

## REVIEW ARTICLE

# Preventive analgesia in hip or knee arthroplasty: A systematic review<sup>☆</sup>



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### KEYWORDS

Knee arthroplasty;  
Hip arthroplasty;  
Preventive analgesia;  
Systematic review

### Abstract

**Objective:** To analyze the efficacy and safety of preventive analgesia in patients undergoing hip or knee arthroplasty due to osteoarthritis.

**Methods:** A systematic literature review was performed, using a defined sensitive strategy on Medline, Embase and Cochrane Library up to May 2013. The inclusion criteria were: patients undergoing knee and/or hip arthroplasty, adults with moderate or severe pain ( $\geq 4$  on a Visual Analog Scale). The intervention, the use (efficacy and safety) of pharmacological treatment (preventive) close to surgery was recorded. Oral, topical and skin patch drugs were included. Systematic reviews, meta-analysis, controlled trials and observational studies were selected.

**Results:** A total of 36 articles, of moderate quality, were selected. The patients included were representative of those undergoing knee and/or hip arthroplasty in Spain. They had a mean age  $>50$  years, higher number of women, and reporting moderate to severe pain ( $\geq 4$  on a Visual Analog Scale). Post-surgical pain was mainly evaluated with a Visual Analog Scale. A wide variation was found as regards the drugs used in the preventive protocols, including acetaminophen, classic NSAID, Cox-2, opioids, corticosteroids, antidepressants, analgesics for neuropathic pain, as well as others, such as magnesium, ketamine, nimodipine or clonidine. In general, all of them decreased post-surgical pain without severe adverse events.

**Conclusions:** The use of one or more pre-surgical analgesics decreases the use of post-surgical drugs, at least for short term pain.

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**PALABRAS CLAVE**

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Artroplastia de cadera;  
Analgésia preventiva;  
Revisión sistemática

**Analgésia preventiva en artroplastia de cadera o rodilla: una revisión sistemática****Resumen**

**Objetivo:** Analizar la eficacia y la seguridad de la analgesia preventiva en pacientes que son sometidos a artroplastia de cadera o rodilla por artrosis.

**Métodos:** Se realizó una revisión sistemática: se definió una estrategia de búsqueda bibliográfica sensible en Medline, Embase y Cochrane Library hasta mayo de 2013; se definió la población con los siguientes criterios: pacientes con indicación de artroplastia de cadera y/o rodilla, adultos, dolor moderado a intenso ( $\geq 4$  en la Escala Visual Analógica), la intervención, el uso (eficacia y seguridad) del tratamiento farmacológico (preventivo) próximo a la cirugía. Se incluyeron formulaciones orales, tópicas y parches. Se incluyeron revisiones sistemáticas, metaanálisis, ensayos clínicos y estudios observacionales.

**Resultados:** Se incluyeron 36 artículos de calidad moderada. Incluían pacientes representativos de aquellos a los que se les indica una artroplastia de cadera o rodilla en nuestro país, adultos, con una edad media superior a 50 años, ligera mayor proporción de mujeres y que presentan dolor de moderado a grave ( $\geq 4$  en la Escala Visual Analógica). El dolor posquirúrgico se evaluó sobre todo con la Escala Visual Analógica. Existe mucha variabilidad en cuanto a los fármacos utilizados incluyendo paracetamol, AINE clásicos, AINE selectivos de la Cox-2, opioides, corticoides, antidepresivos, analgésicos para el tratamiento del dolor neuropático y otros como sulfato magnésico, ketamina, nimodipino o clonidina. Todos en general parecen mejorar el dolor posquirúrgico sin presentar acontecimientos adversos graves.

**Conclusiones:** El uso de uno o varios analgésicos en el preoperatorio disminuye el consumo de analgésicos y el dolor en el posoperatorio, al menos el dolor agudo.

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**Introduction**

Preventive analgesia is defined as a set of pharmacological and non-pharmacological strategies that are implemented before creating a surgical wound with the goal of preventing or minimizing the pain caused by damaging surgical stimuli.<sup>1,2</sup> The main objectives are to reduce acute pain due to tissue damage, prevent pathological modulation associated to pain on the central nervous system and inhibit the persistence of postoperative pain and the development of chronic pain. Preventive analgesia can also reduce the intake of analgesic drugs in the postoperative period.

Several experimental studies<sup>3,4</sup> have confirmed that, at least in animals, the administration of analgesic drugs before tissue aggression is more effective to control pain than their administration subsequent to the damage.

However, these results have not been reproduced in a conclusive manner in everyday clinical practice. Several systematic reviews including the analysis of over 80 controlled clinical trials have shown that the starting time of analgesia did not affect the control of postoperative pain, regardless of the type of preventive analgesia employed.<sup>5</sup> This conclusion is not completely categorical, since most of the existing studies are based on short-term interventions on postoperative pain, so their influence on the development of central hypersensitivity to pain<sup>6-8</sup> cannot be reliably assessed. Moreover, there may be differences depending on the type of surgery.

The objective of the present work is to systematically review the literature to analyze the effectiveness and safety of preventive perioperative treatment using

pharmacological measures in patients with an indication of hip or knee arthroplasty in relation to postoperative pain.

**Materials and methods**

A systematic literature review was conducted following the Cochrane Collaboration guide.<sup>9</sup>

**Study selection criteria**

The studies selected included adult patients with an indication of knee and/or hip arthroplasty who suffered moderate to intense preoperative pain ( $\geq 4$  in the analog visual scale). These studies should assess the use (effectiveness and safety) of a specific pharmacological treatment (preventive) soon before the intervention (not necessarily the previous 24–48 h). The treatments included oral formulations (opioids, non-steroidal anti-inflammatory drugs [NSAIDs], analgesics, corticoids, anticonvulsants and antidepressants), topical (including capsaicin, topical lidocaine, topical NSAIDs and topical massage with vaseline), transdermal patches, etc. The studies should have compared the effect against active drugs, placebo or other procedures (exercise, etc.). The main indicator of the result (effectiveness) was postoperative pain, whilst secondary indicators of the result (effectiveness) included savings on opioids, days of hospital admission, quality of life, function, satisfaction, etc. Other variables analyzed included: digestive hemorrhage, constipation and cost.

Lastly, we only included studies with the following designs: metaanalyses, systematic reviews, clinical trials and observational studies.

We excluded studies conducted on animals, basic science, articles on prosthetic revisions and prostheses due to fractures, studies in which all the patients suffered a chronic inflammatory disease (rheumatoid arthritis, lupus, etc.), non-pharmacological measures, joint infiltrations (of every kind, including infiltrations of hyaluronic acid), symptomatic slow acting drugs for osteoarthritis (SYSADOAS), and articles in which the preventive treatment was based exclusively on anesthetic block.

## Search strategy

In order to conduct this review, we screened through the following bibliographic databases: Medline (from the beginning until May 2013), Embase (from the beginning until May 2013), and Cochrane Library (from the beginning until May 2013). Given the volume of citations retrieved we did not search national and international congresses. Subsequently, we conducted a secondary manual search of the bibliography of the articles which were eventually included in the systematic review.

