Early perioperative versus postoperative meloxicam for pain control in patients undergoing orthopedic surgery: a systematic review and Meta-analysis of randomized controlled trials

Abdelrahman Mahmouda, Mohamed Abuelazmb, Ali Ashraf Salah Ahmeda, Mahmoud Elshinawya, Toka Ashoura, Mohamed Abugdidaa, and Basel Abdelazeemc,d

aFaculty of Medicine, Minia University, Minia, Egypt; bFaculty of Medicine, Tanta University, Tanta, Egypt; cDepartment of Internal Medicine, McLaren Health Care, Flint, MI, USA; dDepartment of Internal Medicine, Michigan State University, East Lansing, MI, USA

ABSTRACT

Objective: Post-orthopaedic operative pain is a serious concern that often requires the administration of analgesics; however, the optimal time of analgesic administration is still inconclusive. Perioperative analgesia is administrating pre-emptive analgesia before and during the surgery followed by postoperative analgesia to decrease the procedure associated nociceptive response. We aim to assess perioperative meloxicam versus postoperative meloxicam for pain control after orthopaedic operations.

Methods: A systematic review and meta-analysis involving randomized controlled trials from PubMed, Embase, Scopus, WOS, and Cochrane until 28th May 2022. We pooled dichotomous outcomes using risk ratio (RR) presented with a 95% confidence interval (CI) and continuous outcomes using mean difference (MD) with 95% CI. We registered our protocol in PROSPERO with ID: CRD42022336046.

Results: We included five RCTs with 964 patients. All the included trials showed high risk of performance and detection biases because of lack of blinding. Pooled analysis favored perioperative meloxicam in reducing pain score after six hours (MD: −0.42 with 95% CI [−0.63, −0.21], p = .0001), 12 h (MD: −0.54 with 95% CI [−0.69, −0.39], p = .0001), and 24 h (MD: −0.23 with 95% CI [−0.36, −0.10]). Pooled analysis favored perioperative meloxicam in improving patient global assessment scale after 12 h (MD: −0.66 with 95% CI [−0.86, −0.46], p = .0001), 24 h (MD: −0.30 with 95% CI [−0.49, −0.11], p = .002), and 48 h (MD: −0.17 with 95% CI [−0.33, −0.01], p = .04). Pooled analysis favored perioperative meloxicam in reducing patient-controlled analgesia (MD: −4.25 with 95% CI [−5.96, −2.54], p = .0001).

Conclusion: Short-term pain management after orthopaedic procedures is better accomplished with perioperative meloxicam than postoperative meloxicam. Before recommending perioperative meloxicam for pain control following orthopaedic surgeries, further multicentre trials are still warranted to examine the impact of perioperative meloxicam in different orthopaedic procedures.

1. Introduction

The main role of orthopaedic surgery is to prevent and manage musculoskeletal diseases which are associated with a high incidence of disability. Orthopaedic operations vary from arthroscopic to open major operations; however, they are associated with severe postoperative pain compared with other surgical procedures, with 58% of total knee replacement patients and 47% of total hip replacement patients reporting moderate to severe pain in the first day after surgery. Postoperative pain is a serious concern to physicians who use a variety of options, including systemic and intra-articular analgesics, to control it. Furthermore, non-steroidal anti-inflammatory drugs (NSAIDs) are widely used as a potent analgesic, antipyretic, and anti-inflammatory, with subtle evidence confirming their superiority for postoperative pain management. Despite the usage of analgesics, some patients experience worse episodes of postoperative pain than others, which affect early ambulation, delay restoring of function, and prolong the recovery period.

Meloxicam is an NSAID that is often used to treat musculoskeletal disorders by inhibiting prostaglandin synthesis and alleviating the inflammatory process. Meloxicam has been widely used to treat musculoskeletal inflammatory disorders, including osteoarthritis and rheumatoid arthritis. Multiple trials showed that pre-and postoperative administration of meloxicam decreases postoperative pain in dental procedures and total abdominal hysterectomy which can support the clinical applicability of meloxicam for perioperative pain management. Moreover, a previously published meta-analysis favored preventive administration of acetaminophen over post-incisional acetaminophen administration for pain
control and opioid consumption reduction after various surgeries.  

