Review Paper

Morphine Treatment in Children With Postoperative Orthopedic Pain: A Systematic Review of Clinical Trials

Sara Saadat[1], Fatemeh Abdi[2], Firoozeh Mirzaee[3], Malihe Afiat[4], Nasibeh Roozbeh[5], Masumeh Ghazanfarpour[6*]

1. Division of Nephrology, Department of Pediatric, Dr Sheikh Hospital, Mashhad University of Medical Sciences, Mashhad, Iran.
2. Reproductive Sciences and Technology Research Center, Iran University of Medical Sciences, Tehran, Iran.
3. Kerman Nursing Research Center, Razi School of Nursing and Midwifery, Faculty of Kerman University of Medical Sciences, Kerman, Iran.
4. Milad Infertility Center, Mashhad University of Medical Sciences, Mashhad, Iran.
5. Mother and Child Welfare Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
6. Reproductive Health, Family and Population Research Center, Kerman University of Medical Sciences, Kerman, Iran.

Use your device to scan and read the article online

Citation Saadat S, Abdi F, Mirzaee F, Afiat M, Roozbeh N, Ghazanfarpour M. Morphine Treatment in Children With Postoperative Orthopedic Pain: A Systematic Review of Clinical Trials. Journal of Pediatrics Review. 2023; 11(4):333-342. http://dx.doi.org/10.32598/jpr.11.4.283.5

doi http://dx.doi.org/10.32598/jpr.11.4.283.5

Article info:
Received: 07 Jul 2023
First Revision: 10 Aug 2023
Accepted: 21 Sep 2023
Published: 01 Oct 2023

ABSTRACT

Background: Given the lack of general standards for pain treatment after orthopedic operations, orthopedists and anesthesiologists need evidence to choose analgesic options for children. Therefore, this paper seeks to evaluate the effectiveness of morphine administration in reducing pain after orthopedic surgery in children in different contexts.

Methods: To find study trials on the effect of morphine on pain relief in children with orthopedic surgery, we systematically reviewed PubMed, ISI Web of Science, Embase, Google Scholar, Cochrane, and Scopus databases until March 2020. The following keywords were searched: "Morphine," " opioid," "children," "pediatric," "preschool," "child," "orthopedic," "orthopedics," and "orthopedic procedures" to find relevant papers. The quality of articles was evaluated using the Jadad scale.

Results: Nine studies were included in the meta-analysis. Analgesia with sublingual buprenorphine had an effect similar to the intramuscular morphine. The effect lasted significantly longer in the buprenorphine group than in the morphine group (P=0.03). About 67% of the children experienced pain relief after the first injection and 94% after the second injection (after 15 minutes) of morphine. In the propacetamol group, 77% of the children had pain relief. It is recommended to administer propacetamol initially. If the propacetamol is not effective, a subsequent injection of morphine is suggested after the first injection of propacetamol. About 84.6% of parents in the ketamine group and 66.6% of parents in the morphine group were very satisfied with the analgesic intervention. However, no significant difference was observed between the two groups (P=0.296). According to two studies, the pain score was significantly lower in the morphine group than in the meperidine group (P<0.005). The morphine administered in combination with ketorolac induced greater analgesia compared to the group receiving morphine alone (P=0.002). According to three studies, morphine was not superior to ibuprofen in relieving children's postoperative pain (P>0.005).

Conclusions: Morphine was more effective than meperidine. However, morphine did not surpass ibuprofen, buprenorphine, and ketamine in treating children with orthopedic pain.

Key Words:
Morphine, Children, Orthopedic, Postoperative pain

** Corresponding Author:*
Masumeh Ghazanfarpour
Address: *Reproductive Health, Family and Population Research Center, Kerman University of Medical Sciences, Kerman, Iran.*
Tel: *+98 (913) 6330656*
E-mail: *masumeh.ghazanfarpour@yahoo.com*

