][a] and placebo [IM] [a]	
K. S. Ong and Tan (2004)	Parallel [university]	Preoperative	TR: 26.9 ± 4.4 [n.r.] KE: 27.1 ± 4.7 [n.r.]	27 [42%]	n.r.	n.r.	Local [2% lidocaine with 1:100 000 epinephrine]	TR: 50 mg prior to surgery [IV][b] KE: 30 mg prior to surgery [IV][c]	64 [4]
Passi et al. (2018)	Parallel [university]	Postoperative	TR: 33 ± 10.4 [n.r.] KE: 31± 8.1 [n.r.] Overall [20–60]	64 [64%]	1	n.r.	Local [n.r.]	TR: Tramadol 50 mg postoperatively [PO][a] KE: ketorolac 10 mg [PO][d]	100 [n.r.]
Pathi et al. (2020)	Parallel [university]	Preoperative	TR: 25.73 ±5.72 [n.r.] KE: 27.37± 6.19 [n.r.] Overall [16–40]	31% [63%]	1	Not specified	Local [2% lignocaine with 1:200,000 adrenaline]	TR: tramadol 50 mg [IV][e] KE: ketorolac 30 mg [IV][f]	200 [n.r.]
Shah et al. (2013)	Crossover [university - hospital]	Preoperative	Overall: 20.6 ± 1.5 [n.r.]	24 [48%]	n.r.	n.r.	Local [2 % lignocaine with 1:80000 adrenaline]	TR: 50 mg 20 min prior to surgery [IM][a] KE: 30 mg 20 min prior to surgery [IM][a]	50 [n.r.]
M. Shaik, J. Kumar, S. Mobina, N. Satyanarayana, and P. J. J. o. C. o. M. S.-N. Sunitha (2010)	Parallel [university - hospital]	Perioperative	n.r. ± n.r. [18-60]	n.r.	n.r.	n.r.	n.r.	TR: 50 mg prior to and every 6 h until 24 h [PO][a] KE: 10 mg prior to and every 6 h until 24h [PO][a]	150 [n.r.]
P. D. J. I. J. o. D. C. Tenglikar (2014)	Parallel [university]	Perioperative	n.r. ± n.r. [18-30]	n.r.	n.r.	n.r.	Local [n.r.]	TR: 50 mg prior to surgery and dose repeated after 6 h [PO][a] KE: 10 mg prior to surgery and dose was repeated after 6 h [PO][a]	150 [n.r.]

ID – identification; SD – standard deviation; yrs – years; TR: Tramadol, n.r. – Not reported; KE: Ketorolac; PO: orally; IV: Intravenous; IM: intra muscular.
[a] Uninformed
[b] Tramal® (Pfizer, New York, United States of America)
[c] Toradol® (Roche, Basel, Switzerland)
[d] Ketorolac DT, Dr. Reddy's lab
[e] Tramadol hydrochloride, batch no. KP949013
[f] Ketorolac tromethamine, batch no. DH5015
Source: Authors.

In six out of the thirteen studies, the drug was only administered preoperatively (Gopalraju et al., 2014; Isiordia-Espinoza et al., 2016; Nasyam, 2020; Ong & Tan, 2004; Pathi et al., 2020; Shah et al., 2013), in four studies the drug was only administered postoperatively (Chethan et al., 2015; Dayashankara Rao, 2010; Mangalgi et al., 2018; Passi et al., 2018) and in three studies the drug was administered perioperatively (Mishra & Khan, 2012; Shaik et al., 2010; P. D. Tenglikar, 2014). Regarding the route of administration, six studies used the oral route (R. Chethan et al., 2015; Dayashankara Rao et al., 2010; Mishra & Khan, 2012; Passi et al., 2018; Shaik et al., 2010; Tenglikar, 2014), two study employed the intramuscular route (Mangalgi et al., 2018; Shah et al., 2013), three used the intravenous route (Gopalraju et al., 2014; Ong & Tan, 2004; Pathi et al., 2020) and two study combined the oral and intramuscular routes (Isiordia-Espinoza et al., 2016; Nasyam, 2020).