Perioperative analgesia is administrating pre-emptive analgesia before and during the operation followed by an around the clock dosing schedule, decreasing the physiological, procedure-provoked nociceptive response. Accordingly, perioperative analgesia can be more effective than other postoperative analgesic treatments. Furthermore, this strategy leads to reaching the therapeutic level of NSAIDs before the surgical procedure; thus, preventing the subsequently secreted prostaglandins and alleviating inflammation. However, it is still inconclusive what is the best time to administrate analgesics for postoperative pain control, with recent trials focusing mainly on orthopaedic procedures comparing perioperative versus postoperative meloxicam and reporting a positive effect of the perioperative regimen. Therefore, we conducted a systematic review and meta-analysis to synthesize evidence comparing perioperative versus postoperative meloxicam to control postoperative pain after orthopaedic operations.

2. Methodology

2.1. Protocol registration

We performed a systematic review and meta-analysis of randomized control trials (RCTs) according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA). We prospectively registered our protocol in the international prospective register of systematic reviews (PROSPERO) with ID: CRD42022336046. The PRISMA 2020 checklist is illustrated in Table S1.

2.2. Data sources and search strategy

Two investigators (M.A. and A.A.) searched the following electronic biomedical databases: Medline (PubMed), Cochrane, WOS, SCOPUS, and EMBASE (up to 28 May 2022). We did not apply any restrictions on language or date of publication. We used the following medical subject headings (MESH) terms in the searches: meloxicam, NSAIDs, Preoperative, postoperative, and pain. The detailed search strategy is available in Table S2.

2.3. Eligibility criteria

We included RCTs with the following PICO criteria: (P) population: adult patients undergoing orthopaedic operations who are not recently on prescribed analgesics; (I) intervention: perioperative meloxicam irrespective of dose, route, and time of administration; (C) control: postoperative meloxicam irrespective of dose, route, and time of administration; and (O) outcomes: our primary outcome is pain assessed using the visual analogue scale (VAS) score. (VAS) is a score that assesses the severity of self-described pain by a unidimensional approach. It is a ten-point pain scale with two endpoints: 0 (no pain) and 10 (pain as severe as one can feel). Our secondary outcomes are the patient global assessment scale (PGA) that provides the patient’s perspective according to their health status in inflammatory joint disease, permitting many holistic assessments of disease under objective tissue damage and inflammation measures, patient-controlled analgesia (PCA) or consumption of opioid analgesics by patients who suffered from intolerable pain, overall satisfaction, and adverse events (nausea, constipation, vomiting, dizziness, and drowsiness).

The exclusion criteria were as the following: observational studies, non-randomized trials, conference abstracts, thesis, editorials, letters, and reviews.

2.4. Study selection

Three reviewers (A.M., M.G., and T.A.) independently screened titles and abstracts using Covidence online software. Two investigators (A.M. and M.G.) reviewed the full manuscripts of all potentially relevant studies and applied the predetermined selection criteria, and any disagreements were settled by a third reviewer (M.A). The results of the study selection process are presented in a PRISMA flow diagram (Figure 1).

2.5. Data extraction

Four reviewers (A.M., M.S., T.A., and M.G.) used a pre-designed pilot texted extraction sheet to extract the following data: summary characteristics of the included trials (study design, patient characteristics, total participants, treatment details, duration of follow-up); baseline data (number of patients in each group, age, gender, surgery type, body mass index, operation duration, and baseline VAS score); efficacy data (VAS at rest, VAS at flexion, PGA, PCA, and overall satisfaction); and safety data (nausea, constipation, vomiting, dizziness, and drowsiness).

2.6. Risk of bias assessment

Three reviewers (A.M., M.G., and T.A.) individually evaluated the risk of bias in the included studies using the Cochrane tool of risk of bias; each study was handled by only two of the three reviewers. Any disagreement was settled by (M.A). We assessed each study on the following domains: allocation concealment, sequence generation (selection bias), blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias), incomplete data outcome (attrition bias), selective reporting (reporting bias) and other sources of bias. The risk of bias was graded as high, low, or unclear.

2.7. Statistical analysis

The statistical analysis was carried out with RevMan v5.3 software. We pooled dichotomous outcomes using risk ratio (RR) presented with a 95% confidence interval (CI) and continuous outcomes using mean difference (MD) with 95% CI. We used the I-square and Chi-square tests to examine heterogeneity; the Chi-square test determines if there is substantial heterogeneity, while the I-square determines the magnitude of
heterogeneity. A substantial heterogeneity (for the Chi-square test) is defined as an alpha level below 0.1, according to the Cochrane Handbook (chapter nine)\(^2\), while the I-square test is interpreted as follows: \((0\text{–}40%: \text{not significant}, 30\text{–}60%: \text{moderate heterogeneity}, 50\text{–}90%: \text{substantial heterogeneity}, \text{and } 75\text{–}100\% \text{ considerable heterogeneity})\). We utilized the fixed-effects model. We also conducted a subgroup analysis depending on the time of assessment and sensitivity analysis in case of significant heterogeneity to investigate the source of heterogeneity. Because we only included less than ten studies in each outcome, we did not conduct funnel plots to reveal publication bias, as advised by Egger et al.\(^2\).