Introduction

Childhood traumatic injuries, especially dislocations and fractures, are a major cause of referral to the pediatric emergency units (PEU) [1]. Moderate to severe pain is the most common complaint of children postoperatively, especially during the first 24 hours, even after minor surgeries [2]. Numerous studies have shown that analgesics and sedatives are used inappropriately in PEUs to relieve pains associated with dislocations or fractures. The ideal drug for sedation and analgesia used in these cases should act fast, be safe, and be appropriately administered [1]. The failure to diagnose and treat pain adequately in children will lead to a delayed healing process, emotional damage, and changes in pain processing [3]. Since acute pain is one of the most common negative stimuli experienced by children due to injuries, rapid and accurate assessment of pain and its effective treatment are key components of pain management, especially in patients with acute orthopedic incidents. A lack of clinical information on the effectiveness of painkillers in children can lead to the provision of inefficient clinical care and pain relief [4]. Oral morphine has been shown to induce beneficial effects in children with orthopedic injuries, especially in the wake of the recommendations of the United States Food and Drug Administration (FDA) about infant mortality due to codeine intake [2]. Morphine, along with other drugs such as oxycodone and hydrocodone, is increasingly used as the primary treatment of pediatric postoperative pain. However, this drug can cause several complications, including respiratory depression, nausea, constipation, and an increased risk of opioid abuse [5]. Given that the management of children's pain is largely the responsibility of home caregivers, oral morphine is typically prescribed for this purpose. However, there is insufficient evidence to support that the administration of morphine can relieve pain after orthopedic surgery in children [2].

Several reasons justify a systematic study in this area, including the limited number of articles in this field and contradictory results reported by these studies. According to some studies, morphine is not more effective than other analgesics, whereas some articles introduce morphine as the first-line treatment [6]. Still, other studies stress using an analgesic supplement for the higher efficacy of this drug [2]. Also, there were different control groups used in previous studies. In one study, ketorolac [6] and in another, ibuprofen [2, 7] and meperidine [8] were administered to the control groups. In addition, previous studies have suggested that the optimal management of pediatric pain affects the physiological components of pain when using opioids. These relationships must be analyzed meticulously [6]. Given that the provision of postoperative analgesia in children is significantly different [9], paying particular attention to measures such as controlling and reducing pain after pediatric surgery seems necessary. Setting minimum standards for pediatric postoperative pain relief can help physicians and anesthesiologists make appropriate decisions to mitigate and prevent postoperative pain in children.

Due to the lack of comprehensive standards for analgesia after pediatric surgery and in light of the growing concern about opioid use in children, evidence is required to guide pain relief alternatives for children. Hence, this study was designed to evaluate the effectiveness of morphine administration in relieving pain after orthopedic surgery in children in different contexts.

Methods

This systematic review study was designed and conducted in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analyzes) checklist [10] and the PICO (patient, intervention, comparison, and outcome) strategy.

Population refers to children under 12 who were investigated in these papers. Intervention includes morphine use. Comparisons include any analgesics that could be included in the study as control, such as Demerol, propacetamol, buprenorphine, meperidine, morphine, ketorolac, and Ibuprofen. The measured primary outcome was pain score.

Search strategy

This review systematically searched PubMed, ISI Web of Science, Embase, Google Scholar, Cochrane, and Scopus databases to find relevant studies. The following keywords were used to explore the above database. The process of selection of articles is displayed in Table 1.

Inclusion and exclusion criteria

The inclusion criteria comprised all clinical trial articles about the effect of morphine on pain relief in pediatric orthopedic surgery, regardless of the control group. In these papers, children under the age of 12 were investigated. There were no restrictions regarding the drug dose, producing company, and duration of use.

Table 1. The search strategy

	Search Term
#1	"Morphine" [tiab] OR "morphia" [tiab] OR "morphine chloride" [tiab] OR "chloride, morphine" [tiab] OR "morphine sulfate" [tiab] OR "sulfate, morphine" [tiab] OR "opioid" [tiab] OR "analgesics" [tiab] OR "opioid analgesics" [tiab] OR "narcotics" [tiab]
#2	"Children" [TIAB] OR pediatric" [TIAB] OR "preschool" [TIAB] OR "child" [TIAB]
#3	"Orthopedic" [TIAB] OR "orthopedics" [TIAB] OR "orthopedic procedures" [TIAB]

Journal of Pediatrics Review

The exclusion criteria included irrelevant articles, letters to editors, and editorials. Review papers, papers whose full text was unavailable or provided insufficient information in the abstract, summaries of papers presented at conferences, letters, editor notes, and case reports were also excluded. In cases when the full text of the articles was inaccessible, the corresponding author would contact the author three times via email. If no response were received, the paper would be removed.

