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Effect of oral preemptive analgesia on pain management after total knee arthroplasty

A systematic review and meta-analysis of randomized control trials

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Abstract

Background: Total knee arthroplasty (TKA) is considered an effective treatment for osteoarthritis of the knee, however some patients may develop lingering postoperative pain and opioid abuse. This study focuses on the effects and safety of oral preemptive analgesia in TKA.

Methods: We searched PubMed, Web of Science, EMBASE, Scopus and the Cochrane Library for randomized controlled trials related to the use of oral preemptive analgesia in managing pain after TKA. The search was performed from the inception dates to December 2023. Primary outcomes included the visual analogue scale score and morphine consumption. Secondary outcomes included range of motion of the knee, duration of surgery, duration of anesthesia, bleeding intraoperatively, time to first analgesia, and adverse events.

Results: This meta-analysis included 28 randomized controlled trials with 2525 patients in total. The results showed a statistically significant decrease in visual analogue scale at several time points postoperatively for oral preemptive analgesia, both at rest and upon ambulation. There was a statistically significant decrease in morphine consumption at 24 hours and 24 to 48 hours postoperatively, as well as in cumulative morphine consumption at 48 hours postoperatively. Furthermore, oral preemptive analgesia demonstrated enhanced range of motion of the knee at 48 hours postoperatively, reduced time to first analgesia, and decreased occurrence of adverse events such as nausea and vomiting. There was no increase in duration of surgery, duration of anesthesia and bleeding intraoperatively.

Conclusion: Our findings suggest a worthwhile benefit of oral preemptive analgesia for TKA, which can improve postoperative pain and knee function while decreasing the need for morphine and adverse events. Nonetheless, the above effects are mainly short-term.

Abbreviations: CIs = confidence intervals, NSAIDs = nonsteroidal anti-inflammatory drugs, OME = oral morphine equivalent, RCTs = randomized controlled trials, ROM = range of motion, RR = relative ratio, SMD = standard mean difference, TKA = total knee arthroplasty, VAS = visual analogue scale.

Keywords: meta-analysis, oral preemptive analgesia, pain management, systematic review, total knee arthroplasty

1. Introduction

As a result of unstoppable population growth and global aging trends, the number of people diagnosed with osteoarthritis is expected to increase by 40% by 2035.[1] Total knee arthroplasty (TKA) is deemed a cost-effective intervention for knee osteoarthritis, and the rise in potential candidates is an expected outcome. Even though the vast majority of patients recover well after surgery, about 30% of patients reported their dissatisfaction, with postoperative pain being one of the main causes.[2,3] However, due to the intricate nature of the mechanisms underlying postoperative pain, a uniform standard analgesic regimen

J-cH and F-jX contributed to this article equally.

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There will be no patients involved in this study.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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for TKA has not yet been clinically developed. Conversely, the conflict between the substantial clinical requirement for postoperative analgesia and the individualized variability in analgesic prescribing has led to the misuse of opioids and spawned a variety of adverse outcomes, delaying the recovery process of patients.[4,5]

With the introduction of the concept of enhanced recovery after surgery, there has been a sustained interest in the optimization of perioperative pain management in relation to TKA.[6,7] It is important to note that the focus should not be limited to intraoperative or postoperative analgesic techniques, and that oral preemptive analgesia, as an important part of analgesic management, will help to minimize the impact of surgery on patients' functioning and expedite their recovery. Various forms of oral preemptive analgesia are presently used in clinical practice, such as nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, gabapentinoids, acetaminophen, and opioids. Single-drug or multi-drug combinations administered before surgery are the main method of pain relief and have been proven to decrease postoperative pain, opioid use, and postoperative complications to different extents.[8,9] Meta-analyses have previously been used for some oral preemptive analgesia, showing limited reliability. At the same time, there is a lack of consistency in the evidence presented on postoperative outcomes in terms of choice of analgesic medication.[10–12] The limited number of trials, small sample size, and narrow scope of the review hinder a comprehensive evaluation of the overall advantages of oral preemptive analgesia regimes in pain management after TKA. A more thorough meta-analysis is required to offer robust information on the effectiveness of oral preemptive analgesia in TKA and to provide evidence-based support for more rational and standardized medication regimens. This systematic review and meta-analysis aim to assess the overall efficacy and safety of oral preemptive analgesia in patients with TKA.

2. Methods

This meta-analysis was performed according to the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) and the AMSTAR (assessing the methodological quality of systematic reviews) guidelines.[13,14] In addition, protocol for meta-analysis was registered with PROSPERO (CRD 42022380782).

2.1. Search strategy

A systematic search of PubMed, Web of Science, EMBASE, Scopus, and the Cochrane Library was performed, covering records from inception to December 2023. There were no restrictions on country, publication status or year of publication in the search. Additionally, the reference lists of all retrieved literature were manually screened as a supplement. Included in the list of predefined search terms are TKA, preemptive analgesia, and similar topics. The search strategy was modified for each individual database (the detailed search strategies were provided in Supplementary File 1, Supplemental Digital Content, https://links.lww.com/MD/Q4).

2.2. Study selection and inclusion criteria

Population: all patients with an indication for TKA as determined by physicians and were scheduled for the procedure. Intervention: oral preemptive analgesia medication for pain management in TKA. The sample size, perioperative care, and underlying treatment of the study were not restricted. Comparison: control groups may employ a different type or dose of oral preoperative analgesic medication, a placebo, or without oral preemptive analgesia medication. Outcomes: primary outcomes: The visual analogue scale (VAS) score at 6, 12, 24, 48, 72 hours, 7 days, and 12 weeks postoperatively. VAS at rest (rVAS) and VAS upon ambulation (aVAS) were recorded separately. Morphine consumption and cumulative consumption about the first and second postoperative days. Secondary outcomes of this study included range of motion (ROM) of the knee, duration of surgery, duration of anesthesia, bleeding intraoperatively, time to first analgesia and adverse events. Study design: we only included randomized controlled trials (RCTs).

EndNote X9 (Thomson Reuters, New York) was used to manage the literature, perform filtering, categorize the document and remove duplicates. After classifying the literature and removing duplicates, 2 independent reviewers reviewed the titles and abstracts of the identified studies to exclude irrelevant parts. The full text was then downloaded and submitted to 2 other reviewers for the whole-length articles screening to identify studies that are ultimately suitable for meta-analysis. Any disputes during the process were settled by a third reviewer.

2.3. Data extraction

Two independent reviewers used Microsoft Excel for data extraction and management. The collected data components included: title, first author name, publication year, country of publication, sample size, gender, average age, types of surgery, types of analgesics, timing of intervention, dosage of oral analgesics, and duration of treatment. Data relating to the primary and secondary outcomes at each measurement time will be recorded. About morphine consumption, we converted relevant drugs to morphine equivalents uniformly to ensure consistency of extracted data.