The dose of the drugs was also variable. Oral ketorolac was used in doses of 10 mg to 20 mg; intravenous and intramuscular doses were 30 mg. The doses of oral tramadol ranged from 50 to 100 mg; intravenous and intramuscular doses were 50 mg (Table 2) (Chethan et al., 2015; Dayashankara Rao, 2010; Gopalraju et al., 2014; Isiordia-Espinoza et al., 2016; Mangalgi et al., 2018; Mishra & Khan, 2012; Nasyam, 2020; Ong & Tan, 2004; Passi et al., 2018; Pathi et al., 2020; Shah et al., 2013; Shaik et al., 2010; Tenglikar, 2014).

The number of participants in the primary studies ranged from 30 to 200 per group. The mean age of all the participants included in the clinical trials was approximately 26.3 years (Dayashankara Rao et al., 2010; Gopalraju et al., 2014; Isiordia-Espinoza et al., 2016; Mangalgi et al., 2018; Mishra & Khan, 2012; Ong & Tan, 2004; Passi et al., 2018; Pathi et al., 2020; Shah et al., 2013). The percentage of males ranged from 36.6% to 70% (Table 2); this information was not reported in four studies (Chethan et al., 2015; Mangalgi et al., 2018; Shaik et al., 2010; Tenglikar, 2014).

For the pain evaluation, four studies employed a visual analog scale (VAS) of 0-10 points (Chethan et al., 2015; Gopalraju et al., 2014; Mangalgi et al., 2018; Passi et al., 2018; Shaik et al., 2010; Tenglikar, 2014) and another four studies employed a VAS of 0-100 points (Dayashankara Rao, 2010; Isiordia-Espinoza et al., 2016; Nasyam, 2020; Ong & Tan, 2004), one study used a verbal rating scale (VRS) of 0-3 (Dayashankara Rao, 2010), one study used a modified verbal rating scale (VRS) (Mishra & Khan, 2012), one study used Wong-Baker pain assessment scale (Pathi et al., 2020), one study used a numerical rating scale (NRS) of 0-10 points (Shah et al., 2013) and one another NRS 1-3 (Nasyam, 2020). The assessment time of pain varied from 30 min to 72 h post-surgery (Table 3).

Seven studies used rescue medication (Gopalraju et al., 2014; Isiordia-Espinoza et al., 2016; Mishra & Khan, 2012; Nasyam, 2020; Ong & Tan, 2004; Pathi et al., 2020; Shah et al., 2013), such as acetaminophen, ketorolac, ibuprofen, diclofenac potassium + paracetamol + serratiopeptidase, aceclofenac + paracetamol + serratiopeptidase. Ondansetron was also used when the patients had pain or nausea after treatment (Table 3).

After the administration of the drugs, eight studies confirmed the presence of adverse effects with both tramadol and ketorolac (Mangalgi et al., 2018; Mishra & Khan, 2012; Ong & Tan, 2004; Passi et al., 2018; Pathi et al., 2020; Shah et al., 2013; Shaik et al., 2010; Tenglikar, 2014). Four studies reported that there were no adverse effects (Dayashankara Rao et al., 2010; Gopalraju et al., 2014; Isiordia-Espinoza et al., 2016; Nasyam, 2020), and one study did not report this information (R. Chethan et al., 2015) (Table 3).

Table 3. Summary of the studies selected for this systematic review (only data from tramadol and ketorolac groups).