3. Results

3.1. Search results and study selection

One thousand and seventy-eight records were retrieved from our searching process. Four hundred sixty-six records were duplicates and removed by Covidence. We conducted title and abstract screening on 612, yielding 607 irrelevant records, then we screened five full-text articles. Eventually, five articles were included in our systematic review and meta-analysis. The selection process is described in a PRISMA flow chart (Figure 1).

3.2. Characteristics of included studies

We included five RCTs\(^1\text{--}18\) with a total of 964 participants, with 485 patients receiving perioperative meloxicam and 479 patients receiving postoperative meloxicam. All the included trials were conducted in China. Three trials included patients undergoing arthroscopic knee surgery (AKS), another trial on total hip arthroplasty (THA), and another trial on total knee arthroplasty (TKA). Furthermore, included trials excluded patients who received analgesics within one week before enrollment. Further summary characteristics of the included trials are shown in Table 1. Male patients made up 62.8% of the perioperative group and 64.7% of the postoperative group. Further baseline characteristics of the participants are presented in Table 2.

3.3. Risk of bias and quality of evidence

The quality of the included studies was assessed in the guide of the Cochrane risk of bias tool, as presented in Figure 2.
A. Mahmoud et al.

Geneity was not explained by sensitivity analysis (Table S3).

The pooled mean difference favored perioperative meloxicam after 36 h (MD: 0.36, 95% CI [0.11, 0.66], p = 0.0003) (Figure 3). Our results were homogenous with (p > 0.1, I-square = 91%). We conducted a sensitivity analysis to investigate the source of heterogeneity; however, heterogeneity was not explained by sensitivity analysis (Table S3).

The pooled mean difference favored perioperative meloxicam over postoperative meloxicam after 12 h (MD: 0.54 with 95% CI [0.33, 0.74], p = 0.0001), and 24 h (MD: 0.26 with 95% CI [0.09, 0.43], p = 0.0003). However, we found no difference between pre and postoperative meloxicam after 36 h (MD: 0.07 with 95% CI [0.24, 0.10], p = 0.42), 48 h (MD: 0.10 with 95% CI [0.01, 0.20], p = 0.07), 72 h (MD: 0.02 with 95% CI [0.00, 0.05], p = 0.17), and 96 h (MD: 0.09 with 95% CI [0.01, 0.17], p = 0.4) (Figure 4). Our results were homogenous with (p > 0.1, I-square = 86%). We conducted a sensitivity analysis to investigate the source of heterogeneity; however, heterogeneity was not explained by sensitivity analysis (Table S4).

3.5. Secondary outcomes

3.5.1. Patient global assessment

The pooled mean difference favored perioperative meloxicam over postoperative meloxicam after 12 h (MD: -0.66 with 95% CI [-0.86, -0.46], p = 0.0001), 24 h (MD: -0.30 with 95% CI [-0.49, -0.11], p = 0.002), and 48 h (MD: -0.17 with 95% CI [-0.33, -0.01], p = 0.04) (Figure 5). Our results were homogenous with (p > 0.1, I-square = 93%), except after 12 h (p = 0.001, I-square = 86%). We conducted a sensitivity analysis to investigate the source of heterogeneity. Heterogeneity was best resolved after the exclusion of Shao et al. (p = 0.21, I-square = 36%) with favoring perioperative over postoperative meloxicam (MD: -1.19 with 95% CI [-1.49, -0.88], p = 0.0001) (Table S4).