For the missing data, attempts will first be made to contact the authors for access. If there is no response, the SDs will be calculated and extracted through recognized methods. For example, the graphic data will be extracted using WebPlotDigitizer 4.6 (Ankit Rohatgi, Oakland). If appropriate data still cannot be obtained, the study will be excluded from meta-analysis. All data were cross-checked. In addition, any objections were checked for accuracy and consistency of data by a third reviewer.

2.4. Quality assessment

Two reviewers independently assessed the risk of bias using The Cochrane Risk of Bias Tool 2.0 (RoB 2.0).[15] Assessments were divided into 6 areas, including sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reports, and other sources of bias. If required, the third reviewer should resolve divergent opinions.

2.5. Quality of evidence

Two reviewers independently assessed the quality of evidence for all outcomes through the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach. The quality of evidence was divided into 4 levels: high, moderate, low, and very low based on 5 components (limitations of design, inconsistency of results, indirectness, imprecision, and other factors).[16]

2.6. Data synthesis and meta-analysis

In this study, continuous outcome variables used the standard mean difference (SMD) as the effect measure. Dichotomous variables used relative ratio (RR) to evaluate the effect measure. All effect measure were expressed with 95% confidence intervals (CIs).

The statistic I^2 was used to measure the percentage of total variability due to heterogeneity between studies. If I^2 over 50%, indicating significant heterogeneity, the potential origins of major heterogeneity were further investigated by subgroup

analysis and/or meta-regression analysis. Types of oral preemptive analgesia medications, control modality, number of preoperative oral medications, country and type of surgery are among the complicating factors that need to be analyzed. To determine the stability of the study results, sensitivity analysis was performed for results with $I^2 > 50\%$.

When we considered the included studies to be sufficiently similar, we will further conduct a meta-analysis of the outcomes of each RCT individually. In cases where the number of studies was <5 or studies were substantially heterogeneous, we used a random-effects model.[15] Random-effects estimates will be calculated using the method based on DerSimonian and Laird.[17] RevMan 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Denmark) and STATA 13.0 (Stata Corp, College Station) were used to perform the meta-analysis. Additionally, if more than 10 studies are ultimately included, we drew the funnel plot to assess publication bias. The Egger's test was used to assess the asymmetry of the funnel plot.[18]

2.7. Ethical approvals

Ethical approvals were obtained for the original studies that were included, so no additional ethical approvals were required for this study.

3. Results

3.1. Literature search

Figure 1 is a schematic diagram of the literature selection in this study. Our initial search yielded 3522 records, of which 2845 were deleted due to duplicates. After reading the titles and abstracts of the remaining 677 records, 45 of them were selected for further full-text review. In addition, 1 RCT was manually supplemented during the full-text review process by reference. Through careful verification of the inclusion criteria, we excluded 18 RCTs and documented the reasons for exclusion in Supplementary File 2, Supplemental Digital Content, https://links.lww.com/MD/Q4. There were ultimately 28 RCTs with a total of 2525 patients included in this meta-analysis.[19–46] The included studies were published from 1999 to 2023.

3.2. Characteristics of studies

Table 1 summarizes the basic characteristics of the included RCTs. The sample sizes ranged from 7 to 113. About 11 studies were from China, and the remaining 17 studies were from countries other than China. About 14 studies were clearly unilateral TKA procedures, and the remaining 14 studies did not specify the type of procedure.

About 27 studies involved single-agent oral preemptive analgesia, including NSAIDs, gabapentinoids, antidepressants, and opioids totaling 4 categories. About 3 studies[38,44,45] involved the combination of gabapentinoids and NSAIDs as oral preemptive analgesia. About 10 studies were controlled without preemptive analgesia, 17 studies were controlled with placebo, and 1 study was controlled with NSAIDs.[45] About 25 studies set the window of time for preemptive analgesia up to 24 hours before surgery. We considered the effect of preoperative oral routine medications, with 8 studies of 3 preoperative oral medications, 7 of 2, and 16 of 1.

About 20 studies reported rVAS or aVAS scores at different postoperative time points, of which 1 study did not obtain

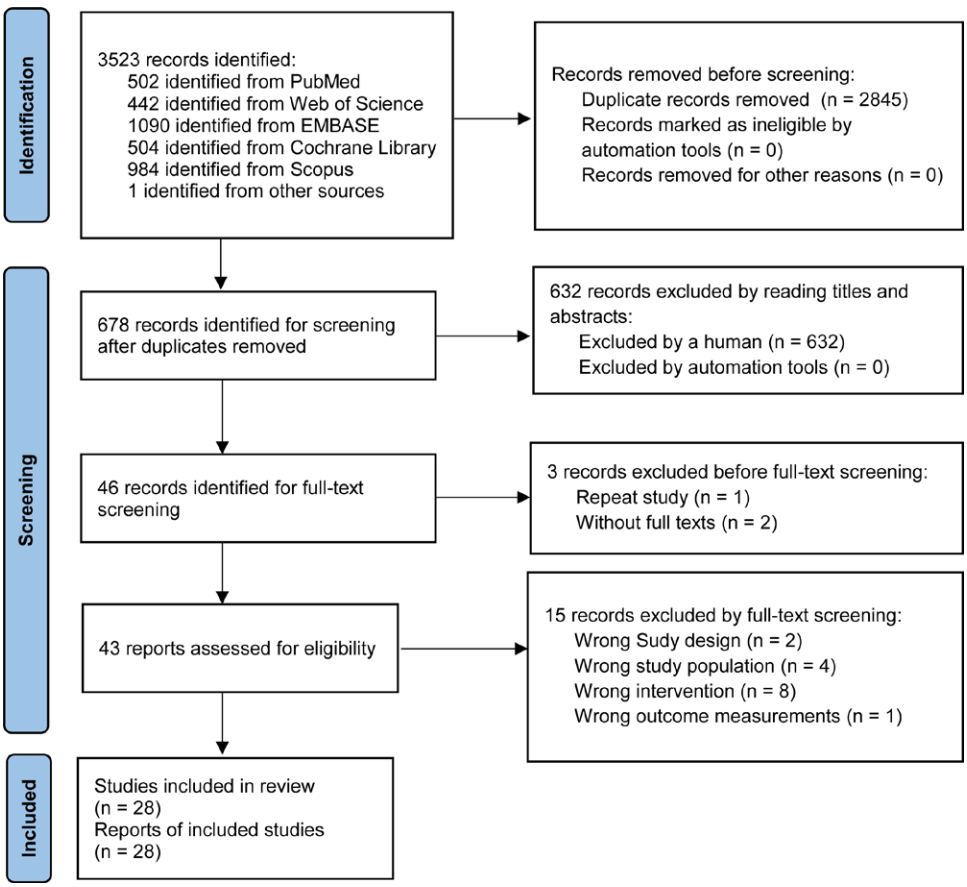

Figure 1. EMBASE = Excerpta Medica dataBASE, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PubMed = Public/Publisher MEDLINE (NLM journal articles database).