Table 1 shows the search strategies on Medline, as well as the number of citations retrieved. This search used the terms *Mesh* and terms in free text. As limitations, we only searched for articles which worked with human subjects and which were published in English or Spanish.

## Selection of studies

Three reviewers independently analyzed the articles retrieved with the search strategy in the different bibliographic databases to select those which fulfilled the criteria defined and analyzed the articles included in detail. Discrepancies were resolved by one of the reviewers, expert in methodology. The results of the searches were initially depurated by title and abstract or by the entire article in cases without an abstract, in sessions with a maximum duration of 20 min. After this process, the articles selected were analyzed in detail (read in their entirety). Fig. 1 shows the flow diagram of the article selection process.

Lastly, we conducted a manual search of the references included in the articles selected for a detailed analysis. All references were retrieved through the Internet and entered into the EndNote software program to facilitate their management.

## Data collection and quality assessment of the studies

The three reviewers gathered data from the included studies using specific templates which were previously designed for this review. The Oxford quality scale<sup>10</sup> was used to assess the methodological quality of the studies included.

## Analysis and presentation of data

We created evidence tables to describe the main features of the studies included. Some of the results were expressed as number and percentage (%), mean and standard deviation, median and interquartile range (p25–p75), others as odds ratio, relative risk or hazard ratio and 95% confidence intervals. We only assessed the possibility of conducting a metaanalysis in case of homogeneity.

## Results

We initially included 60 articles to be read in detail (Fig. 1). Out of these, we finally included 36 (Table 2). The articles excluded and the reasons for their exclusion are shown in Table 3, and their references in Annex 1. The main conclusions, along with their level of evidence and recommendation grade are shown in Table 4.

The epidemiological data of the study populations are shown in Table 1. The patients were adults with a mean age over 50 years, with a slightly higher proportion of females, who presented moderate to severe pain  $\geq 4$  in the analog visual scale. Postoperative pain was mainly assessed through an analog visual scale. In general, the quality of the studies was moderate, with some isolated studies of higher quality but with a small "n".

There was considerable variability in terms of the drugs used, which included paracetamol, non-selective NSAIDs, Cox-2 (Coxib) selective NSAIDs, opioids, corticoids, antidepressants, anticonvulsants and others, such as magnesium sulfate, ketamine, nimodipine and clonidine.

The preventive analgesia strategy was also highly variable. We included one study which defined "preventive" administration as that administered in the 2 weeks prior to the surgery,<sup>11</sup> but most of the studies referred to analgesia administered 24–48h prior to the intervention or at the time of inducing anesthesia. In many studies, the strategy not only consisted preoperative administration, but also included analgesic treatment during the surgery and/or in the following hours.

Overall, we observed that, in most studies, preventive analgesia decreased postoperative pain and the intake of opioids during the first hours after surgery. Below are the results obtained, grouped by analgesia strategy.

### Preventive treatment with NSAIDs

In general, the administration of NSAIDs as a preventive strategy was effective and seemed to decrease both pain and consumption of opioids in the immediate postoperative period. Coxib presented the advantage of not causing alterations in platelet aggregation, which did not alter the rate of hemorrhagic complications.

The use of ibuprofen<sup>11</sup> 2 weeks prior to the surgery was not found to influence pain control in the postoperative period. A single dose of diclofenac and ketorolac<sup>12,13</sup> before inducing anesthesia decreased the consumption of morphine and its secondary effects compared to placebo in the first 24h after the intervention. On the other hand, dexketoprofen<sup>14</sup> administered 24h prior to the surgery and

**Table 1** Search strategy in Medline.

#	Search terms	Citations
7	#6 Filters: Humans; English; Spanish	2977
6	#4 AND #5	3258
5	((((( ((((((((((«Review»[Publication Type] OR Review, Systematic OR Review, Multicase OR Review Literature OR Review, Academic OR Review of Reported Cases OR Review)) OR (((«Clinical Trial»[Publication Type]) OR «Validation Studies»[Publication Type]) OR «Evaluation Studies»[Publication Type])) OR («Clinical Trial, Phase I»[Publication Type] OR Clinical Trial, Phase 1)) OR («Clinical Trial, Phase II»[Publication Type] OR Clinical Trial, Phase 2 OR Clinical Trial, Phase II)) OR («Clinical Trial, Phase III»[Publication Type] OR Clinical Trial, Phase 3 OR Clinical Trial, Phase III)) OR («Clinical Trial, Phase IV»[Publication Type] OR Clinical Trial, Phase 4 OR Clinical Trial, Phase IV)) OR («Controlled Clinical Trial»[Publication Type]) OR («Multicenter Study»[Publication Type] OR Multicenter Studies OR Multicenter Study)) OR («Randomized Controlled Trial»[Publication Type] OR Randomized Controlled Trial)) OR («Cohort Studies»[Mesh] OR Cohort Study OR Studies, Cohort OR Study, Cohort OR Concurrent Studies OR Studies, Concurrent OR Concurrent Study OR Study, Concurrent OR Historical Cohort Studies OR Studies, Historical Cohort OR Cohort Studies, Historical Cohort OR Cohort Study, Historical OR Historical Cohort Study OR Study, Historical Cohort OR Analysis, Cohort OR Analyses, Cohort OR Cohort Analyses OR Cohort Analysis OR Closed Cohort Studies OR Cohort Studies, Closed OR Closed Cohort Study OR Cohort Study, Closed OR Study, Closed Cohort OR Studies, Closed Cohort OR Incidence Studies OR Incidence Study OR Studies, Incidence OR Study, Incidence OR Cohort Studies)) OR («Cohort Studies»[Mesh] OR cohort study OR studies, cohort OR study, cohort OR concurrent studies OR studies, concurrent OR concurrent study OR study, concurrent OR historical cohort studies OR studies, historical cohort OR cohort studies, historical OR cohort study, historical OR historical cohort study OR study, historical cohort OR analysis, cohort OR analysis, cohort OR cohort analyses OR cohort analysis OR closed cohort studies OR cohort studies, closed OR closed cohort study OR cohort study, closed OR study, closed cohort OR studies, closed cohort OR incidence studies OR incidence study OR studies, incidence OR study, incidence OR cohort studies)) OR («Longitudinal Studies»[Mesh] OR Longitudinal Study OR Studies, Longitudinal OR Study, Longitudinal OR Longitudinal Survey OR Longitudinal Surveys OR Survey, Longitudinal OR Surveys, Longitudinal OR Longitudinal Studies)) OR («Follow-Up Studies»[Mesh] OR Follow Up Studies OR Follow-Up Study OR Studies, Follow-Up OR Study, Follow-Up OR Followup Studies OR Followup Study OR Studies, Followup OR Study, Followup OR Follow-Up Studies)) OR («Prospective Studies»[Mesh] OR Prospective Study OR Studies, Prospective OR Study, Prospective OR Prospective Studies)) OR («meta-analysis»[Publication Type] OR «meta-analysis as topic»[MeSH Terms] OR «meta-analysis»[All Fields]))	4,426,305
4	#1 AND #2 AND #3	4729
3	Risk factors[MH] OR causalities OR multifactorial causality OR causalities, multifactorial OR causality, multifactorial OR multifactorial causalities OR multiple causation OR causation, multiple OR causalities, multiple OR multiple causalities OR reinforcing factors OR factors, reinforcing OR factors, reinforcing OR reinforcing factor OR causation OR causalities OR enabling factors OR enabling factor OR factors, enabling OR factors, enabling OR predisposing factors OR factors, predisposing OR factors, predisposing OR predisposing factor OR determinant OR predictor OR predict* OR prognostic	1,542,865
2	Search «pain, postoperative»[MeSH Terms] OR («pain»[All Fields] AND «postoperative»[All Fields]) OR «postoperative pain»[All Fields] OR («postoperative»[All Fields] AND «pain»[All Fields]) OR («pain, postoperative»[MeSH Terms] OR («pain»[All Fields] AND «postoperative»[All Fields]) OR «postoperative pain»[All Fields] OR («postoperative»[All Fields] AND «pains»[All Fields]) OR «postoperative pains»[All Fields]) OR «pain»[MeSH Terms] OR «pain»[All Fields]	536,118
1	Osteoarthritis OR Osteoarthrosis OR Osteoarthroses OR Arthritis, Degenerative OR Arthritides, Degenerative OR Coxarthrosis OR Arthroplasties, Replacement, Hip OR Arthroplasties, Replacement, Hip OR Hip Prosthesis Implantation OR Hip Replacement, Total OR Hip Replacements, Total OR Arthroplasties, Replacement, Knee OR Knee Replacement, Total OR Knee Replacements, Total	315,207