Study ID	Pain evaluation				Rescue medication			Adverse effects	
	Criteria	Pain Intensity mean ± SD	Assessment time	Overall global assessment?	Name	Total analgesic consumption – number of tablets/ mean ± SD	Average time of rescue medication (h)/ mean ± SD	Common adverse effects	Number of all adverse effects [#of events/total]
R Chethan et al. (2015)	VAS 0-10[a]	TR: 2.2 ± n.r. KE: 4.3 ± n.r.	1 h after medication, 2 h, 3 h, 4 h, 5 h, 6 h	No	n.r.	n.r.	n.r.	TR: n.r. KE: n.r.	TR: n.r./20 KE: n.r./20
Dayashankara Rao JK (2010)	VAS 0-100[b] VRS 0-3[c]	TR: 13.2 ± 5.0 KE: 20.6 ± 7.7	24 h, 44 h and 72 h	No	n.r.	n.r.	n.r.	TR: no KE: no	TR: 0/20 KE: 0/20
Gopalraju et al. (2014)	VAS 0-10[d]	TR: 54.6 ± 7.1 KE: 32.9 ± 8.18	Hourly for 12 h	0-4[e]	Acetaminophen 500 mg[f]	TR: 10.2 ± 1.76 KE: 6.8 ± 1.67	TR: 7 ± n.r. h KE: 10 h	TR: no KE: no	TR: 0/20 KE: 0/20
Isiordia-Espinoza et al. (2016)	VAS 0-100[b]	TR: 24.01 ± n.r. KE: 8.16 ± n.r.	Each hour for 8 h after completion of surgery, and a last evaluation was done at 24 h post-surgery	1-3[f]	Ketorolac[g] 30 mg sublingual	TR: 3 (0-4) KE: 2 (0-3)* * Median and interquartile range	TR: 3.1 (3 - 24) h KE: 4.8 (3.4 - 9.5)* h * Median and interquartile range	TR: no KE: no	TR: 0/15 KE: 0/15
Mangalgi et al. (2018)	VAS 0-10[d]	Sum of pain intensity TR: 27.85 KE: 23.05	Every hourly by 12 hours	0-4[e]	n.r.	TR: 6.2± n.r. KE: 5.5± n.r.	n.r.	TR: Nausea, vomiting KE: no	TR: 1/20 KE: 0/20
Mishra and Khan (2012)	VRS modified[h]	TR: 2.11 ± n.r. KE: 2.14 ± n.r.	30 min, 2 h, 4 h, 6 h	No	Ibuprofen[g] 400 mg	n.r.	Preoperative TR: 5.2 h KE: 6.8 h Postoperative TR: 6.2 h KE: 6.2 h	TR: weakness/tiredness, sleepy, dizziness/ giddiness KE: sleepy, dizziness/giddiness, nausea/vomiting	TR: 8/25 KE: 6/25
Nasyam (2020)	VAS 0-100[b]	TR: n.r. ± n.r. KE: n.r. ± n.r	VAS was recorded every hour till 8 hr postoperatively and finally 24 hr post-surgery	n.r.	Ketorolac 10 mg	TR: 5 (0-6) KE: 4 (0-5)	Ketorolac: 4.6 (3.1 to 8.8) Tramadol: 3.2 (2.8 to 8.2)	TR: no KE: no	TR: 0/30 KE: 0/30
K. S. Ong and Tan	VAS 0-100[b]	TR: 20.0 ± 10.1	Every hour for 12 h	0-4[e]	Acetaminophen[g] 1000 mg	TR: 6.4 ± 3.8	TR: 7.6 ± 2.7 h	TR and KE: Mild without treatment	TR: n.r./32

(2004)		KE: 15.1 ± 7.7				KE: 4.4 ± 3.1	KE: 9.5 ± 3.0 h		KE: n.r./32
Passi et al. (2018)	VAS 0-10[d]	TR: [1.65 - 7.68] KE: [2.68 - 6.20] *min/max	After surgical VAS 30 minutes; 1 h, 4h, 6h, 12h 1st, 2nd and 3rd days 1h, 3h, 5h, 7h, 8h, 11h, 13h, 15h, 18h	n.r.	n.r.	n.r.	n.r.	TR: nausea/ vomiting, gastric pain/ acidity, drowsiness/ sedation, sweating KE: oral ulcers, nausea/vomiting, gastric pain/acidity, bleeding, sweating, diarrhea/ constipation	TR: 9/50 KE: 12/50
Pathi et al. (2020)	Wong-Baker pain assessment scale[i]	Sum of pain intensity scores of 12 h TR: 53.23±4.49 KE: 33.56±6.98	Throughout 6 h	n.r.	Aceclofenac 100 mg + paracetamol 500 mg + serratiopeptidase 10 mg	TR: 7.93±3.016 KE: 3.03± 2.45	n.r.	TR: nausea and vomiting. KE: severe pain at the site of injection but none of them had local skin reactions	TR:15/100 KE: 5/100
Shah et al. (2013)	NRS 0-10[j]	TR: 2.36 ± 0.95 KE: 2.4 ± 0.92	1 h, 3 h, 5 h, 12 h,	0-4[e]	Diclofenac potassium 50 mg/paracetamol 500 mg/serratiopeptidase 10 mg[k] Ondansetron 4 mg[l]	TR 8.92 ± 1.91 KE: 7.36 ± 1.7	TR:7.4 ± 1.1 h KE:8.9 ± 0.9 h	TR: nausea KE: pain at the site of injection	TR: 4/25 KE: 1/25
M. Shaik et al. (2010)	VAS 0-10[a]	TR: 3.89 ± 0.72 KE: 4.12 ± 0.53	After extraction, 30 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 12 h, 18 h and 24 h	No	n.r.	n.r.	n.r.	TR: Sweating, sedation, decrease in blood pressure KE: Bleeding and epigastric pain	TR: 18/75 KE: 59/75
P. D. J. I. J. o. D. C. Tenglikar (2014)	VAS 0-10[a]	TR: 3.77 ± 0.16 KE: 4.89 ± 0.65	30 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 12 h, 18 h and 24 h	No	n.r.	n.r.	n.r.	TR: sedation KE: epigastric pain, nausea	TR: 4/75 KE: 22/75