Data extraction

All extracted data were evaluated by two authors independently. An external referee resolved disagreements between the authors. Initially, the titles and abstracts of the papers were checked. If relevant, they were included in the study. Then, the full text was examined. In the second stage, the full text of the remaining articles was thoroughly reviewed, and the articles that matched the inclusion and exclusion criteria were systematically reviewed. In addition, the references of included articles and reviewed papers were carefully explored to ensure the search was exhaustive. The data extraction table, which the researcher made, included the year, country, type of study design, outcomes, sample size, type of intervention, characteristics of the control and intervention group, dropouts, outcome measurement tool, and drug side effects (Table 2).

Risk of bias assessment

Included studies were assessed for risk of bias by two independent authors using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [11]. Disagreements in bias assessment were set by discussion or consultation with a third party (Table 3).

Results

Buprenorphine versus morphine

Maunuksela et al. [12] studied 60 participants aged 4 to 14 years with elective orthopedic surgery on the upper or lower extremities. They found that analgesia with sublingual buprenorphine had a similar effect with the intramuscular morphine. The effect was significantly more long-lasting in the buprenorphine group (Mean±SD 248±314 minutes) than in the morphine group (Mean±SD 114±109 minutes) (P=0.03).

Morphine versus propacetamol

Rod et al. compared the analgesic effect of morphine and propacetamol on pain relief following either orthopedic or visceral surgery. In the morphine group, 67% of the children had pain relief following the first injection and 94% after the second injection. In the propacetamol group, 77% of the children experienced pain relief, which was insufficient in 23% of the cases [13].

Ketamine versus morphine

Thirteen patients were allocated to the ketamine and 12 to the morphine groups. The median pain (pain scale) scores were calculated after the procedure in both groups. About 84.6% of parents in the ketamine group and 66.6% in the morphine group were very satisfied with the analgesic intervention. However, the difference between the two groups was not significant (P=0.296). Also, 92.3% of orthopedists in the ketamine group and 75% in the morphine group were satisfied with the intervention outcomes. The difference between the two groups was significant (P=0.222) [1].

Morphine versus ibuprofen

In the study of Poonai et al., no significant difference was observed in terms of pain scores between the two groups. The oral morphine (n=77) and ibuprofen (n=77) were assessed eight times: First dose (P=0.2), second dose (P=0.9), third dose (P=0.5), fourth dose (P=0.9), fifth dose (P=0.6), sixth dose (P=0.9), seventh dose (P=0.8), and eighth dose (P=0.6) [2]. Groenewald et al. suggested that oral morphine was no better than oral ibuprofen for postoperative pain relief in children at home [5]. In the study of Poonai et al., children with extremity fractures were randomized to either morphine (n=66) or ibuprofen groups (n=66). Also, no significant difference was observed in pain scores between morphine and ibuprofen groups in 4 time points (P=0.6) [7].

Morphine versus meperidine

In the study of Vetter et al., 50 patients were randomized to either morphine or meperidine pain groups. Pain scores were significantly higher in the group receiving morphine than in the group receiving meperidine (P<0.001) [14]. O'Hara et al. studied 25 children with orthopedic surgery aged 7 to 17 years, assigning them randomly to groups receiving morphine and meperidine. The frequency of pain-free children was higher in the morphine group than in the meperidine group (demerol) on day 1 (P=0.03) and day 2 (P=0.01) [8].

Morphine plus ketorolac versus morphine

In Vetter's study, administering morphine combined with ketorolac provided more effective analgesia than the group receiving only morphine (P=0.002) [6].

The articles were extracted by two researchers independently. A table was drawn by the research team, which contained information about the first author, year of publication, type of study, blinding, type of intervention, duration of intervention, inclusion criteria, sample size, and primary results.

Discussion

This review study is the first one to comprehensively examine the effectiveness of morphine in relieving pediatric surgical pain. In general, this review study investigated the effects of morphine in comparison with intravenous acetaminophen, ibuprofen, ketamine, and ketorolac. The findings suggested that morphine was more effective than meperidine. However, morphine was not superior to ibuprofen, buprenorphine, and ketamine in treating children with orthopedic pain.