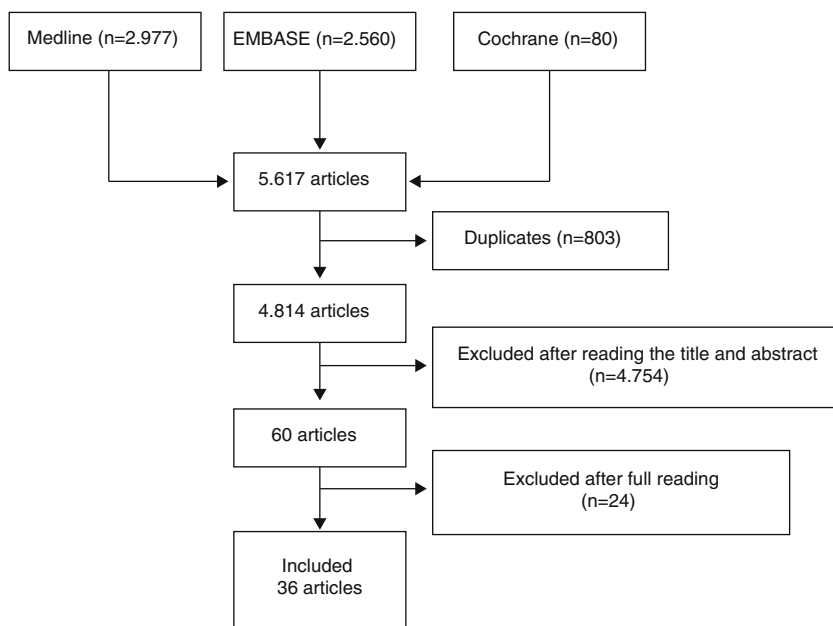


Figure 1 Flow diagram of the articles included.

up to 48 h after the intervention improved pain at 15 h and decreased the consumption of opioids.

A total of five studies used celecoxib preventively,<sup>15-19</sup> administered between 1 h and 2 weeks before surgery. The result was a decrease in pain and consumption of opioids in the immediate postoperative period (the first 72 h). Long-term results were not as consistent. One study<sup>17</sup> which used celecoxib 1 h before and for 3 weeks after the surgery observed an improvement of postoperative pain compared to placebo up to 28 days later. The use of tenoxicam<sup>20</sup> 1 h before the intervention did not influence pain improvement and consumption of opioids in the short term. After 9 postoperative days, despite no differences in pain compared to placebo being observed, the consumption of opioids was lower among the treated group.

The effect of etoricoxib 1 and 2 h prior to the surgery was also assessed,<sup>21</sup> and a decrease in the levels of interleukin-6 and prostaglandin E-2 in the blood compared to the control group was observed, as well as a lower level of pain, which was maintained until the third or fourth day. The consumption of opioids was higher among the control group during the first postoperative 12 h. The use of rofecoxib<sup>22-24</sup> 1 h before the intervention decreased the length of hospital admission and improved postoperative pain and analgesic intake after 2 days. These results were not maintained after discharge.

It was observed that lornoxicam<sup>25</sup> at high doses 15 min before the surgery and at low doses in the postoperative period decreased the consumption of opioids, but this was not associated to a clear decrease of postoperative pain. Parecoxib<sup>16,26</sup> during induction of anesthesia and 12 h after it improved postoperative pain and decreased the intake of morphine. The analgesic effects were still evident after 24 h when two injections separated by 12 h were administered.

Preventive analgesia strategies with NSAIDs were safe, except for an increase of perioperative bleeding, which was observed with ibuprofen<sup>11</sup> and ketorolac.<sup>13</sup> This effect was not observed with parecoxib<sup>16,26</sup> and celecoxib.<sup>15,17-19</sup>

### Preventive treatment with opioids

In general, preventive administration of opioids is safe and decreases the consumption of opioids in the immediate postoperative period. Several studies also reported an improvement in immediate postoperative analgesia. There are no data regarding their long-term effects.

Several studies have used morphine<sup>21,27-32</sup> in oral, intravenous and intramuscular formulations applied from 1 h before the surgery up to the moment of anesthetic induction and have observed a decrease in the levels of pain and consumption of opioids during the first postoperative hours, except in the case of a low quality study,<sup>27</sup> in which the pain increased among patients treated with oral morphine 1 h prior to the surgery.

The use of oxycodone<sup>18,19</sup> was assessed in two low-quality studies and obtained contradictory results both for pain control and opioid intake in the postoperative period. The use of methadone<sup>33</sup> just after the induction and before the intervention decreased the postoperative requirement for analgesia.

### Preventive treatment with corticoids

In general, preventive use of corticoids seems to decrease both pain and opioid consumption in the postoperative period at 48 h, but not after 6 months or 1 year.