Table 1

Characteristics of the included studies.

Study	Country	Patient number		Mean (SD or range) age, yr		Sex (female/male)		Surgical approach	Intervention	Additional basic oral preemptive analgesia
		E	C	E	C	E	C			
Buvanendran et al[19]	USA	E1: 16, E2: 16	16	E1: 67 ± 6, E2: 65 ± 4	66 ± 5	E1:3, E2: 1.29	4.33	Elective primary TKR	E1: Pregabalin 150 mg orally 1 h preoperatively, 12 and 24 h postoperatively, E2: Pregabalin 150 mg orally 1 h preoperatively, placebo 12 and 24 h postoperatively, C: Placebo 1 h preoperatively, 12 and 24 h postoperatively	NA
Buvanendran et al[20]	USA	35	35	60 ± 10	62.1 ± 9.8	3.38	1.33	Elective primary TKA	E: Rofecoxib 50 mg orally at 24 h and at 1–2 h preoperatively, 50 mg daily for 5 d postoperatively, and 25 mg daily for another 8 d, C: Placebo at the same times	NA
Clarke et al[21]	Canada	E1: 7, E2: 8, E3: 7, E4: 7	7	E1:63.9 ± 5.6, E2:57.3 ± 7.4, E3:65.8 ± 6.5, E4:62.33 ± 6.6	60.7 ± 6.6	E1: 2.5, E2: 1, E3: 1.33, E4: 2.5	1.33	TKA	E1: Preoperative GBP 600 mg/postoperative placebo, E2: preoperative GBP 600 mg/postoperative GBP 100 mg 3 times per d, E3: Preoperative GBP 600 mg/postoperative GBP 200 mg 3 times/d, E4: Preoperative GBP 600 mg/postoperative GBP 300 mg 3 times/d, C: Preoperative placebo/postoperative placebo	NA
Eggers et al[22]	Australia	34	33	66.50 (46.80–79.90)	67.54 (42.80–80.50)	0.62	1.54	Elective unilateral TKA	E: Tenoxicam 40 mg orally preoperatively, 40 mg intravenously for 1 d postoperatively, and 20 mg orally daily for another 7 d, C: Placebo at the same times	Temazepam 20 mg orally 1 h preoperatively
Erkılıç et al[23]	Turkey	26	26	65.54 ± 8.93	68.65 ± 6.84	4.2	3.33	Elective TKA	E: GBP 800 mg orally 30 min preoperatively, C: Placebo 30 min preoperatively	NA
Feng et al[24]	China	17	20	69.8 ± 4.7	64.4 ± 9.1	2.75	6.5	Elective bilateral TKR	E: Rofecoxib 25 mg orally 1 h preoperatively, C: Placebo 1 h preoperatively	NA
Feng et al[25]	China	15	15	69.8 ± 4.7	64.4 ± 9.1	2.75	6.5	TKA	E: Rofecoxib 25 mg orally preoperatively, C: No oral medication preoperatively	NA
Huang et al[26]	China	40	40	70 ± 7	70 ± 7	–	–	Elective TKA	E: Celecoxib 400 mg orally 1 h preoperatively, 200 mg every 12 h for 5 d postoperatively, C: No oral medication preoperatively	NA
Ho et al[27]	Singapore	23	24	65.2 (50–80)	65.7 (51–79)	2.29	2.43	Elective knee replacement surgery	E: Duloxetine 60 mg orally 2 h preoperatively, 60 mg orally for 1 d postoperatively, C: Placebo at the same times	NA
Kim et al[28]	Korea	19	20	71.2 ± 6.5	67.0 ± 7.1	8.5	4	Primary TKA	E: Duloxetine 30 mg orally 2 wk preoperatively, 30 mg orally daily for 8 wk postoperatively, C: Placebo at the same times	Celecoxib 200 mg and pregabalin 150 mg orally 2 h preoperatively
Koh et al[29]	South Korea	40	40	69.1 ± 5.8	68.6 ± 9.5	7	5.67	Primary unilateral TKA	E: Duloxetine 30 mg orally 1 d preoperatively, 30 mg orally daily for 6 wk postoperatively, C: No oral medication preoperatively	Celecoxib 200 mg and pregabalin 150 mg orally 2 h preoperatively
Lee et al[30]	Korea	21	20	63.38 ± 10.71	67.60 ± 8.98	–	–	Elective, primary, unilateral TKA	E: Celecoxib 400 mg and pregabalin 150 mg orally 1 h preoperatively, C: Celecoxib 400 mg orally 1 h preoperatively	NA
Liszka et al[31]	Poland	80	80	73.5 ± 7.47	71.36 ± 5.23	–	–	Unilateral TKA	E: GBP 300 mg orally and methylprednisolone 125 mg intravenously preoperatively, C: Placebo at the same times	NA
Liu et al[32]	China	113	113	64.8 ± 7.3	66.0 ± 8.1	1.69	2.14	Unilateral TKA	E: Celecoxib 400 mg orally 24 h preoperatively, 200 mg every 12 h for 3 d postoperatively, C: Celecoxib 400 mg orally 2 h postoperatively, then 200 mg every 12 h for 3 d	NA
Lunn et al[33]	Denmark	59	59	68 (43–78)	67 (36–80)	1.03	0.9	Elective, unilateral, primary TKA	E: Escitalopram 10 mg orally preoperatively, 10 mg orally daily for 6 d postoperatively, C: Placebo at the same times	Celecoxib 400 mg and acetaminophen 2 g orally 1–2 h preoperatively
Meunier et al[34]	Sweden	25	25	68 ± 6.3	69 ± 7.7	2.43	0.67	Elective primary unilateral TKR	E: Celecoxib 200 mg orally 1 h preoperatively, 400 mg orally daily for 3 wk postoperatively, C: Placebo at the same times	Paracetamol 1 g orally preoperatively

(*Continued*)

Table 1

(Continued)