Morphine can reduce and inhibit pain transmission. The analgesic effects of opioids are due to their ability to inhibit the transmission of nociceptive information from the posterior horn of the spinal cord and to activate pain control mechanisms in higher nerve centers. Morphine has low-fat solubility, and its penetration into and out of the brain is slower than that of other drugs. It is mainly metabolized in the liver, but the kidneys play a crucial role in extrahepatic metabolism. The plasma half-life of morphine is about 2-4 hours [15]. Two studies investigated the effectiveness of pethidine and morphine in pediatric orthopedic surgery. Pethidine is a synthetic drug [16] derived from opium [17]. This drug is generally known in the United States as meperidine [17], and its effect lasts for 2 to 3 hours. Pethidine exerts its analgesic effect through ascending and descending pathway receptors and neurons of the hypothalamic basal ganglia, limbic structure, and cerebral cortex [18]. According to these studies, morphine is more effective than pethidine in controlling pain with fewer side effects [17]. Morphine may be preferred when rapid control of acute pain is necessary [16]. Due to the small number of samples in these two studies, morphine was found to be more effective than pethidine. Still, more studies with a larger sample size are required to verify this finding. Another study examined the efficacy of intravenous acetaminophen (paracetamol) and morphine [13]. Intravenous acetaminophen (paracetamol) is an acetaminophen water-soluble intravenous product used for rapid and strong onset of analgesic effect. Paracetamol is a prodrug that is hydrolyzed to paracetamol in the blood. It produces analgesic and antipyretic effects with few side effects at the recommended doses (1 to 2 g). Intravenous injection of paracetamol exerts its effect after about half to one hour. It has a half-life of about 1-4 hours, and its effect lasts 6-8 hours [19].

According to the findings of a study, morphine is more effective than paracetamol in relieving pediatric surgical pain. Hence, based on the above findings, acetaminophen does not induce complete pain relief and should be used in combination with morphine [13]. However, given the lack of studies and the low sample size, future research with a larger sample size must explore this drug's secondary side effects, cost-effectiveness, and pain relief. The acting mechanism of this drug is based on prostaglandin synthesis. Cyclooxygenase is the first enzyme in the prostaglandin production cycle, while paracetamol hinders its production by entering the cycle and exerting its analgesic effect [19]. Three studies compared the effects of morphine and ibuprofen in pediatric surgery. According to three studies, the effects of morphine and ibuprofen on pain relief in pediatric surgery are similar [2, 5, 7]. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to control mild pain. These drugs have also been shown to help opioids control and manage moderate to severe pain. Recent studies have shown that NSAIDs alone or in combination with opioids are more effective than previously thought [19]. A body of research has investigated the effect of NSAIDs. As generally effective and safe analgesics, NSAIDs have received increasing attention for pain

Table 2. The characteristics of included studies

Study, Year, Country	Study Design	Outcomes	Subject Case/ Control	Intervention	Control	Drop-out	Assessment Tool	Results	Adverse Effects
Barcelos et al. 2014, Brazil [1]	RCT	Times to perform the procedures, analgesia, parent satisfaction, and orthopedic team	13 patients receiving ketamine and 12 morphine	One group received morphine 0.1 mg/kg intravenously, the other group received ketamine 2 mg/kg intravenously	Ketamine	-	Faces pain scale	Analgesia with ketamine for reducing fracture pain and dislocations showed clinical results comparable to the morphine	Not reported
Groenewald et al. 2017, USA [5]	RCT	Morphine and ibuprofen for children's pain	77 patients were randomized to each medication	Researchers performed an intention to treat randomized controlled trial	Ibuprofen	-	Faces pain scale-revised	Morphine was not superior to ibuprofen in relieving children's pain	Morphine was associated with more side effects compared with ibuprofen
O'Hara et al. 1987, Canada [8]	RCT	Morphine and demerol to control the children's pain	13 patients receiving morphine and 12 Demerol	48h after surgery, every 3-4 h morphine and Demerol	Demerol	7	Visual analog scale (VAS)	Oral morphine is better at mitigating children's pain	Not reported
Maunuksela et al. 1988, Finland [12]	RCT	Safety and efficacy of buprenorphine and morphine	60 boys and girls	5.2 µg/kg buprenorphine and 166 µg/kg morphine	Buprenorphine	-	Visual	Analgesia with sublingual buprenorphine was as effective and reliable as intramuscular morphine	Buprenorphine Vomiting/nausea, n=8; micturition difficulties/urinary retention, n=6; drowsiness, n=2 confusion, n=1; dizziness, n=2; headache, n=1 Morphine Vomiting/nausea, n=5; micturition difficulties/urinary retention, n=6; confusion, n=1; headache, n=2; bad dreams, n=1
Poonai et al. 2017, London [2]	RCT	Oral morphine versus ibuprofen for orthopedic pain	77 patients receiving each medication	Oral morphine (0.5 mg/kg) with ibuprofen (10 mg/kg)	Buprenorphine	22	Faces pain scale – revised	Morphine was not superior to ibuprofen	Oral morphine nausea, 30(46%); vomiting, 12 (18%); drowsiness, 31 48% dizziness, 20 (31%); constipation, 9(14%) Ibuprofen nausea, 13 (19%); vomiting, 3 (4%); dizziness, 4 (6%); constipation, 3 (4%)