The use of dexamethasone<sup>34-36</sup> and methylprednisolone<sup>37,38</sup> were also assessed. One low-quality study<sup>36</sup> used dexamethasone during anesthetic induction and

**Table 2** Evidence table.

#	Study	Population	Intervention	Measurement of outcome	Comments
1	Adam 2005, <sup>42</sup> RCT, 3 month follow-up	<ul style="list-style-type: none"> <li>• <math>n = 40</math> TKA</li> <li>• Mean age 68 years</li> <li>• 70% females</li> <li>• Criteria ASA I–III</li> </ul>	<ul style="list-style-type: none"> <li>• Ketamine - <math>&gt;0.05</math> ml/kg, iv in bolus following anesthetic induction</li> <li>- <math>3 \mu\text{g kg}^{-1} \text{min}^{-1}</math> iv (continuous infusion) intraoperator</li> <li>- <math>1.5 \mu\text{g kg}^{-1} \text{min}^{-1}</math> iv (continuous infusion) during 48 h after surgery</li> <li>• Saline solution (same volume)</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain</li> <li>• Postoperative opioid intake</li> <li>• Knee flexion</li> <li>• Days of hospital admission</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>
2	Alexander 2002, <sup>12</sup> RCT double blind placebo control, 24 h follow-up	<ul style="list-style-type: none"> <li>• <math>n = 99</math> TKA or THA</li> <li>• Mean age 64 years</li> <li>• 63% females</li> <li>• Moderate basal pain</li> </ul>	<ul style="list-style-type: none"> <li>• Diclofenac 75 mg iv and ketorolac 60 mg iv (before anesthetic induction) in a single dose</li> <li>• Placebo iv</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain</li> <li>• Postoperative opioid intake</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>
3	Beaupre 2012, <sup>18</sup> observational prospective, 12 weeks follow-up	<ul style="list-style-type: none"> <li>• <math>n = 39</math> TKA</li> <li>• Mean age 65 years</li> <li>• 50% females</li> <li>• Moderate basal pain</li> </ul>	<ul style="list-style-type: none"> <li>• Oxycodone 10 mg oral and celecoxib 100–200 mg oral (2–12 h before surgery)</li> <li>• Anesthetic block (femoral nerve)</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain up to 12 weeks</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 2b</li> <li>• Very small sample size</li> </ul>
4	Bergeron 2009, <sup>36</sup> RCT double blind, 6 weeks follow-up, evaluation 1 year later	<ul style="list-style-type: none"> <li>• <math>n = 50</math> TKA</li> <li>• do not provide more information</li> </ul>	<ul style="list-style-type: none"> <li>• Dexamethasone 40 mg iv in anesthetic induction</li> <li>• Saline solution</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain at 6 weeks and 1 year</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1c</li> <li>• multiple biases</li> </ul>
5	Bugter 2003 <sup>11</sup> , RCT double blind placebo control, 16 days follow-up	<ul style="list-style-type: none"> <li>• <math>n = 36</math> THA</li> <li>• Mean age 61 years</li> <li>• 70% females</li> </ul>	<ul style="list-style-type: none"> <li>• Ibuprofen 600 mg/8 h oral 2 weeks before surgery</li> <li>• Placebo</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain at 24 h</li> <li>• Postoperative opioid intake at 24 h</li> <li>• Perioperative bleeding</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1c</li> <li>• multiple biases</li> <li>• Very small sample size</li> </ul>
6	Buvanendran 2003, <sup>22</sup> RCT double blind placebo control, 8 days follow-up	<ul style="list-style-type: none"> <li>• <math>n = 70</math> TKA</li> <li>• Mean age 61 years</li> <li>• 67% females</li> </ul>	<ul style="list-style-type: none"> <li>• Rofecoxib 50 mg oral preoperative 24 h before and 2 weeks after surgery</li> <li>• Placebo</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain</li> <li>• Postoperative intake of opioids and other related drugs during hospital admission</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>



Table 2 (Continued)

#	Study	Population	Intervention	Measurement of outcome	Comments
7	Buvanendran 2010, <sup>39</sup> RCT double blind placebo control, 6 months follow-up	<ul style="list-style-type: none"> <li>• <math>n = 240</math> TKA</li> <li>• Mean age 21 years</li> <li>• 68% females</li> </ul>	<ul style="list-style-type: none"> <li>• Pregabalin 300 mg oral 24 h before and 2 weeks after surgery</li> <li>• Placebo</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain until 6 months</li> <li>• Postoperative opioid intake</li> <li>• Days of hospital admission</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>
8	Casey 2006, <sup>44</sup> RCT double blind placebo control, 2 days follow-up	<ul style="list-style-type: none"> <li>• <math>n = 40</math> TKA</li> <li>• Mean age 71 years</li> <li>• 58% females</li> </ul>	<ul style="list-style-type: none"> <li>• Nimodipine 90 mg oral 1 h prior to surgery and for 48 h more</li> <li>• Placebo</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative opioid intake</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 2b</li> </ul>
9	Clarke 2009.1, <sup>40</sup> RCT placebo control, 6 months follow-up	<ul style="list-style-type: none"> <li>• <math>n = 126</math> TKA</li> <li>• Mean age 62 years</li> <li>• 35% females</li> </ul>	<ul style="list-style-type: none"> <li>• Gabapentin 100–600 mg 2 h before and 2 h after surgery</li> <li>• Placebo</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain until 6 months</li> <li>• Postoperative opioid intake until 6 months</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>
10	Clarke 2009.2, <sup>41</sup> RCT placebo control, 2 days follow-up	<ul style="list-style-type: none"> <li>• <math>n = 40</math> TKA</li> <li>• Mean age 61 years</li> <li>• 61% females</li> </ul>	<ul style="list-style-type: none"> <li>• Gabapentin 100–600 mg 2 h before and 2 h after surgery</li> <li>• Placebo</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain at 2 days</li> <li>• Postoperative opioid intake at 2 days</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 2b</li> </ul>
11	Duellman 2009, <sup>19</sup> observational retrospective	<ul style="list-style-type: none"> <li>• <math>n = 127</math> TKA or THA</li> <li>• Mean age 62 years</li> <li>• 48% females</li> </ul>	<ul style="list-style-type: none"> <li>• Oxycodone and celecoxib or valdecoxib (from surgery, different doses and patterns) and during postoperative period</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative opioid intake</li> <li>• Days of hospital admission</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 2b</li> </ul>
12	Eggers 1999, <sup>20</sup> RCT placebo control, 9 days follow-up	<ul style="list-style-type: none"> <li>• <math>n = 101</math> TKA</li> <li>• Mean age 67 years</li> <li>• &lt;50% females</li> </ul>	<ul style="list-style-type: none"> <li>• Tenoxicam 40 mg oral 1 h before surgery +20 mg iv at 24 h + 20 mg oral 8 days</li> <li>• Tenoxicam 40 mg iv 1 h after surgery + 20 mg iv at 24 h + 20 mg oral 8 days</li> <li>• Placebo</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain at 48 h and 3–9 days</li> <li>• Postoperative opioid intake at 48 h and at 3–9 days</li> <li>• Postoperative consumption of analgesics at 48 h, 3–9 days</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>

Table 2 (Continued)