ID – identification; SD – standard deviation; TR: Tramadol, n.r. – Not reported; KE: Ketorolac; NRS: numerical rating scale; VAS: Visual Analog Scale; VRS: verbal rating scale.

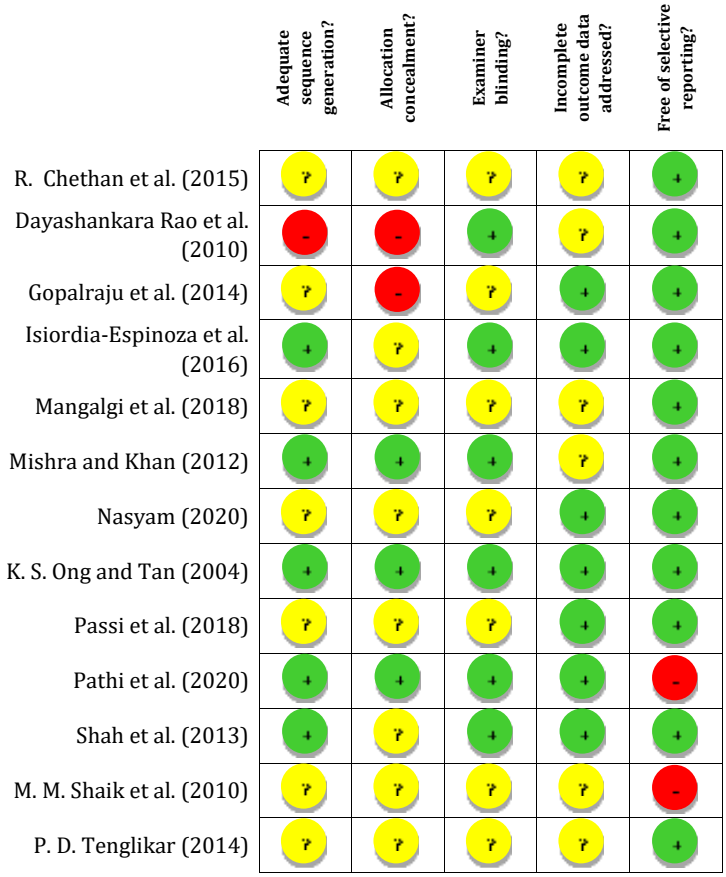
[a] VAS 0-10 (0 – no pain, 2 - mild pain, 4 - tolerable, 6 – distressful pain, 8 – severe pain and 10 – totally disabling pain)
[b] VAS 0-100 (0 – no pain, 100 - worst pain)
[c] VRS 0-3 (Slight-0 - No Discomfort; Moderate - 1 - Mild discomfort; Severe - 2 - Marked discomfort; Agonizing - 3 - Marked discomfort that lasted more than 10s)
[d] VAS 0-10 (0 – no pain, 10 - worst pain)
[e] Overall 0-4 (0 = poor, 1=fair, 2=good, 3=very good and 4=excellent)
[f] Overall 1-3 (1 = poor, 2=fair, 3=good)
[g] Uninformed
[h] VRS modified: Before rescue -1-3 (1-no pain, 2- some pain, but no need for rescue, 3 - pain severe enough to take rescue) and After rescue -4-7 (4- no pain, 5- some pain, but less than when rescue was, 6 - pain same was when rescue was taken, 7- pain more severe than when rescue was taken)
[i] Wong-Baker pain assessment scale.
[j] NRS 0-10 (0- no pain, 1-3 mild pain, 4-6 moderate pain and 7-10 severe pain)
[k] Biozobid plus (Piramal Healthcare, Mumbai, Maharashtra, India)
[l] Ondem (Alkem laboratories Ltd, Mumbai, Maharashtra, India)
Source: Authors.