### Table 1. Summary characteristics of the included studies.

| Study ID   | Study design | Country          | Total participants | Operation | Pre-operative group | Post-operative group | Adjuvant patient-controlled analgesics |
|------------|--------------|------------------|--------------------|-----------|---------------------|----------------------|----------------------------------------|
| Hou et al. | RCT          | One center in China | 296               | AKS       | 15 mg at 24 h before AKS, followed by 7.5 mg orally at 1 h before the AKS, then 7.5 mg at 24 h post-AKS. | 15 mg orally at 4 h after AKS, and 7.5 mg orally at 24 h after AKS. | Pethidine (meperidine) rescue analgesia |
| Ma et al.  | RCT          | Four centers in China | 136               | AKS       | 15 mg at 2 h before AKS, then 7.5 mg at 24 h after AKS. | 15 mg at 4 h after AKS, then 7.5 mg at 24 h after AKS. | Pethidine (meperidine) rescue analgesia |
| Ren et al. | RCT          | One center in China | 132               | THA       | 15 mg at 24 h before THA, then 7.5 mg at 4, 24, 48, and 72 h after THA. | 15 mg at 4 h after THA, then 7.5 mg at 24, 48, and 72 h after THA. | 1 mg fentanyl, 50 mg tramadol, and 6 mg tropisetron mesylate, with a basal rate of 1.0 mL/h, a lock-out time of 15 min and a bolus dose of 0.5 mL |
| Shao et al.| RCT          | One center in China | 196               | TKA       | 15 mg at 24 h before TKA, 7.5 mg at 4, 24, 48, and 72 h after TKA. | 15 mg at 4 h after TKA, then 7.5 mg at 24, 48, and 72 h after TKA. | 1 mg fentanyl, 50 mg tramadol, and 6 mg tropisetron mesylate, with a basal rate of 1.0 mL/h, a lock-out time of 15 min and a bolus dose of 1.0 mL |
| Yuan et al.| RCT          | One center in China | 204               | AKS       | 15 mg at 24 h before AKS, then 7.5 mg at 1 h before AKS, and 7.5 mg at 24 h after AKS. | 15 mg at 4 h after AKS, and 7.5 mg at 24 h after AKS. | Pethidine (meperidine) rescue analgesia |

Abbreviations. AKS: Arthroscopic knee surgery, THA: Total hip arthroplasty, TKA: Total knee arthroplasty, mg: milligram, mL: milliliter, h: hour, RCT: Randomized controlled trial.

All studies had a low risk of selection, attrition, and other biases. All studies had a high risk of bias of performance and detection biases. All studies had an unclear risk of bias of reporting bias. The detailed rationales for authors’ judgments are presented in Table S3.

### 3.4. Primary outcomes

#### 3.4.1. Visual analogue scale at rest

The pooled mean difference favored perioperative meloxicam over postoperative meloxicam after six hours (MD: -0.42 with 95% CI [-0.63, -0.21], p = 0.001), 12 h (MD: -0.54 with 95% CI [-0.69, -0.39], p = 0.0001), and 24 h (MD: -0.23 with 95% CI [-0.36, -0.10], p = 0.0006). However, we found no difference between pre and postoperative meloxicam after 36 h (MD: -0.02 with 95% CI [-0.19, 0.14], p = 0.77), 48 h (MD: -0.03 with 95% CI [-0.12, 0.06], p = 0.54), 72 h (MD: -0.01 with 95% CI [-0.14, 0.12], p = 0.92), and 96 h (MD: 0.04 with 95% CI [-0.09, 0.17], p = 0.52) (Figure 3). Our results were homogenous with (p > 0.1, I-square = 0%), except after 12 h (p = 0.001, I-square = 84%), 72 h (p = 0.01, I-square = 83%), and 96 h (p = 0.09, I-square = 66%). We conducted a sensitivity analysis to investigate the source of heterogeneity; however, heterogeneity was not explained by sensitivity analysis (Table S3).

#### 3.4.2. Visual analogue scale at flexion

The pooled mean difference favored perioperative meloxicam over postoperative meloxicam after six hours (MD: -0.39 with 95% CI [-0.62, -0.16], p = 0.0009), 12 h (MD: -0.56 with 95% CI [-0.72, -0.40], p = 0.0001), and 24 h (MD: -0.26 with 95% CI [-0.39, -0.12], p = 0.0003). However, we found no difference between pre and postoperative meloxicam after 36 h (MD: -0.07 with 95% CI [-0.24, 0.10], p = 0.42), 48 h (MD: -0.10 with 95% CI [-0.21, 0.01], p = 0.07), 72 h (MD: -0.12 with 95% CI [-0.29, 0.05], p = 0.17), and 96 h (MD: -0.02 with 95% CI [-0.16, 0.12], p = 0.8) (Figure 4). Our results were homogenous with (p > 0.1, I-square = 0%), except after 12 h (p = 0.001, I-square = 86%). We conducted a sensitivity analysis to investigate the source of heterogeneity; however, heterogeneity was not explained by sensitivity analysis (Table S4).
3.5.2. Patient controlled analgesia

The pooled mean difference favored perioperative meloxicam over postoperative meloxicam (MD: -4.25 with 95% CI [-5.96 - 2.54], p = .00001) (Figure 5). Our results were homogenous with (p = .73, I-square = 0%).