#	Study	Population	Intervention	Measurement of outcome	Comments
13	Feng 2008, <sup>23</sup> RCT placebo control, 3 days follow-up	<ul style="list-style-type: none"> <li>• <math>n = 34</math> TKA</li> <li>• Mean age 66 years</li> <li>• 69% females</li> </ul>	<ul style="list-style-type: none"> <li>• Rofecoxib 25 mg 1 h before surgery</li> <li>• Placebo</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain at 48–72 h</li> <li>• Postoperative opioid intake at 48–72 h</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 2b</li> <li>• Very small sample size</li> </ul>
14	Fletcher 1995, <sup>13</sup> RCT double blind placebo control, 5 days follow-up	<ul style="list-style-type: none"> <li>• <math>n = 60</math> THA</li> <li>• Mean age 64 years</li> <li>• 60% females</li> </ul>	<ul style="list-style-type: none"> <li>• Ketorolac 60 mg some hours before surgery</li> <li>• Placebo</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain</li> <li>• Postoperative opioid intake</li> <li>• Perioperative bleeding</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>
15	Hendolin 1996, <sup>27</sup> RCT, follow-up 24 h	<ul style="list-style-type: none"> <li>• <math>n = 41</math> TKA</li> <li>• Mean age 70 years</li> <li>• 90% females</li> </ul>	<ul style="list-style-type: none"> <li>• Morphine 0.14 mg/kg intramuscular 1 h before surgery</li> </ul>	<ul style="list-style-type: none"> <li>• Pain post-operative</li> <li>• Postoperative opioid intake</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 2b</li> </ul>
16	Ho 2010, <sup>45</sup> observational prospective, 2 days follow-up	<ul style="list-style-type: none"> <li>• <math>n = 50</math> TKA</li> </ul>	<ul style="list-style-type: none"> <li>• Duloxetine 60 mg 2 h before surgery and following day</li> <li>• Placebo</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain</li> <li>• Postoperative opioid intake</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>
17	Huang 2008, <sup>15</sup> RCT, 7 days follow-up	<ul style="list-style-type: none"> <li>• <math>n = 80</math> TKA</li> <li>• Mean age 70 years</li> <li>• Moderate basal pain</li> </ul>	<ul style="list-style-type: none"> <li>• Celecoxib 400 mg 1 h prior to surgery + 200 mg/12 h 5 days</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain at 48–72 h</li> <li>• Postoperative opioid intake at 48–72 h</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 2a</li> </ul>
18	Inan 2007, <sup>25</sup> RCT double blind placebo control, 2 days follow-up	<ul style="list-style-type: none"> <li>• <math>n = 46</math> TKA</li> <li>• Elderly</li> <li>• &gt;80% females</li> </ul>	<ul style="list-style-type: none"> <li>• Lornoxicam high dose 15 min before surgery and a low postoperative dose</li> <li>• Placebo</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain</li> <li>• Postoperative opioid intake</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>
19	Iohom 2002, <sup>14</sup> RCT placebo control, 2 days follow-up	<ul style="list-style-type: none"> <li>• <math>n = 30</math> THA</li> <li>• Mean age 62 years</li> <li>• ASA I–II</li> </ul>	<ul style="list-style-type: none"> <li>• Dexketoprofen 25 mg 24 h prior to surgery and up to 48 h after surgery</li> <li>• Placebo</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain at 15 h</li> <li>• Postoperative opioid intake</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> <li>• Very small sample size</li> </ul>



Table 2 (Continued)

#	Study	Population	Intervention	Measurement of outcome	Comments
20	Ittichaikulthol 2010, <sup>16</sup> RCT placebo control, 2 days follow-up	<ul style="list-style-type: none"> <li>• <i>n</i> = 120</li> <li>• THA and TKA</li> <li>• Age 18–75 years</li> <li>• ASA I–II</li> </ul>	<ul style="list-style-type: none"> <li>• Parecoxib 40 mg 1 h before surgery</li> <li>• Celecoxib 400 mg preoperative</li> <li>• Placebo</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain</li> <li>• Postoperative opioid intake</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>
21	Hwang 2009, <sup>43</sup> observational prospective, 2 days follow-up	<ul style="list-style-type: none"> <li>• <i>n</i> = 40 ARC</li> <li>• Mean age &lt;50 years</li> <li>• 45% females</li> <li>• Criteria ASA I–II</li> </ul>	<ul style="list-style-type: none"> <li>• Magnesium sulfate - 50 mg/kg infusion iv 15 min before surgery</li> <li>• 15 mg/kg infusion iv during surgery</li> <li>• Saline solution (same volume)</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain at 48 h</li> <li>• Postoperative opioid intake 48 h</li> <li>• Global satisfaction</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>
22	Kardash 2008, <sup>34</sup> RCT double blind placebo control, 2 days follow-up	<ul style="list-style-type: none"> <li>• <i>n</i> = 50</li> <li>• THA, unilateral or total</li> <li>• Mean age 68 years</li> <li>• 50% females</li> </ul>	<ul style="list-style-type: none"> <li>• Dexamethasone 40 mg iv, 10 min before surgery</li> <li>• Ibuprofen 400 mg/6 h oral (during 48 h)</li> <li>• Paracetamol 650 mg/6 h oral (during 48 h)</li> <li>• Placebo</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain</li> <li>• Postoperative opioid intake</li> <li>• CRP levels</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>
23	Lunn 2011, <sup>38</sup> RCT double blind placebo control, 2 days follow-up	<ul style="list-style-type: none"> <li>• <i>n</i> = 48 TKA</li> <li>• Mean age 66 years</li> <li>• 50% females</li> <li>• ASA I–II</li> </ul>	<ul style="list-style-type: none"> <li>• Methylprednisolone 125 mg (2 ml) iv, single dose before surgery</li> <li>• Placebo</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain at 48 h</li> <li>• Opioid savings at 48 h</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>
24	Lunn 2013, <sup>37</sup> double blind placebo control, 2 days follow-up	<ul style="list-style-type: none"> <li>• <i>n</i> = 48 THA</li> <li>• Mean age 66 years</li> <li>• 56% females</li> <li>• ASA I–II</li> </ul>	<ul style="list-style-type: none"> <li>• Methylprednisolone 125 mg (2 ml) iv, single dose before surgery</li> <li>• Placebo</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain at 48 h</li> <li>• Opioid savings at 48 h</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>
25	Mallory 2002, <sup>24</sup> observational prospective, 24 days follow-up	<ul style="list-style-type: none"> <li>• <i>n</i> = 317</li> <li>• TKA or THA</li> <li>• Mean age 64 years</li> <li>• 50% females</li> </ul>	<ul style="list-style-type: none"> <li>• Rofecoxib or celecoxib 2 weeks before surgery and for 10 days after</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain</li> <li>• Days of hospital admission</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 2a</li> </ul>

Table 2 (Continued)