Study	Country	Patient number		Mean (SD or range) age, yr		Sex (female/male)		Surgical approach	Intervention	Additional basic oral preemptive analgesia
		E	C	E	C	E	C			
Motififard et al[35]	Iran	49	49	62.53 ± 5.319	64.18 ± 4.902	15.33	15.33	Primary unilateral TKA	E: Celecoxib 200 mg orally preoperatively, C: No oral medication preoperatively	NA
Munteanu et al[36]	Romania	55	55	66.7 ± 7	64.9 ± 7	4	8.17	Primary TKA	E: Etoricoxib 120 mg orally 1 h preoperatively, 120 mg orally 24 h postoperatively, C: Placebo at the same times	NA
Niruthisard et al[37]	Thailand	E1: 25, E2: 24, E3: 24	27	E1: 69 ± 5, E2: 66 ± 7, E3: 67 ± 6	67 ± 6	E1: 11.5, E2: 11, E3: 7	12.5	Primary TKA	E1: Pregabalin 150 mg and placebo orally 1 h preoperatively, E2: Celecoxib 400 mg and placebo orally 1 h preoperatively, E3: Pregabalin 150 mg and celecoxib 400 mg orally 1 h preoperatively, C: Placebo at the same times	NA
Paul et al[38]	Canada	52	49	62.1 ± 6.4	63.5 ± 6.7	1.74	1.72	Primary TKA	E: GBP 600 mg orally 2 h preoperatively, 600 mg orally daily for 2 d postoperatively, C: Placebo at the same times	Acetaminophen 1 g orally 2 h preoperatively
Shao et al[39]	China	98	98	68.2 ± 5.1	69.0 ± 5.8	2.16	1.8	TKA	E: Meloxicam 15 mg orally 24 h preoperatively, 15 mg at 4 h postoperatively, then 7.5 mg at 24, 48, 72 h postoperatively, C: Meloxicam 15 mg orally at 4 h postoperatively, then 7.5 mg at 24, 48, 72 h postoperatively	NA
Shen et al[40]	China	30	30	66 ± 6	65 ± 6	1.5	2	Unilateral TKA	E: Celecoxib 400 mg orally daily for 3 d preoperatively, 400 mg orally daily for 5 d postoperatively, C: Celecoxib 400 mg orally at 2 h postoperatively, then 400 mg orally daily for 4 d	NA
Wang et al[41]	China	40	40	65.9 ± 8.5	65.7 ± 6.3	2.08	1.86	Primary unilateral TKA	E: Acetaminophen 300 mg orally 2 h preoperatively, C: Placebo at the same times	Celecoxib 400 mg and pregabalin 150 mg orally 2 h preoperatively
Wang et al[42]	China	50	50	66 (50–80)	64 (50–78)	0.43	0.61	Primary unilateral TKA	E: Extended-release oxycodone hydrochloride 10 mg orally 2 h preoperatively, C: Placebo at the same times	Celecoxib 400 mg and pregabalin 150 mg orally 2 h preoperatively
Jianda et al[43]	China	38	37	67.8 ± 7.2	68.8 ± 6.5	2.17	1.85	Unilateral primary TKA	E: Celecoxib 400 mg orally 1 h preoperatively, 200 mg orally every 12 h postoperatively, C: No oral medication preoperatively	NA
YaDeau et al[44]	USA	E1: 30, E2: 30, E3: 30	30	E1: 67 (54–77), E2: 65 (53–79), E3: 68 (44–80)	66 (34–79)	E1: 1.5, E2: 0.75, E3: 3.35	0.88	Primary TKA	E1: Pregabalin 100 mg orally 30 min preoperatively, 100 mg orally daily for 14 d postoperatively, then 50 mg orally daily for 2 d, E2: Pregabalin 200 mg orally 30 min preoperatively, 200 mg orally daily for 14 d postoperatively, then 50 mg orally daily for 2 d, E3: Pregabalin 300 mg orally 30 min preoperatively, 300 mg orally daily for 14 d postoperatively, then 50 mg orally daily for 2 d, C: Placebo at the same times	Meloxicam 7.5 or 15 mg and dexamethasone 6 mg orally preoperatively
Yuan et al[45]	China	50	50	67.8 ± 10.12	66.2 ± 9.83	1.5	1.17	Unilateral primary TKA	E: Duloxetine 60 mg orally daily for 2 d preoperatively, 60 mg orally daily for 14 d postoperatively, C: Placebo at the same times	Celecoxib 400 mg orally daily for 2 d preoperatively
Zhou et al[46]	China	E1: 38, E2: 38, E3: 37	36	E1: 64.9 ± 7.7, E2: 61.5 ± 7.1, E3: 63.0 ± 6.5	62.6 ± 7.9	E1: 3.75, E2: 2.8, E3: 3.63	3	Elective, initial, and single TKA	E1: Pregabalin 150 mg and placebo orally at 12 and 2 h preoperatively, E2: Celecoxib 200 mg and placebo orally at 12 and 2 h preoperatively, E3: Pregabalin 150 mg and celecoxib 200 mg orally at 12 and 2 h preoperatively, C: Placebo at the same times	NA

C = control group, E = experimental group, GBP = gabapentin, NA = not available, SD = standard deviation, TKA = total knee arthroplasty.

data,[24] and 3 did not specify the measurement status of the scores.[22,28,29] About 15 studies reported postoperative morphine consumption. About 8 studies reported 24 and 48 hours postoperative ROM of the knee. About 19 studies reported duration of surgery, duration of anesthesia, bleeding intraoperatively or time to first analgesia. Adverse events were mentioned in 22 studies, but 3 of them did not report the frequency of specific events.[20,26,33]

3.3. Quality assessment

All studies were assessed for risk of bias (Fig. 2). In 3 studies, the method of random allocation was "unclear."[24,27,39] About 8 studies did not further describe allocation program concealment.[21,24,27,35,37,39,44,45] About 3 studies did not detail blinding of investigators and patients or outcome assessors.[23,26,35] All studies demonstrated a low risk of bias in terms of completeness of outcome data and selective reporting.

3.4. Certainty of evidence

The GRADE quality of evidence certainty level of evidence assessment was reported in Supplementary File 3, Supplemental Digital Content, https://links.lww.com/MD/Q4.