Study, Year, Country	Study Design	Outcomes	Subject Case/ Control	Intervention	Control	Drop-out	Assessment Tool	Results	Adverse Effects	
Rod et al. 1989, France [13]	RCT	Morphine and propacetamol for pain	239 patients receiving morphine and 100 propacetamol	50 µg/kg of morphine/15 mg/kg propacetamol	Propacetamol	-	Visual	Propacetamol should be administered initially and, if insufficient, followed by only an injection of morphine.	Not reported	
Vetter et al. 1994, France [6]	RCT	Ketorolac and morphine for the quality of analgesia	50 patients receiving each medication	0.8 mg/kg ketorolac and 0.05 to 0.3 mg/kg morphine	Ketorolac	-	Visual analog scale (VAS)	Ketorolac appears to be opioid dose sparing, to provide superior analgesia.	Ketorolac and morphine Vomiting, n=11 (44%); pruritis, n=3 (12%); urinary retention, n=1 (4%)	Morphine Vomiting, n=13 (52%); pruritis, n=5 (20%); urinary retention, n=7 (28%)
Vetter et al. 1992, France [14]	RCT	Side effects and pain score of morphine vs meperidine	50 patients receiving each medication	0.1-0.3 mg/kg morphine 1.0-3.0 mg/kg Meperidine	Meperidine	-	Visual	Morphine is better	Morphine Nausea and vomiting, 28%; pruritis, 20%; urinary retention, 4%	Meperidine Nausea and vomiting, 40%; pruritis, 12%; urinary retention 4%

Poonai et al. 2014, London [7]	RCT	Morphine vs. ibuprofen for orthopedic pain/type and frequency of adverse effects and the number of participants requiring acetaminophen.	183 participants	Oral morphine (0.5 mg/kg) with ibuprofen (10 mg/kg)	Buprenorphine	49	Faces Pain scale—revised (FPS-R).	no significant differences-ence in analgesic efficacy between orally administered morphine and ibuprofen.	Morphine
									Nausea, n=18 (27.3%);
									vomiting, n=8 (12.1%);
									drowsiness, n=23 (34.8%);
									dizziness, n=8 (12.1%);
									constipation, n=4 (6.1%);
									others, n=8 (12.1%)
										Ibuprofen
										Nausea, n=4 (5.9);
										vomiting, n=2 (2.9%);
										drowsiness, n=14 (20.6%);
										dizziness, n=6 (8.8%);
										constipation, n=1 (1.5%);
										Others, n= 3 (4.4%)

Journal of Pediatrics Review

RCT: Randomoized controlled trial.

Study ID	Random sequence generation (selection bias	Allocation concealment (selection bias)	Blinding of participants and personnel	Blinding of outcome assessment (detection bias)	Measurement of the outcome	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bia		
Barcelos et al, 2014	?	-	-	-	+	+	+	?	Low risk	+
Groenewald et al, 2017	+	?	-	-	+	+	+	?	Some concerns	?
O'Hara et al, 1987	+	-	-	-	+	+	+	?	High risk	-
Poonai et al, 2017	+	+	-	+	+	+	+	+		
Rod et al, 1989	+	+	-	-	+	+	+	?		
Vetter et al et al, 1992	-	-	-	-	+	+	+	-		
Vetter et al et al,199	?	-	-	-	+	+	+	?		
Maunuksela et al 198	+	+	-	-	+	+	+	?		
Poonai et al, 2014	+	?	-	-	+	+	+	+		

Table 3. Risk of bias assessment for randomized controlled trials (RCTs)

Journal of Pediatrics Review

management associated with acute fractures. However, they work by directly inhibiting the enzyme cyclooxygenase, which is important for the production of prostaglandins in the early inflammatory stages of fracture repair [20].