#	Study	Population	Intervention	Measurement of outcome	Comments
26	Martinez 2007, <sup>26</sup> RCT placebo control, 5 days follow-up	<ul style="list-style-type: none"> <li>• <math>n = 78</math> THA</li> <li>• Mean age 63 years</li> <li>• 50% females</li> </ul>	<ul style="list-style-type: none"> <li>• Pre group:               <ul style="list-style-type: none"> <li>- Parecoxib 40 mg iv in induction and 12 h after induction</li> <li>- Placebo 40 mg iv.</li> </ul>               During surgical wound closure             </li> <li>• Post group:               <ul style="list-style-type: none"> <li>- Parecoxib 40 mg iv.</li> </ul>               During wound closure and 12 h after induction             </li> <li>• Control group:               <ul style="list-style-type: none"> <li>- Placebo 40 mg iv.</li> </ul>               During induction, wound closure and 12 h after induction             </li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain</li> <li>• Postoperative opioid intake</li> <li>• Perioperative bleeding</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>
27	Mc Swiney 1997 <sup>29</sup> , RCT double blind, 24 h follow-up	<ul style="list-style-type: none"> <li>• <math>n = 50</math> TKA</li> <li>• No explicit data provided on basal characteristics. Authors indicate that there were no differences between groups</li> </ul>	<ul style="list-style-type: none"> <li>• Experimental group:               <ul style="list-style-type: none"> <li>- Morphine 0.125 mg/kg (60 ml saline solution) iv</li> </ul> </li> <li>• Control group:               <ul style="list-style-type: none"> <li>- Morphine 0.125 mg/kg intramuscular in opposite leg</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain</li> <li>• Postoperative opioid intake</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>
28	Meurnier 2007, <sup>17</sup> RCT placebo control, 1 year follow-up	<ul style="list-style-type: none"> <li>• <math>n = 44</math> TKA</li> <li>• Mean age 68 years</li> <li>• 55% females</li> <li>• ASA I–II</li> </ul>	<ul style="list-style-type: none"> <li>• Celecoxib 200 mg oral 1 h before surgery and during 3 weeks after (2 times per day)</li> <li>• Placebo 200 mg oral 1 h before surgery and during 3 weeks after (2 times per day)</li> <li>• Anesthetic technique: subarachnoid spinal with 17.5 isobaric bupivacaine at 20 mg</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain until 28 days</li> <li>• Perioperative bleeding</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>
29	Park 1996, <sup>46</sup> RCT double blind placebo control, 36 h follow-up	<ul style="list-style-type: none"> <li>• Population (<math>n = 39</math>) TKA</li> <li>• Mean age 67 years</li> <li>• 60% females</li> <li>• ASA I–III</li> </ul>	<ul style="list-style-type: none"> <li>• Clonidine 5 <math>\mu\text{g kg}^{-1}</math> oral 1.5 h before surgery, 12 h and 24 h after initial dose</li> <li>• Placebo same dose oral</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain</li> <li>• Postoperative opioid intake</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>

Table 2 (Continued)

#	Study	Population	Intervention	Measurement of outcome	Comments
30	Porter 1983, <sup>33</sup> RCT double blind	<ul style="list-style-type: none"> <li>• <i>n</i> = 26 THA or TKA</li> <li>• Mean age 63 years</li> <li>• 50% females</li> </ul>	<ul style="list-style-type: none"> <li>• Group I: methadone 10 mg iv just after induction of anesthesia</li> <li>• Group P: methadone 10 mg, iv. After intervention (3 h after induction)</li> <li>• Group I: neuromuscular block pancuronium 0.1 mg/kg</li> <li>• Group P: bupivacaine 0.5% extradural</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative opioid intake</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> <li>• Very small sample size</li> </ul>
31	Rasmussen 2010, <sup>35</sup> RCT double blind placebo control, 24 h follow-up	<ul style="list-style-type: none"> <li>• <i>n</i> = 42 THA</li> <li>• Mean age 71 years</li> <li>• 57% females</li> <li>• ASA I–III</li> <li>• Moderate basal pain</li> </ul>	<ul style="list-style-type: none"> <li>• Experimental group: <ul style="list-style-type: none"> <li>- Gabapentin 1200 mg 1 h before anesthesia</li> <li>- Dexamethasone 8 mg iv before anesthetic induction</li> <li>- Ketamine 0.15 mg/kg preoperative</li> <li>- Paracetamol 1 g q hour before anesthesia</li> <li>- Ketorolac 15 mg at the end of surgery</li> </ul> </li> <li>• Control group: <ul style="list-style-type: none"> <li>- Placebo 1200 mg 1 h before anesthesia</li> <li>- Placebo 8 mg iv before anesthetic induction</li> <li>- Paracetamol 1 g 1 h before anesthesia</li> <li>- Ketorolac 15 mg at the end of surgery</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain</li> <li>• Postoperative opioid intake</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>
32	Reiter 2003, <sup>32</sup> RCT double blind placebo control, 24 h follow-up	<ul style="list-style-type: none"> <li>• <i>n</i> = 98 TKA or THA</li> <li>• Mean age 62 years</li> <li>• 60% females</li> <li>• ASA I–III</li> </ul>	<ul style="list-style-type: none"> <li>• Morphine 20 mg oral 1 h before surgery</li> <li>• Placebo 20 mg oral 1 h before surgery</li> <li>• Anesthesia with phentanyl 3 µg/kg iv, thiopental 3–5 mg/kg iv and vecuronium 0.1 mg/kg iv. Maintained with isoflurane and nitrous oxide at 60% in O<sub>2</sub></li> </ul>	<ul style="list-style-type: none"> <li>• Pain postoperative</li> <li>• Postoperative opioid intake</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>
33	Renner 2011, <sup>21</sup> RCT double blind, 24 h follow-up	<ul style="list-style-type: none"> <li>• <i>n</i> = 11 THA</li> <li>• Mean age 68 years</li> <li>• 83% females</li> </ul>	<ul style="list-style-type: none"> <li>• Etoricoxib 120 mg oral 2 h before surgery; 120 mg oral 1 day after surgery</li> <li>• Placebo oral 2 h before surgery, oral 1 day after surgery</li> </ul>	<ul style="list-style-type: none"> <li>• Inhibition of prostaglandin production</li> <li>• Suppression of IL-6 increase</li> <li>• Postoperative pain</li> <li>• Postoperative opioid intake</li> <li>• Overall satisfaction</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> <li>• Very small sample size</li> </ul>

Table 2 (Continued)

#	Study	Population	Intervention	Measurement of outcome	Comments
34	Skinner 2004, <sup>47</sup> observational prospective	<ul style="list-style-type: none"> <li>• <i>n</i> = 102 TKA or THA</li> <li>• Mean age 63 years</li> <li>• 65% females</li> </ul>	<ul style="list-style-type: none"> <li>• Experimental group:               <ul style="list-style-type: none"> <li>- Preoperative (immediately before surgery): rofecoxib 50 mg oral; tramadol 50 mg oral; paracetamol 650 mg oral; dexamethasone 2 mg oral</li> <li>- Postoperative (hospital): rofecoxib 50 mg/day oral; tramadol 50 mg/6 h oral; paracetamol 650 mg/6 h oral; hydrocodone 5 mg/paracetamol 500 mg oral, 1–2 tablets/4 h and iv opioids on demand</li> <li>- Postoperative (following discharge): rofecoxib 50 mg/day oral; tramadol 50 mg/6 h oral; hydrocodone 5 mg/paracetamol 500 mg oral 1–2 comp/4 h</li> <li>- Postoperative (following heparin, 14 days): rofecoxib 50 mg/day oral; tramadol 50 mg/6 h oral; aspirin 350 mg/day</li> <li>- Bupivacaine 0.25% intraarticular 2 ml/h during 48 h (for TKA patients)</li> </ul> </li> <li>• Control group: conventional therapy</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain</li> <li>• Adverse events</li> </ul>	Quality 2b
35	Slowey 1985, <sup>30</sup> RCT, 24 h follow-up	<ul style="list-style-type: none"> <li>• <i>n</i> = 30 THA</li> <li>• Mean age 65 years</li> <li>• 60% females</li> <li>• ASA I–II</li> </ul>	<ul style="list-style-type: none"> <li>• Intramuscular group: morphine 15 mg intramuscular 1 h before surgery; placebo oral 1 h before surgery (3 tablets)</li> <li>• Oral group-60: placebo intramuscular 1 h before surgery; morphine 30 mg LC oral 1 h before surgery (2 tablets); placebo oral 1 h before surgery (1 tablet)</li> <li>• Oral group-90: placebo intramuscular 1 h before surgery; morphine 30 mg LC oral 1 h before surgery (3 tablets)</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> <li>• Very small sample size</li> </ul>