3.3 Assessment of the risk of bias

The assessment of the risk of bias of the selected studies is presented in Figure 2. In the sequence generation domain, five studies were considered to be at "low" risk of bias (Isiordia-Espinoza et al., 2016; Mishra & Khan, 2012; Ong & Tan, 2004; Pathi et al., 2020; Shah et al., 2013), seven studies were judged as at "unclear" risk (Chethan et al., 2015; Gopalraju et al., 2014; Mangalgi et al., 2018; Nasyam, 2020; Passi et al., 2018; Shaik et al., 2010; Tenglikar, 2014) and one study was judged at a "high" risk of bias (Dayashankara Rao, 2010).

In the allocation concealment domain, three studies were considered to be at "low" risk of bias (Mishra & Khan, 2012; Ong & Tan, 2004; Pathi et al., 2020), eight were judged as at "unclear" risk (Chethan et al., 2015; Isiordia-Espinoza et al., 2016; Mangalgi et al., 2018; Nasyam, 2020; Passi et al., 2018; Shah et al., 2013; Shaik et al., 2010; Tenglikar, 2014), and two studies were classified at a "high" risk of bias (Dayashankara Rao, 2010; Gopalraju et al., 2014).

Figure 2. Summary of the risk of bias assessment according to the Cochrane Collaboration tool. Underlined authors provided extra information by e-mail to allow assessment of the risk of bias.



Source: Authors.

In regard to blinding, six studies were considered to be at "low" risk of bias (Dayashankara Rao, 2010; Isiordia-Espinoza et al., 2016; Mishra & Khan, 2012; Ong & Tan, 2004; Pathi et al., 2020; Shah et al., 2013), and seven were judged as at "unclear" risk (Chethan et al., 2015; Gopalraju et al., 2014; Mangalgi et al., 2018; Nasyam, 2020; Passi et al., 2018; Shaik et al., 2010; Tenglikar, 2014).

Only three studies were judged at "low" risk of bias in all the key domains. Therefore, at the study level, only these three full texts were considered to be at "low" risk of bias (Mishra & Khan, 2012; Ong & Tan, 2004; Pathi et al., 2020).

However, the study of Pathi et al. (2020) was not included in the meta-analysis as the outcome was the sum of hourly pain intensity scores, making it impossible mix with the other two studies, which measured the average intensity of pain. Important to say that the authors described the outcome in a very unusual way, which put the study at high risk of bias in selective outcome reporting.

3.4 Meta-analysis

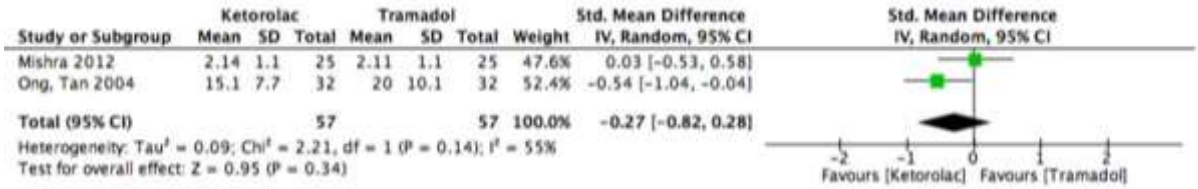
The meta-analysis was performed on studies classified as a "low" risk of bias in the key domains and from which the information could be extracted. In the study protocol registered at the Prospero database, we planned to extract other secondary outcomes, which were described earlier in the materials and methods section. However, in the two studies at "low" risk of bias, the secondary outcomes (time to take the first rescue analgesic drug in hours, total amount of analgesics consumed in mg or in number of capsules and the total number of adverse effects) were not described, which prevented us from running their meta-analyses (Table 3). Only data from the intensity of pain could be meta-analyzed.