3.5. Primary and secondary outcomes

3.5.1. VAS at rest (rVAS). As shown in Figures S1–S7, Supplemental Digital Content, https://links.lww.com/MD/Q5 under rVAS scores, there was a significant decrease in the experimental group compared to the control group at 6 hours (SMD: −0.67, 95% CI: −0.97 to −0.38, $P < .00001$, $I^2 = 80\%$), 12 hours (SMD: −0.97, 95% CI: −1.38 to −0.56, $P < .00001$, $I^2 = 84\%$), 24 hours (SMD: −0.78, 95% CI: −1.13 to −0.43, $P < .00001$, $I^2 = 89\%$), 48 hours (SMD: −0.66, 95% CI: −1.04 to −0.28, $P = .0007$, $I^2 = 90\%$), and 72 hours (SMD: −1.02, 95% CI: −1.68 to −0.35, $P = .003$, $I^2 = 96\%$) postoperatively. The experimental group did not show significant differences in rVAS at 7 days (SMD: −0.41, 95% CI: −1.56–0.73, $P = .48$, $I^2 = 96\%$) and 12 weeks (SMD: −0.35, 95% CI: −0.71–0.02, $P = .06$, $I^2 = 61\%$) postoperatively compared with the control group. Further subgroup analysis (Table 2, data not shown) based on types of oral preemptive analgesia medications showed that NSAIDs involved in preemptive analgesia had reduced rVAS at 6, 12, 24, 48, 72 hours postoperatively. Gabapentinoids involved in preemptive analgesia reduced the rVAS at 12 hours postoperatively, but there were no significant differences at 6, 24, 48, and 72 hours. Antidepressants involved in preemptive analgesia significantly reduced rVAS at 6, 24, 72 hours, 7 days, and 12 weeks postoperatively, but did not show a difference at 48 hours postoperatively. Only 1 study investigated the involvement of opioids in preemptive analgesia in the rVAS, but no significant differences were found at 6, 12, 24 and 48 hours postoperatively compared to the control group. Gabapentinoids in combination with NSAIDs for preemptive analgesia resulted in a significant reduction in rVAS at 12 hours postoperatively, but there were no significant differences at 6, 24, and 48 hours postoperatively.

3.5.2. VAS upon ambulation (aVAS). As shown in Figures S8–S14, Supplemental Digital Content, https://links.lww.com/MD/Q5 aVAS was significantly decreased in the experimental group at 6 hours (SMD: −0.39, 95% CI: −0.63 to −0.16, $P = .001$, $I^2 = 58\%$), 12 hours (SMD: −0.55, 95% CI: −0.98 to −0.13, $P = .01$, $I^2 = 78\%$), 24 hours (SMD: −0.71, 95% CI: −1.12 to −0.30, $P = .0007$, $I^2 = 90\%$), 48 hours (SMD: −0.90, 95% CI: −1.34 to −0.46, $P < .0001$, $I^2 = 90\%$), 72 hours (SMD: −1.16, 95% CI: −1.85 to −0.47, $P = .0009$, $I^2 = 94\%$), and 7 days (SMD: −0.90, 95% CI: −1.32 to −0.48, $P < .0001$, $I^2 = 73\%$) postoperatively compared to the control group. There was no significant difference at 12 weeks (SMD: −0.48, 95% CI: −1.05–0.08, $P = .1$, $I^2 = 84\%$) postoperatively. Further subgroup analysis (Table 3, data not shown) based on types of oral preemptive analgesia medications showed that preemptive analgesia with the involvement of

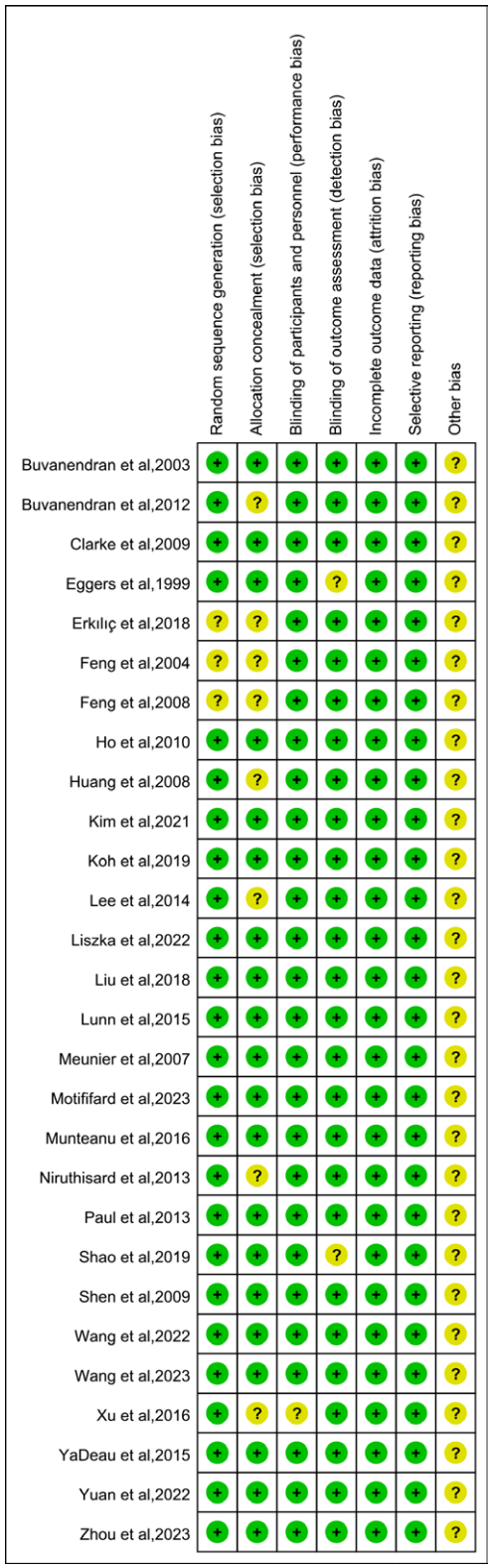

Figure 2. Risk of bias graph.

NSAIDs had reduced aVAS at 24, 48, 72 hours and 7 days postoperatively, with no significant difference at 6 and 12 hours postoperatively. Gabapentinoids involved in preemptive analgesia did not have differences at 6, 12, 24 and 48 hours postoperatively. Antidepressants involved in preemptive analgesia reduced aVAS at 6, 24, 72 hours, 7 days and 12 weeks postoperatively, but did not show a difference at 48 hours postoperatively. Opioids involved in preemptive analgesia showed no differences at 6, 12, 24, 48 hours and 12 weeks postoperatively. Gabapentinoids in combination with NSAIDs for preemptive analgesia reduced aVAS at 12 and 48 hours postoperatively. However, there was no difference at 6 and 24 hours postoperatively.