Table 2 (Continued)

#	Study	Population	Intervention	Measurement of outcome	Comments
36	Wong 1997, <sup>31</sup> observational prospective 3 days follow-up	<ul style="list-style-type: none"> <li>• <i>n</i> = 45 TKA</li> <li>• Mean age 61 years</li> <li>• 50% females</li> <li>• ASA I–II</li> </ul>	<ul style="list-style-type: none"> <li>• Group G:               <ul style="list-style-type: none"> <li>- 30 min before surgery and upon incision: saline solution 15 ml iv</li> <li>- 30 and 60 min postoperative: saline solution 10 ml</li> </ul> </li> <li>• Group EA:               <ul style="list-style-type: none"> <li>- 30 min before surgery and upon incision: lidocaine 2% 15 ml iv</li> <li>- 30 and 60 min postoperative: lidocaine 2% 10 ml; morphine 1.5 mg, ketamine 20 mg</li> </ul> </li> <li>• Group EB:               <ul style="list-style-type: none"> <li>-30 min before surgery and upon incision: lidocaine 2% 15 ml iv, morphine 1.5 mg, ketamine 20 mg</li> <li>-30 and 60 min postoperative: lidocaine 2% 10 ml</li> </ul> </li> <li>• Anesthetic technique: general anesthesia (group G), epidural lidocaine (groups EA, EB)</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative pain</li> <li>• Postoperative opioid intake</li> <li>• Overall satisfaction</li> <li>• Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Quality 1b</li> </ul>

h: hours; iv: intravenous; kg: kilogram; mg: milligram; min: minute; ml: milliliter; RCT: randomized clinical trial; THA: total hip arthroplasty; TKA: total knee arthroplasty.

the results, assessed at 6 months and 1 year, showed no improvement in pain and opioid consumption. Another study, in which dexamethasone was used minutes before surgery,<sup>34</sup> reported an improvement of dynamic pain during rehabilitation and a decrease in opioid consumption during the postoperative period, albeit with no effect on pain at rest. One study<sup>35</sup> associated dexamethasone with gabapentin and ketamine in a multimodal analgesia protocol and observed an improvement in the levels of postoperative pain, but no decrease in opioid intake. Two studies<sup>26,27</sup> reported that the use of methylprednisolone prior to surgery improved postoperative pain at 48 h and decreased opioid intake.

### Preventive treatment with anticonvulsants

In general, preventive administration of pregabalin seemed to decrease neuropathic pain and opioid consumption in the immediate and long-term postoperative period. However, there is not enough evidence of its effect on postoperative nociceptive pain. Its secondary effects could represent a limitation. There is not enough conclusive evidence about gabapentin.

One study<sup>39</sup> assessed neuropathic pain following knee arthroplasty after administering pregabalin 24 h before the surgery and 2 weeks after the intervention and reported a decrease in neuropathic pain up to 6 months after the surgery, as well as reduced intrahospital consumption of opioids, shorter hospital stay and increased range of movement during the first 30 days of rehabilitation (compared to placebo). However, the secondary effects, particularly somnolence and obtundation, were more pronounced with pregabalin.

Gabapentin has been used on its own and as part of multimodal analgesia protocols. Isolated gabapentin administered 2 h prior to the surgery was used in two studies.<sup>40,41</sup> The first of them<sup>40</sup> concluded that it did not decrease the level of pain and opioid consumption compared to placebo in the immediate postoperative period and after 6 months, whereas the second study<sup>41</sup> did observe a reduced consumption of opioids among patients treated with gabapentin. However, the latter was a low-quality study, with a short follow-up period. Gabapentin<sup>35</sup> used as part of a multimodal analgesia protocol including dexamethasone, ketamine and NSAIDs improved postoperative pain with no differences regarding opioid intake compared to the use of isolated NSAIDs.

**Table 3** Studies excluded after full reading and reasons for exclusion.

#	Study	Reasons for exclusion
1	Barreveld 2013	Systematic review including studies of hip and knee arthroplasties, as well as other types of surgery
2	Becchi 2007	Main objective was analgesia with continuous psoas compartment block (no preventive analgesia with drug treatment)
3	Berger 2009	No comparison group
4	Brooks 2003	Case report describing an epidural catheter
5	Bullingham 1984	Description of a treatment with sublingual buprenorphine initially administered perioperatively. The preemptive effect was not evaluated
6	Buvanendran 2010	Study evaluating plasma concentrations of pregabalin in blood and in LCR. Pain was not evaluated
7	Clarke 2012	Review of articles on the use of gabapentin and pregabalin in different pathologies not exclusively TKA and THA
8	De Oliveira 2012	Metaanalysis on the preoperative use of ketorolac. Mixing articles from various specialties
9	Du Manoir 2003	Use of nefopam in postoperative treatment
10	Fransen 2004	Inclusion of revision surgeries
11	Fu 2010	Inclusion of intraarticular infiltrations
12	Kilickan 2000	Evolution of epidural analgesia
13	Moretti 2012	Evaluation of a postoperative treatment
14	Hebl 2008	Three patients in the intervention group and four patients in the control group presented a diagnosis of rheumatoid arthritis
15	Koinig 1988	Arthroscopy
16	Notarnicola 2011	Only anesthetic block
17	Perrin 2009	Series of cases, pilot study with a very small sample size
18	Reuben 2002	The author retracted
19	Reuben 2007	The author retracted
20	Reuben 2008	The author retracted
21	Rosenberg 2006	Summary of several studies, insufficient data to complete data collection form
22	Schroer 2011	Preventive treatment was the same for all patients, placebo was administered in the postoperative period
23	Southworth 2009	Inclusion of other types of surgeries
24	Straube 2005	Inclusion of other types of surgeries

### Preventive treatment with other drugs

The use of ketamine and magnesium sulfate during induction of anesthesia seemed to have a beneficial effect on pain control and opioid intake during the immediate postoperative period. There is insufficient evidence about nimodipine, duloxetine and clonidine as a preventive strategy for postoperative analgesia and opioid consumption.