Conclusion

According to the results, morphine was more effective than meperidine. However, morphine was not superior to ibuprofen, buprenorphine, and ketamine in mitigating orthopedic pain in children. Yet, the findings should be interpreted cautiously due to the small sample size and limited number of studies reviewed. Given the scant number of studies and the small sample size of this review, it is necessary to undertake future research with a higher sample size. These studies should also explore the secondary side effects, cost-effectiveness, and pain relief time.

Study limitations

The primary limitation of this study was the need for a fixed dosage in equal intervals to preserve blinding. Participants underwent various orthopedic and surgical procedures, which may have contributed to the baseline heterogeneity. In some studies, a valid instrument had not been adopted. The researchers used the faces pain scale-revised, but this instrument was not validated for home use. The efficacy of oral morphine in postoperative pain after minor pediatric surgery was assessed. However, the findings may not be generalized to children undergoing surgical procedures associated with severe rather than moderate levels of pain. However, effectiveness and safety considerations must underline sedation and analgesia. Future studies need to assess the costs of using these methods. One limitation of the studies included in this review is that they did not consider these drugs' side effects and cost-effectiveness. The last limitation of this review is that the protocol was not registered in PROSPERO (the international prospective register of systematic reviews).

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors contributions

Conceptualization and investigation: Masumeh Ghazanfarpour, Firoozeh Mirzaee and Sara Saadat; Methodology: Masumeh Ghazanfarpour, Nasibeh Roozbeh and Sara Saadat; Visualization: Masumeh Ghazanfarpour and Firoozeh Mirzaee; Software: Masumeh Ghazanfarpour, Firoozeh Mirzaee, Fatemeh Abdi; Validation and writing – original draft preparation: Masumeh Ghazanfarpour, Sara Saadat, Fatemeh Abdi; Formal analysis and data curation: Masumeh Ghazanfarpour, Nasibeh Roozbeh, Malihe Afiat; Resources: Masumeh Ghazanfarpour and Nasibeh Roozbeh; Review, editing and final approval: All authors; Supervision: Masumeh Ghazanfarpour and Sara Saadat; Project administration, and funding acquisition: Masumeh Ghazanfarpour.

Conflicts of interest

The authors declared no conflict of interest.

Acknowledgements

The authors want to thank the Alborz University of Medical Sciences and Kerman University of Medical Sciences.

References

1. Barcelos A, Garcia PC, Portela JL, Piva JP, Garcia JP, Santana JC. Comparison of two analgesia protocols for the treatment of pediatric orthopedic emergencies. Rev Assoc Med Bras. 2015; 61(4):362-7. [DOI:10.1590/1806-9282.61.04.362] [PMID]

2. Poonai N, Datoo N, Ali S, Cashin M, Drendel AL, Zhu R, et al. Oral morphine versus ibuprofen administered at home for postoperative orthopedic pain in children: A randomized controlled trial. CMAJ. 2017; 189(40):E1252-8. [DOI:10.1503/cmaj.170017] [PMID]

3. Reynolds SL, Studnek JR, Bryant K, VanderHave K, Grossman E, Moore CG, et al. Study protocol of a randomised controlled trial of intranasal ketamine compared with intranasal fentanyl for analgesia in children with suspected, isolated extremity fractures in the paediatric emergency department. BMJ Open. 2016; 6(9):e012190. [DOI:10.1136/bmjopen-2016-012190] [PMID]

4. Koller DM, Myers AB, Lorenz D, Godambe SA. Effectiveness of oxycodone, ibuprofen, or the combination in the initial management of orthopedic injury-related pain in children. Pediatr Emerg Care. 2007; 23(9):627-33. [DOI:10.1097/PEC.0b013e31814a6a39] [PMID]