3.5.3. Overall satisfaction

The pooled mean difference favored perioperative meloxicam over postoperative meloxicam after 24 h (MD: 0.43 with 95% CI [0.17, 0.69], p = .001) and after 48 h (MD: 0.26 with 95% CI [0.02, 0.50], p = .03) (Figure S1). Our results were homogenous with (p > .1, I-square = 0%).
3.5.4. Adverse events

We found no difference between perioperative and postoperative meloxicam regarding the incidence of: vomiting (RR: 0.84 with 95% CI [0.57, 1.23], \( p = .36 \)), constipation (RR: 1.01 with 95% CI [0.78, 1.31], \( p = .92 \)), dizziness (RR: 0.78 with 95% CI [0.43, 1.42], \( p = .41 \)), drowsiness (RR: 0.83 with 95% CI [0.42, 1.62], \( p = .58 \)). However, perioperative meloxicam was significantly associated with nausea (RR: 0.76 with 95% CI [0.61, 0.95], \( p = .02 \)) (Figure S2). Our results were homogeneous with (\( p = .73 \), I-square = 0%).

4. Discussion

Our meta-analysis involving 964 patients yielded that perioperative meloxicam is effective in reducing VAS up to 24 h, reducing PCA, improving PGA, and improving overall satisfaction compared to postoperative meloxicam. Furthermore, perioperative meloxicam was safe and well tolerable, with a similar rate of adverse events compared to postoperative meloxicam; however, perioperative meloxicam was associated with more incidence of nausea.

Regarding VAS, perioperative meloxicam was associated with a reduction in VAS at rest or at flexion after six, 12, and 24 h. We can attribute the efficacy of perioperative versus postoperative meloxicam in decreasing VAS to the following mechanisms: first, administrating meloxicam perioperatively can reach maximal plasma concentration and adequate steady-state plasma concentration earlier than administrating meloxicam postoperatively\(^{14-18}\). Second, patients in the perioperative meloxicam group show better psychological comfort compared to the postoperative group, leading to a less subjective perception of pain\(^{26}\). Third, the anti-inflammatory properties of meloxicam led to ameliorating pain earlier in patients receiving perioperative meloxicam\(^{27,28}\). Finally, perioperative meloxicam was associated with a reduction in VAS at rest or at flexion after six, 12, and 24 h. We can attribute the efficacy of perioperative versus postoperative meloxicam in decreasing VAS to the following mechanisms: first, administrating meloxicam perioperatively can reach maximal plasma concentration and adequate steady-state plasma concentration earlier than administrating meloxicam postoperatively\(^{14-18}\). Second, patients in the perioperative meloxicam group show better psychological comfort compared to the postoperative group, leading to a less subjective perception of pain\(^{26}\). Third, the anti-inflammatory properties of meloxicam led to ameliorating pain earlier in patients receiving perioperative meloxicam\(^{27,28}\). Finally, perioperative
meloxicam reduces afferent noxious stimuli by slowing down noxious neuronal transmission to the central nervous system more rapidly and/or modifying the afferent input processing that can exaggerate pain sensation postoperatively. In summary, perioperative administration of meloxicam leads to postoperative short-term amelioration of pain because of the rapid increase of meloxicam plasma concentration reaching compared to postoperative administration; however, perioperative meloxicam’s superiority ceased after 24 h postoperatively. We can attribute this short-term effect to the fact that meloxicam in 15 mg dosage reaches maximal plasma concentration in 10 h; thus, meloxicam plasma concentration is higher in the perioperative group compared to the postoperative group. Furthermore, three of the included trials were on AKS, which is a minimally invasive surgery, and pain is most likely to gradually disappear within 12 h, leading to no difference afterward. Regarding PGA, PGA was decreased in the perioperative group compared to the postoperative group up to 48 h. This furtherly supports the perioperative meloxicam superiority in ameliorating pain and reducing inflammation. In inflammatory joint disorders, PGA is frequently implemented to assess the patient’s perception of their overall health status, providing more comprehensive evaluation of the disease that goes beyond objective markers of inflammation or structural damage. Moreover, PCA was significantly reduced with perioperative meloxicam. This finding is clinically significant because reducing opioid consumption can reduce opioid-associated adverse events, including vomiting, nausea, and dizziness, leading to better overall satisfaction. Some of the included trials assessed the joint function recovery after perioperative versus postoperative meloxicam.
administration. Hou et al.\textsuperscript{15} and Shao et al.\textsuperscript{18} reported no difference in knee function recovery between perioperative or postoperative meloxicam after AKS and TKA, respectively. Indicating that short-term improvement in the overall status of the patient does not affect the long-term functionality of the knee joint\textsuperscript{15}. Because the main contributors to knee function recovery are postoperative rehabilitation and the TKA procedure\textsuperscript{15,18}. Furthermore, Ren et al.\textsuperscript{17} reported no difference between perioperative and postoperative meloxicam regarding hip function recovery after THA, also indicating that early joint rehabilitation is more critical for long-term functional recovery than the short-term analgesic effect of meloxicam\textsuperscript{17}.