Ketamine administered during anesthetic induction could have a preventive effect. One study<sup>42</sup> administered it on its own and reported that, although no variations in the level of pain were observed during the first 48 h after the intervention, there was a decrease in opioid intake and knee flexion was recovered faster. Another study<sup>31</sup> associated ketamine and morphine and reported an improvement in postoperative analgesia.

The use of magnesium sulfate<sup>43</sup> in anesthetic induction reduced postoperative pain and opioid consumption during the first 48 h after the intervention. Nimodipine<sup>44</sup> administered 1 h prior to the surgery and for 48 h in the postoperative period did not reduce the level of pain and increased the use of morphine 12 h after the surgery. On the

other hand, the use of duloxetine<sup>45</sup> 2 h before the surgery and on the morning after did not change postoperative pain, but decreased the use of opioids during hospital admission. Clonidine<sup>46</sup> administered 1.5 h before the surgery, and 12 and 24 h after the initial dose, did not improve postoperative pain, but reduced the use of morphine.

### Preventive treatment with various interventions

It seems that the use of combinations of several analgesics as a preventive strategy has a beneficial effect and reduces postoperative pain and analgesic requirements.

One study<sup>47</sup> using a preoperative protocol with rofecoxib, tramadol, paracetamol and dexamethasone and a postoperative combination of rofecoxib, tramadol, paracetamol, hydrocodone and opioids reported a significant reduction in the level of pain compared to placebo.

It has not been proven that adding anesthetic blocks (femoral nerve) to oxycodone and celecoxib (2–12 h before the surgery) improved postoperative analgesia up to 12 weeks.<sup>18</sup> The preventive use of oxycodone and celecoxib or



**Table 4** Main conclusions along with level of evidence and recommendation grade<sup>a</sup>

Conclusion	LE; RG
- Preventive analgesia with NSAIDs seems to decrease both pain and opioid consumption in the postoperative period - Results were more consistent and longer-lasting with Cox-2 than with traditional NSAIDs - With traditional NSAIDs there were no significant adverse events except for perioperative bleeding, which did not appear with Cox-2	1b; A
- Preventive analgesia with opioids reduced the consumption of analgesics in the postoperative period. An improvement of analgesia was also observed in the immediate postoperative period, albeit not in the long term - Safe strategies, with no significant adverse events	1b; A
- Preventive analgesia with corticoids seems to reduce both pain and opioid consumption in the postoperative period at 48 h, but not after 6 months or 1 year	2a; B
- Preventive analgesia with pregabalin seemed to reduce neuropathic pain in the short and long term - There is insufficient evidence to determine the effect on postoperative nociceptive pain and consumption of opioids - Preventive analgesia with gabapentin did not influence postoperative pain	2b; B
- The use of ketamine and magnesium sulfate during analgesic induction seemed to have a beneficial effect on pain control and opioid consumption in the immediate postoperative period	1b; A
- There is insufficient evidence to determine the effect of preventive analgesia with nimodipine, duloxetine and clonidine	2b; B
- Preventive analgesia with combinations of various analgesics reduced pain and the need for analgesics after surgery	2b; B
- There is insufficient evidence to recommend a specific strategy for preventive analgesia or administration protocol. However, it seems that administration of one or more analgesics at some point during the preoperative process reduces postoperative pain and consumption of analgesics	2b; B

LE: level of evidence; RG: recommendation grade.

<sup>a</sup> Level of evidence and recommendation grade were established according to the Oxford quality scale.

valdecoxib from the time of surgery and in the postoperative period decreased the consumption of opioids, nausea, vomiting and the length of hospital admission.<sup>19</sup>

Furthermore, the preoperative use of gabapentin, ketamine and dexamethasone, combined with paracetamol and ketorolac improved postoperative pain compared to the use of paracetamol and ketorolac alone. There were no differences regarding morphine consumption.<sup>35</sup> The use of ketamine with morphine and epidural anesthesia with lidocaine prior to the intervention provided better postoperative analgesia compared to general anesthesia.<sup>31</sup>

## Discussion

Preventive analgesia refers to treatments started on the days before the intervention or during anesthetic induction with the objective of reducing pain and drug intake in the postoperative period. This strategy is particularly relevant among patients undergoing hip and knee arthroplasty, as these are aggressive procedures with extensive tissue damage which are usually performed on patients with previously established chronic pain.<sup>48</sup>

There are no clinical guidelines which determine the most adequate medication and pattern. In a similar review to the present one which included various types of interventions, Buvanendran<sup>49</sup> highlighted that NSAIDs had consistently proven their capacity to reduce postoperative pain levels and opioid consumption. On the other hand, the study also recommended the preoperative use of gabapentin

and local anesthetic during surgery as part of multimodal analgesia protocols. NSAIDs proved their effectiveness in a metaanalysis conducted by Ong<sup>50</sup> which evaluated studies including all types of surgeries.

This systematic literature review analyzed the effectiveness and safety of drug treatments proposed in different studies, as well as the patterns described for patients undergoing knee or hip arthroplasty.

There are no homogeneous, high-quality studies providing sufficient evidence to recommend a specific preventive strategy or administration protocol. However, it seems that the administration of one or several analgesics at some point during the preoperative process reduces the consumption of analgesics and pain during the postoperative period.<sup>18,19</sup>

Both traditional<sup>11-14</sup> and Cox-2<sup>15-17,20-23,25,26</sup> NSAIDs, as well as opioids<sup>27-33</sup> and corticoids<sup>34,37,38</sup> have been shown to be effective. The use of neuroleptics<sup>39,41</sup> could have some beneficial effect on the management of postoperative neuropathic pain, with no evidence of its effect on nociceptive pain.<sup>35,40</sup> The use of ketamine<sup>42</sup> and magnesium sulfate<sup>43</sup> during anesthetic induction seems to have a beneficial effect. There is insufficient evidence to determine the effects of nimodipine,<sup>44</sup> duloxetine<sup>45</sup> and clonidine<sup>46</sup> as part of a preventive strategy. It appears that using combinations of several analgesics as part of a preventive strategy decreases pain and the need for postoperative analgesics.<sup>19,35,47</sup>

As a limitation of our review, we could highlight that the considerable variability of drugs and preventive strategies described in the literature have notably hindered a

generalization of results. We also observed the presence of various different types of bias which affected the validity of numerous studies, therefore conditioning the reproducibility of results. However, the epidemiological characteristics of the population included in the studies selected were similar to those of patients in whom knee or hip arthroplasty is indicated in our country.<sup>51</sup> Another limitation of the present study is that it only conducts a systematic review, without delving into a metaanalysis enabling the results of the different studies to be synthesized and thus allowing a better assessment of the strength of the treatments. However, the wide variability in drugs and doses used in the studies made this approach unfeasible.

In conclusion, there is insufficient evidence to recommend a specific preventive strategy or administration protocol. However, we believe that administration of Cox-2 and/or opioids during the weeks prior to the intervention, associated to the use of drugs such as corticoids, ketamine and magnesium sulfate during anesthetic induction could be safe and effective strategies for the management of postoperative pain in patients undergoing hip or knee arthroplasty.

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## Level of evidence

Level of evidence II.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that no patient data appear in this article.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

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