5. Groenewald CB. Morphine is not superior to ibuprofen for managing children's pain following minor orthopedic surgery. Evid Based Nurs. 2018; 21(2):48. [DOI:10.1136/eb-2017-102855] [PMID]

6. Vetter TR, Heiner EJ. Intravenous ketorolac as an adjuvant to pediatric patient-controlled analgesia with morphine. J Clin Anesth. 1994; 6(2):110-3. [DOI:10.1016/0952-8180(94)90006-X] [PMID]

7. Poonai N, Bhullar G, Lin K, Papini A, Mainprize D, Howard J, et al. Oral administration of morphine versus ibuprofen to manage postfracture pain in children: A randomized trial. CMAJ. 2014; 186(18):1358-63. [DOI:10.1503/cmaj.140907] [PMID]

8. O'Hara M, McGrath PJ, D'Astous J, Vair CA. Oral morphine versus injected meperidine (Demerol) for pain relief in children after orthopedic surgery. J Pediatr Orthop. 1987; 7(1):78-82. [DOI:10.1097/01241398-198701000-00016] [PMID]

9. Vittinghoff M, Lönnqvist PA, Mossetti V, Heschl S, Simic D, Colovic V, et al. Postoperative pain management in children: Guidance from the pain committee of the european society for paediatric anaesthesiology (ESPA pain management ladder initiative). Paediatr Anaesth. 2018; 28(6):493-506. [DOI:10.1111/pan.13373] [PMID]

10. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Ann Intern Med. 2009; 151(4):264-9. [DOI:10.7326/0003-4819-151-4-200908180-00135] [PMID]

11. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions. Hoboken: Wiley; 2011. [Link]

12. Maunuksela EL, Korpela R, Olkkola KT. Comparison of buprenorphine with morphine in the treatment of postoperative pain in children. Anesth Analg. 1988; 67(3):233-9. [DOI:10.1213/00000539-198803000-00005]

13. Rod B, Monrigal JP, Lepoittevin L, Granry JC, Cavellat M. [Treatment of postoperative pain in children in the recovery room. Use of morphine and propacetamol by the intravenous route (French)]. Cah Anesthesiol. 1989; 37(7):525-30. [PMID]

14. Vetter TR. Pediatric patient-controlled analgesia with morphine versus meperidine. J Pain Symptom Manage. 1992; 7(4):204-8. [DOI:10.1016/0885-3924(92)90076-T] [PMID]

15. Hasani V, Farahmand Rad R, Ali Anvari H. [Comparison of intramuscular morphine and methadone on postoperative analgesia in patients with tibial fracture (Persian)]. J Iran Soc Anaesthesiol Intensive Care. 2018; 2(41):63-72. [Link]

16. Sattari H, Haghbin M, Etminan M, Dehghani A. [Survey of the effect of intraoperative intravenous lidocaine infusion on postoperative pain in laparoscopic cholecystectomy surgery (Persian)]. J Rafsanjan Univ Med Sci. 2015; 13(10):937-48. [Link]

17. Pouyan M, Ozmaie S, Sakha M, Asghari A. [Evaluation of the analgesic and sedative effects of pethidine (meperidine) with xylazine in the horse (Persian)]. J Comp Pathobiol. 2017; 14(1):2091-6. [Link]

18. Sereshti M, Asefi F, Shabanian M, Banaeian S. [Comparing the effects of massage and intra intramuscular pethidine on pain relief in the stages of labor and the length of labor (Persian)]. Iran J Obstet Gynecol Infertil. 2013; 16(80):6-16. [DOI:10.22038/IJOGI.2013.2213]

19. Mohammadsadegh S, Navid K, Mohammad R, Hassan Z, Hamidreza D. [The effect of paracetamol on the level of drug use during and after orthopedic surgery of the upper limb (Persian)]. JJahrom Univ Med Sci. 2015; 13(2):33-8. [DOI:10.29252/jmj.13.2.5]

20. Fader L, Whitaker J, Lopez M, Vivace B, Parra M, Carlson J, et al. Tibia fractures and NSAIDs. Does it make a difference? A multicenter retrospective study. Injury. 2018; 49(12):2290-4. [DOI:10.1016/j.injury.2018.09.024] [PMID]

This Page Intentionally Left Blank