3.5.3. Morphine consumption. As shown in Figure 3A, meta-analysis of the 24 hours postoperative morphine consumption showed a significant reduction in the experimental group compared to the control group (SMD: −0.61, 95% CI: −0.97 to −0.25, $P = .0009$, $I^2 = 83\%$). Subgroup analysis (Table S3, Supplemental Digital Content, https://links.lww.com/MD/Q6) showed a reduction in 24 hours postoperative morphine consumption with NSAIDs (SMD: −0.86, 95% CI: −1.56 to −0.15, $P = .02$, $I^2 = 92\%$) or antidepressants (SMD: −0.49, 95% CI: −0.82 to −0.16, $P = .003$, $I^2 = 0\%$) as preemptive analgesia. Meta-analysis of the 24 to 48 hours postoperative morphine consumption (Fig. 3B) showed a significant reduction in the experimental group compared to the control group (SMD: −0.37, 95% CI: −0.67 to −0.08, $P = .01$, $I^2 = 41\%$). Subgroup analysis showed (Table S3, Supplemental Digital Content, https://links.lww.com/MD/Q6) that there was a decrease in morphine consumption with either NSAIDs (SMD: −0.54, 95% CI: −0.92 to −0.16, $P = .005$, $I^2 = 0\%$) or antidepressants (SMD: −0.52, 95% CI: −0.92 to −0.12, $P = .01$, I^2 = not applicable) for 24 to 48 hours postoperative morphine consumption, but there was no difference for gabapentinoids (SMD: 0.00, 95% CI: −0.39–0.39, $P = .99$, I^2 = not applicable). Meta-analysis of cumulative morphine consumption at 48 hours postoperatively (Fig. 3C) showed a significant reduction in the experimental group compared to the control group (SMD: −0.70, 95% CI: −1.18 to −0.22, $P = .004$, $I^2 = 88\%$). Subgroup analysis (Table S3, Supplemental Digital Content, https://links.lww.com/MD/Q6) showed that antidepressants (SMD: −0.44, 95% CI: −0.75 to −0.13, $P = .005$, $I^2 = 0\%$) or gabapentinoids combined with NSAIDs (SMD: −0.70–95% CI: −1.19, −0.20, $P = .006$, $I^2 = 0\%$) as preemptive analgesia had a significant reduction in cumulative morphine consumption at 48 hours postoperatively, while the remaining single drugs had no influence.

3.5.4. ROM of the knee. At 24 hours postoperatively, no significant difference in ROM of the knee was observed between groups (SMD: 0.75, 95% CI: −0.01–1.51, $P = .05$, $I^2 = 94\%$; Fig. S15, Supplemental Digital Content, https://links.lww.com/MD/Q5). However, meta-analysis at 48 hours revealed a significantly greater ROM in the experimental group compared to controls (SMD: 0.81, 95% CI: 0.12–1.50, $P = .02$, $I^2 = 94\%$; Fig. S16, Supplemental Digital Content, https://links.lww.com/MD/Q5).

3.5.5. Bleeding intraoperatively, time to first analgesia, duration of anesthesia and duration of surgery. As shown in Figure S17, Supplemental Digital Content, https://links.lww.com/MD/Q5 our assessment found no significant difference in bleeding intraoperatively in the experimental group compared to the control group (SMD: 0.12, 95% CI: −0.11–0.34, $P = .31$, $I^2 = 0\%$). In addition, the time to first analgesia was significantly longer in the experimental group (SMD: 0.93, 95%

Table 2

Visual analogue scale at rest – subgroup analysis based on types of oral preemptive analgesia.

Variable	Number. of studies	Number of participants	SMD effect estimate (95% CI)	*P*	*P*, %
NSAIDs					
6 h postoperatively	6	685	−0.75 [−1.25, −0.25]	.004	88
12 h postoperatively	6	712	−0.92 [−1.42, −0.42]	.0003	89
24 h postoperatively	9	850	−1.21 [−1.87, −0.55]	.0004	94
48 h postoperatively	9	850	−1.30 [−2.06, −0.54]	.0008	96
72 h postoperatively	6	667	−1.34 [−2.47, −0.22]	.02	97
7 d postoperatively	2	155	−0.14 [−3.86, 3.59]	.94	99
12 wk postoperatively	1	100	0.11 [−0.28, 0.50]	.58	NA
Gabapentinoids					
6 h postoperatively	2	84	−0.41 [−0.91, 0.09]	.11	0
12 h postoperatively	2	86	−0.84 [−1.47, −0.21]	.009	11
24 h postoperatively	4	221	−0.14 [−0.63, 0.34]	.57	43
48 h postoperatively	4	221	−0.07 [−0.36, 0.22]	.63	0
72 h postoperatively	1	101	0.08 [−0.31, 0.47]	.67	NA
Antidepressants					
6 h postoperatively	2	218	−0.62 [−0.90, −0.35]	< .00001	0
24 h postoperatively	4	337	−0.48 [−0.94, −0.02]	.04	76
48 h postoperatively	2	218	−0.24 [−0.62, 0.14]	.22	49
72 h postoperatively	4	337	−0.89 [−1.72, −0.06]	.04	92
7 d postoperatively	3	219	−0.53 [−0.95, −0.12]	.01	54
12 wk postoperatively	3	219	−0.52 [−0.79, −0.25]	.0001	0
Opioids					
6 h postoperatively	1	80	−0.20 [−0.64, 0.24]	.37	NA
12 h postoperatively	1	80	−0.27 [−0.71, 0.17]	.22	NA
24 h postoperatively	1	80	−0.30 [−0.74, 0.14]	.18	NA
48 h postoperatively	1	80	0.06 [−0.38, 0.50]	.79	NA
Gabapentinoids in combination with NSAIDs					
6 h postoperatively	2	82	−1.10 [−2.69, 0.48]	.17	88
12 h postoperatively	1	49	−2.61 [−3.45, −1.76]	<.00001	NA
24 h postoperatively	2	82	−1.28 [−3.39, 0.83]	.23	93
48 h postoperatively	2	82	−0.40 [−1.00, 0.19]	.19	29

CI = confidence interval, NA = not applicable, NSAIDs = nonsteroidal anti-inflammatory drugs, SMD = standard mean difference.

Table 3

Visual analogue scale upon ambulation – subgroup analysis based on types of oral preemptive analgesia.