3.4.1 Intensity of pain using VAS pain scales

This analysis was based on two studies that totalized 138 patients. Data on postoperative pain intensity between 6 h and 12 h post-surgery was extracted, depending on the information provided by the authors. The standardized difference in means was - 0.27 (95% CI - 0.82 to 0.28; p = 0.34), and therefore we do not have enough evidence to show superiority of one drug over the other (Figure 3). Data was not heterogeneous (chi2 test p = 0.14; I2 = 55%). The statistical heterogeneity of only 2 studies does not provide reliable information and should only be seen as an exploratory analysis.

The standard deviations of the study by Mishra and Khan (2012) was not described in the text. In face of that, we arbitrarily imputed a standard deviation corresponding to half of the mean. This decision was based on the coefficient of variation of the other primary included studies, which was around 50%. A sensitivity analysis was run using more extreme standard deviations, and no deviation from the findings reported herein was observed.

Figure 3. Forest plot of the pain intensity of ketorolac and tramadol after impacted third molars surgery.



Source: Authors.

3.5 Assessment of the quality of evidence using GRADE

For the main outcome pain intensity, the GRADE quality of evidence was moderate due to "serious" limitations in imprecision (Table 4). The large confidence interval of the standardized mean difference included potential improvement as well as inferiority of ketorolac compared to tramadol. For the outcome total number of adverse effects, the GRADE quality of evidence was low due to "very serious" limitations for imprecision, where only a single study was included with very low sample size.

Table 4. Summary of findings table.

Patient or population: third molars surgery
Setting: University care
Intervention: ketorolac
Comparison: tramadol

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with tramadol	**Risk with ketorolac**				
Pain intensity assessed with: pain scales	-	SMD 0.27 SD lower (0.82 lower to 0.28 higher)	-	114 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]	
Total number of adverse effects assessed with: yes/no scale	32 per 100	**24 per 100**	not estimable	50 (1 RCT)	⊕⊕◯◯ LOW [b]	TR: weakness/tiredness, sleepy, dizziness/ giddiness KE: sleepy, dizziness/giddiness, nausea/vomiting

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI); **CI:** Confidence interval; **SMD:** Standardised mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Imprecision due to large confidence interval, small sample; b. Data provided by a single study with small sample size.
Source: Authors.

4. Discussion

The qualitative evaluation of the studies included in this systematic review showed that there is great diversity in the protocols used for both drugs, in either the route of administration or dosage.

For ketorolac, different routes of administration (oral, intramuscular and intravenous) resulted in similar pharmacokinetic profiles with only a few differences (Catapano, 1996; Jung, Mroszczak, & Bynum, 1988; Jung et al., 1989). The absorption is rapid for all three forms of dosing. The time to reach peak serum concentration is shortest after intravenous use, which takes approximately 5 min. After oral use, peak concentration takes 30-53 min (Catapano, 1996), while in intramuscular use, it takes 45-50 min (Catapano, 1996). The serum half-life ranges from 5 to 6 h for all three forms of administration (Catapano, 1996). It is also reported that there is no difference between ketorolac 10 and 20 mg taken orally for pain control (Brown et al., 1990; Buckley & Brogden, 1990; Forbes, Butterworth, Burchfield, & Beaver, 1990; Forbes, Kehm, Grodin, & Beaver, 1990; Olmedo, Gálvez, & Vallecillo, 2001), suggesting that there is a plateau in this agent's analgesic efficacy at the 10 mg level (Olmedo et al., 2001). On the other hand, an increase in analgesic efficacy can be obtained with 30 mg of ketorolac taken intramuscularly when compared with 10 mg taken per the oral rote for surgery models (Fricke et al., 1992).

In regard to tramadol, its concentrations in the intramuscular and intravenous routes 30 min after administration were equivalent (Lintz, Beier, & Gerloff, 1999). Peak serum concentrations after intramuscular injection occurred after 45 min and were approximately half those occurring during intravenous infusion (le Roux & Coetzee, 2000). Tramadol is rapidly and

extensively absorbed after oral administration, appearing in the plasma 15-45 min after administration, with peak levels occurring after 2 h (Gaynes & Barkin, 1999; le Roux & Coetzee, 2000).