The main concern of analgesia administration is the adverse events that cause longer discharge time and low quality of recover. Therefore, assessing the tolerability of pain control is essential\textsuperscript{13}. In our study, perioperative meloxicam was similar to postoperative meloxicam regarding the incidence of dizziness, drowsiness, constipation, and vomiting. However, nausea was significantly associated with perioperative meloxicam. It is established that gastrointestinal adverse events frequently occur with NSAIDs, which is consistent with our findings\textsuperscript{15,34}. The reason why nausea was the only adverse event associated with perioperative meloxicam is still to be investigated. Despite that, nausea, vomiting, and constipation are far more associated with opioid intake than NSAID intake\textsuperscript{15}. Furthermore, included trials used common meloxicam dosages (7.5 mg/15 mg) with two to three times of administration which have low adverse events incidence rates\textsuperscript{6,15}.

4.1. Strengths

To the best of our knowledge, this is the first systematic review and meta-analysis of RCTs to assess the efficacy of perioperative meloxicam versus postoperative meloxicam for pain control after orthopaedic operations constituting the gold standard evidence in this regard. Furthermore, our review was conducted in accordance with PRISMA\textsuperscript{19}.

4.2. Limitations

Our review has a few limitations: first, we only included five trials with a relatively small number of patients. Second, all the included trials were conducted in China limiting the generalization of our findings elsewhere. Third, three trials were
on AKS, one on THA, and another on TKA, with the latter two typically associated with greater postoperative pain. However, our results were consistent with minimal to no heterogeneity. Fourth, all the included trials showed a high risk of detection and performance bias because of lack of blinding. Fifth, the pain VAS score measures the magnitude of self-reported pain in a subjective nature, which can be significantly affected by patients’ characteristics and ethnicities that affects patients’ perception and expression of pain. Sixth, the co-administrated analgesics for PCA may significantly affect our findings. To clarify, three trials used pethidine as PCA, and another two trials used a mixture of fentanyl, tramadol, and tropisetron mesylate. Finally, the difference in the surgical skills can lead to significant inter-operator bias, which is considered a major confounding variable that we could not control.

5. Conclusion
Perioperative meloxicam is more effective than postoperative meloxicam for short-term pain control after AKS, THA, or TKA. However, more multicenter RCTs are still required to investigate the effect of perioperative meloxicam in other orthopedic procedures before endorsing perioperative meloxicam for pain control after orthopedic operations.

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Author contributions
AM conceived the idea. BA and MA designed the research workflow. AA and MA searched the databases. FL, RF, and BK screened the retrieved records, and MA resolved the conflicts. AK, FL, RF, and BK extracted relevant data, assessed the quality of evidence, and MA resolved the conflicts. MA and BA performed the analysis. MA and AG wrote the final manuscript. All authors have read and agreed to the final version of the manuscript.

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Data availability statement
The data are available on request.

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ORCID
Abdelrahman Mahmoud http://orcid.org/0000-0001-7514-1623
Mohamed Abuelazm http://orcid.org/0000-0002-2514-0689
Ali Ashraf Salah Ahmed http://orcid.org/0000-0003-3870-5148
Mahmoud Elshinawy http://orcid.org/0000-0003-2561-0692
Toka Ashour http://orcid.org/0000-0002-7479-9244
Mohamed Abugdida http://orcid.org/0000-0002-9294-496X
Basel Abdelazeem http://orcid.org/0000-0002-2919-6196
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