Variable	Number. of studies	Number. of participants	SMD effect estimate (95% CI)	*P*	I^2, %
NSAIDs					
6 h postoperatively	4	359	−0.15 [−0.53, 0.23]	.44	57
12 h postoperatively	3	326	−0.31 [−0.72, 0.09]	.13	61
24 h postoperatively	7	544	−0.87 [−1.71, −0.03]	.04	94
48 h postoperatively	7	544	−1.35 [−2.18, −0.52]	.001	94
72 h postoperatively	4	381	−1.62 [−3.04, −0.20]	.03	97
7 d postoperatively	2	155	−1.25 [−1.74, −0.76]	<.00001	49
Gabapentinoids					
6 h postoperatively	2	84	−0.40 [−0.90, 0.10]	.12	0
12 h postoperatively	1	50	−0.59 [−1.25, 0.07]	.08	NA
24 h postoperatively	2	84	−0.34 [−1.13, 0.45]	.39	59
48 h postoperatively	2	84	−0.35 [−0.84, 0.15]	.17	0
Antidepressants					
6 h postoperatively	2	218	−0.66 [−0.93, −0.39]	<.00001	0
24 h postoperatively	4	337	−0.71 [−1.13, −0.28]	.001	70
48 h postoperatively	2	218	−0.20 [−0.60, 0.21]	.34	56
72 h postoperatively	4	337	−0.77 [−1.51, −0.03]	.04	90
7 d postoperatively	3	219	−0.63 [−1.04, −0.23]	.002	51
12 wk postoperatively	3	219	−0.74 [−1.08, −0.39]	<.0001	33
Opioids					
6 h postoperatively	1	100	−0.13 [−0.52, 0.26]	.51	NA
12 h postoperatively	1	100	−0.18 [−0.57, 0.22]	.38	NA
24 h postoperatively	1	100	0.21 [−0.18, 0.60]	.3	NA
48 h postoperatively	1	100	−0.23 [−0.63, 0.16]	.25	NA
12 wk postoperatively	1	100	0.23 [−0.16, 0.62]	.25	NA
Gabapentinoids in combination with NSAIDs					
6 h postoperatively	2	82	−0.85 [−1.85, 0.15]	.09	72
12 h postoperatively	1	49	−1.91 [−2.67, −1.15]	<.00001	NA
24 h postoperatively	2	82	−1.16 [−2.70, 0.38]	.14	88
48 h postoperatively	2	82	−1.31 [−2.53, −0.09]	.03	80

CI = confidence interval, NA = not applicable, NSAIDs = nonsteroidal anti-inflammatory drugs, SMD = standard mean difference.

CI: 0.26–1.60, $P = .006$, $I^2 = 92\%$; Fig. S18, Supplemental Digital Content, https://links.lww.com/MD/Q5).

Meanwhile, we found that the experimental group did not show significant differences in the duration of anesthesia (SMD: 0.11, 95% CI: −0.14–0.36, $P = .39$, $I^2 = 0\%$) and the duration of surgery (SMD: −0.08, 95% CI: −0.20–0.03, $P = .14$, $I^2 = 2\%$; Figs. S19 and S20, Supplemental Digital Content, https://links.lww.com/MD/Q5).

3.5.6. Adverse events. When analyzed separately, the incidence of nausea and vomiting each decreased in the experimental group, though neither reduction reached statistical significance compared to the control group (Figs. S21 and S22, Supplemental Digital Content, https://links.lww.com/MD/Q5). However, analysis of the composite outcome (overall nausea and vomiting) revealed a significantly lower incidence in the experimental group (RR: 0.68, 95% CI: 0.55–0.84, $P = .0003$, $I^2 = 0\%$; Fig. S23, Supplemental Digital Content, https://links.lww.com/MD/Q5). About 5 studies observed the occurrence of drowsiness (Fig. S24, Supplemental Digital Content, https://links.lww.com/MD/Q5), with a reduced incidence in the experimental group compared to the control group (RR: 1.48, 95% CI: 1.01–2.16, $P = .04$, $I^2 = 0\%$). In addition, by observing the occurrence of dizziness, pruritus, fatigue, dryness of mouth, and constipation, the total frequency of all of them decreased in the experimental group, but there was no significant difference compared with the control group (Figs. S25–S29, Supplemental Digital Content, https://links.lww.com/MD/Q5). We reviewed all included studies, and there were no studies reporting serious adverse events explicitly related to oral preemptive analgesia.

3.6. Investigation of heterogeneity

To search for potential sources of heterogeneity, we performed subgroup analysis or meta-regression analysis for types of oral preemptive analgesia medications, control modality, number of preoperative oral medications, country or type of surgery, suggesting that the above factors do not significantly affect the results (Tables 2 and 3, Tables S1–S6, and Figs. S30–S39, Supplemental Digital Content, https://links.lww.com/MD/Q6; https://links.lww.com/MD/Q5).

3.7. Publication of bias and sensitivity analyses

As shown in Figures S40–S63, Supplemental Digital Content, https://links.lww.com/MD/Q5, the results of all meta-analysis with >10 included studies were tested for publication bias by plotting funnel plots and Egger's test. The results suggested a potential publication bias for rVAS at 24 hours ($P = .036$), 72 hours ($P = .017$) and aVAS at 48 hours ($P = .019$) postoperatively, and the rest of the results did not significant asymmetric models were found. Further sensitivity analysis (Figs. S64–S82, Supplemental Digital Content, https://links.lww.com/MD/Q5) of the combined meta results for $I^2 > 50\%$ showed that no single study had a significant impact on their stability.

4. Discussion

Oral preemptive analgesia is considered part of a multimodal approach to optimizing post-TKA efficacy and contributing to rapid postoperative recovery.[47] Preemptive analgesia, which involves analgesic interventions prior to the onset of noxious stimuli to prevent central hypersensitivity, incisional and inflammatory damage, has been shown to be more effective than the same interventions performed postoperatively.[48,49]

Post-TKA pain is usually worse with movement than at rest and peaks 3 to 6 hours after surgery and lasts at least 72 hours.[50] This meta-analysis found that oral preemptive analgesia does relieve pain at rest or during activity after TKA, and that