Another factor that may influence the effect of the drugs is the moment they were given to patients, which may be before or after surgery. This may play a significant role, as pain resulting from surgery is most severe between 6 and 8 h after the surgery (Ong & Tan, 2004; Seymour et al., 1985). In theory, the strategy of pre-surgical analgesic administration is to establish effective blood levels for maximum analgesic effect at the time pain is most severe. The analgesic effect of tramadol begins within 1 h and reaches a peak in approximately 2 to 3 h (Mishra & Khan, 2012), while ketorolac's effect begins 10-20 min after intramuscular administration and 30-60 min after oral administration (Vadivelu et al., 2015) and reaches a peak in 1-3 min (intravenous), 30-60 min (intramuscular) and approximately 1 h (orally) (Flores-Murrieta & Granados-Soto, 1996).

To the extent of our knowledge, this systematic review and meta-analysis is the first to compare ketorolac and tramadol in the management of pain intensity after surgery of impacted third molars. Unfortunately, we could not find evidence to support ketorolac being superior to tramadol for reduction of pain intensity. However, this conclusion was only based on the findings of two studies classified at "low" risk of bias. This leads to a conclusion with moderate quality of evidence due to the low number of studies and participants included in the meta-analysis, leading to a high imprecision of the data.

Bias is a systematic error that leads to deviation from the truth in the results. It can underestimate or overestimate the true intervention effect (Higgins et al., 2019). Meta-analysis of results from biased studies can result in false positive or false negative results. The most conservative approach is to meta-analyze only data from studies with a "low" risk of bias, as performed in this study.

Among the thirteen studies that compared both drugs, ten were judged to be at "high" risk of bias. The adequate management of the domains of sequence generation and allocation concealment allows minimization of selection bias. It was already demonstrated that odds ratios were exaggerated by 41% for inadequately concealed trials and by 30% for unclearly concealed trials (adjusted for other aspects of quality) (Schulz, Chalmers, Hayes, & Altman, 1995).

The judgment of the risk of bias of these two domains was not straightforward and the great majority of the studies included in the qualitative synthesis, required contact with the authors. However, the response rate from the authors was very low. This highlights the fact that the quality of the RCTs that compared both drugs is still far from the ideal, preventing us from being confident in their findings.

For the same reason, we could not compare the total number of adverse effects of the drugs or the most frequent adverse effect for both drugs, as only two studies remained for quantitative evaluation. Among these two, only Mishra and Khan (2012) reported the presence of adverse effects of both medicines. For tramadol, weakness, tiredness, sleepiness, dizziness and giddiness were the most frequent adverse effects, while for ketorolac sleepiness, dizziness, giddiness, nausea and vomiting were reported. The quality of evidence for this outcome was judeged as low in the GRADE approach, due to very serious issues in imprecision (very low number of participants).

Contrary to our findings, another systematic review and meta-analysis that evaluated the analgesic efficacy of a single dose of tramadol in comparison with an NSAID (Isiordia-Espinoza et al., 2014) concluded that the analgesic efficacy of tramadol was lower than that of the NSAID for the management of pain after surgery on the third molars. However, this systematic review (Isiordia-Espinoza et al., 2014) meta-analyzed all included studies without taking into consideration their risk of bias. This may have resulted in a biased meta-analysis.

Although the present meta-analysis found no evidence of better analgesic efficacy for management of postoperative pain after impacted third molar surgery, the imprecision of the effect size for the intensity of pain, represented by a large

confidence interval, does not allow us to conclude that a difference between the two drugs does not exist. More RCTs with a high standard and "low" risk of bias should be conducted to help clinicians in their choices of prescribing a drug for postoperative pain control after impacted third molar surgery.

Finally, the limitations of this systematic review should be reported. The two studies included in the meta-analysis used a single dose of the drugs, and the pain was evaluated at different time periods. Ideally, a study to evaluate the analgesic efficacy of drugs should focus on post-extraction pain, which should include the highest pain peak (6-8 h) (K. S. Ong & Tan, 2004). In the study of K. S. Ong and Tan (2004), the pain was assessed at 12 h, while Mishra and Khan (2012) evaluated the pain only during the first 6 h, which prevented the authors from evaluating pain at its highest level. Lastly, we should mention that the low sample size of the studies is also a limitation, as it does not allow the detection of clinically important differences.

5. Conclusion

This systematic review and meta-analysis of randomized clinical trials showed that there is a lack of evidence to conclude that ketorolac is better than tramadol for reduction of postoperative pain after extraction of impacted third molars, although only two randomized clinical trials were included.

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