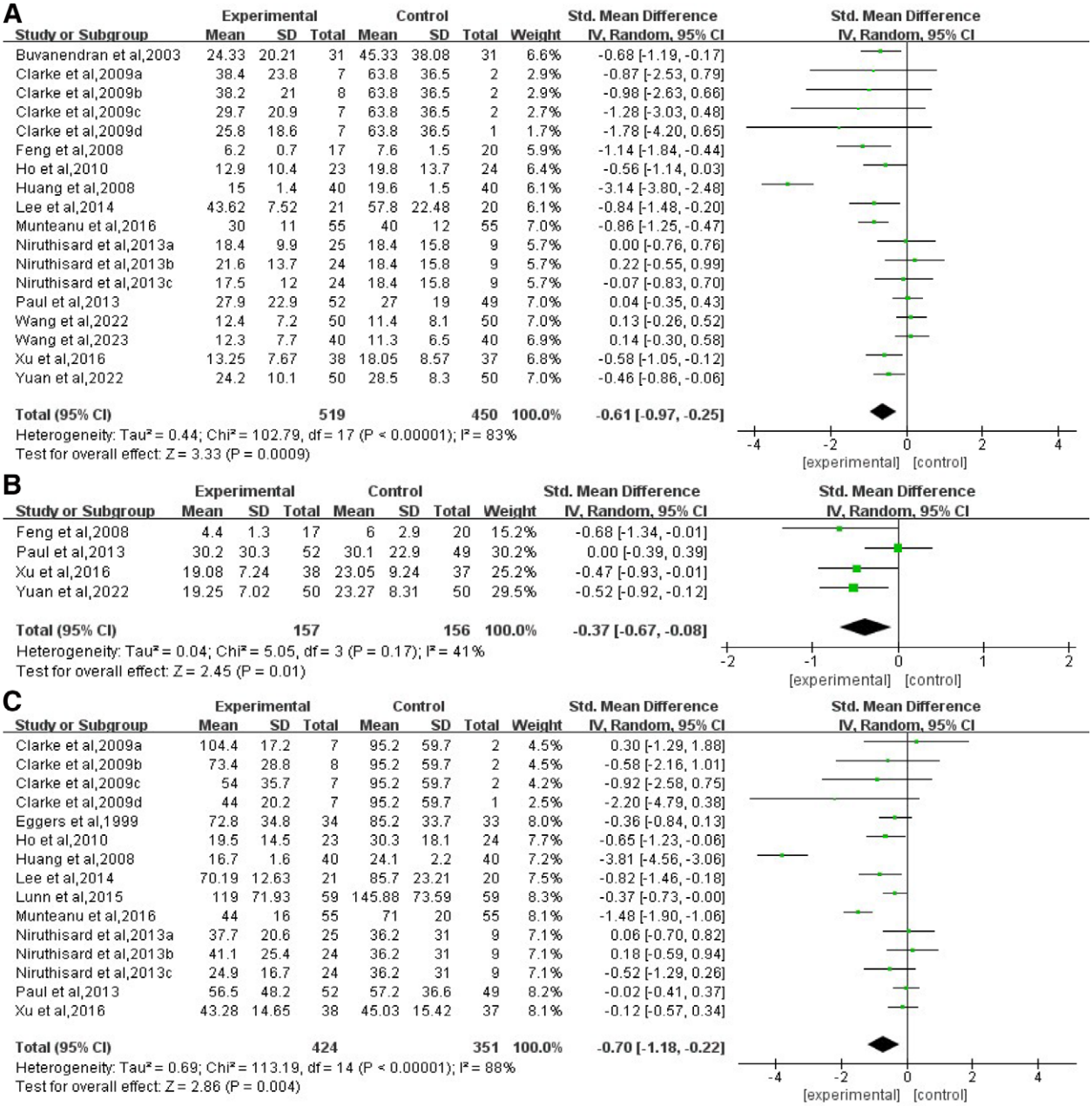

Figure 3. Forest plot of meta-analysis for morphine consumption. CI = confidence interval, SD = standard deviation.

this effect is mainly concentrated up to 72 hours postoperatively, with NSAIDs and antidepressants dominating. This study classified acetaminophen as an atypical NSAID due to its weak, nonspecific cyclooxygenase/PGHS-inhibitory and antipyretic action for combined analysis.[51] Over a longer time span, due to limited data, we could not observe the role of oral preemptive analgesia in long-term pain management. However, in subgroup analysis, we found that antidepressants had significantly lower VAS scores at 7 days and 12 weeks, both at rest and during activity. This is at variance with the trend of the findings of Yang et al,[9] and our results support the view that antidepressants may be considered for patients with potential chronic pain after TKA to help with prevention and relief. Secondly, preoperative oral opioids were not observed to provide an ameliorative effect on pain at any of the time points. The involvement of gabapentinoids alone or in combination with NSAIDs in preemptive analgesia was also only observed at a relatively small number of time points (12 hours and/or 48 hours) with positive effects on pain.

Oral preemptive analgesia overall reduced morphine consumption at 24, 24 to 48 hours, and cumulative morphine consumption at 48 hours. However, in subgroup analysis, no positive effect of gabapentinoids or opioids in 24, 24 to 48 hours morphine consumption was observed. In terms of cumulative morphine consumption at 48 hours, the combination of gabapentinoids and NSAIDs demonstrated an advantage over the use of gabapentinoids or NSAIDs alone. At 48 hours postoperatively, when pain is at its peak, the choice of combination medication appears to be more effective in managing pain while reducing morphine consumption, helping to reduce the range of risks associated with opioid abuse.

Restoration of joint function after TKA is an important part of rehabilitation, and enhanced recovery after surgery advises resumption of activity as soon as possible postoperatively. A retrospective study showed that early activity after TKA was associated with improved knee function.[52] The results of our meta-analysis were consistent with the above findings in terms

of trends, that is, oral preemptive analgesia increased in ROM of the knee at 48 hours postoperatively, but there was no difference at 24 hours postoperatively. Considering the relationship between pain relief and temporal progression as well as differences in postoperative care regimens, the short-term facilitation of joint recovery after TKA by oral preemptive analgesia (especially NSAIDs) is supported.

In addition, our results showed that the use of oral preemptive analgesia did not have additional negative effects on TKA and did not increase the duration of surgery, duration of anesthesia or bleeding intraoperatively. In view of the risk of bleeding associated with the pharmacological effects of NSAIDs, some experts recommend discontinuing NSAIDs preoperatively.[53] However, our summary conclusions suggest that its short single-dose use is safe for TKA. The results of the meta-analysis by Teerawattananon et al[54] support our view. In contrast, the use of oral preemptive analgesia overall prolonged the time to first analgesia, which was similarly beneficial in reducing opioid use. At the same time, to a certain extent, oral preemptive analgesia reduces the overall incidence of adverse events and may help to promote patient recovery and shorten the length of hospital stay.

This study has limitations primarily related to heterogeneity among the included trials. While our aim was to evaluate the overall effect of oral preemptive analgesia in TKA, variations in specific drug types, dosing regimens, and treatment courses across studies contribute to this heterogeneity. We addressed this through sensitivity analyses and careful assessment of evidence certainty (e.g., GRADE), which support the robustness of our primary conclusions regarding efficacy and safety. Secondly, exploratory analyses based on factors like patient age or gender were not performed. Future studies could investigate how these factors influence optimal dosing strategies. Furthermore, considering that the oral morphine equivalent conversion was utilized in this study, it is important to emphasize that oral morphine equivalent conversion primarily serves the purpose of dose standardization. However, the pharmacodynamic profiles and side effect patterns of different opioid medications may differ significantly. This limitation should be taken into account when interpreting the study results.

5. Conclusion

Our findings suggest a worthwhile benefit of oral preemptive analgesia for TKA, which can improve postoperative pain and knee function and reduce morphine consumption and adverse events. For pain within 72 hours postoperatively, single-agent (mainly NSAIDs or antidepressants) involvement in preemptive analgesia does not seem to be inferior to combinations. However, the long-term impact of the above effects is not clear.

Author contributions

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