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Pain Management after Surgery: An Educational Study with the Purpose of Reviewing and Comparing Analgesics for Medical Providers

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Abstract

Background: The purpose of the present study is to review and compare the effect of analgesics after surgery on children, adults, and the elderly.

Materials and Methods: This review was conducted through a systematic search of electronic resources in English, including Medline, Scopus, Web of Science, Cochrane Library, and EMBASE, SID, Magiran, CIVILICA, and Google Scholar search engine with no time limit from inception up to March 2020, using the following keywords on their own or in combination: "Pain management", "Pain", "Advantage", "Disadvantage", "Drugs", and "Analgesic".

Results: Three studies were found that compared the effects of pethidine and morphine on postsurgical pain. The findings demonstrated that in pediatric surgery, pain intensity in those who received morphine was significantly lower than those who received meperidine. On the other hand, the results of one study did not find a significant difference between the two drugs in post-operative sedation and satisfaction of patients who underwent cesarean section. Of the two studies comparing the effects of pethidine and paracetamol on postsurgical pain, one study reported that pethidine reduced the pain score significantly more than paracetamol. In contrast, the other study found that pain intensity in patients who received intravenous acetaminophen was significantly lower than those who received meperidine after six hours ($P<0.001$). According to one study, ketorolac was more effective than intravenous pethidine in reducing the pain score, and in another study, a mixture of pethidine and bupivacaine was able to aggravate the effects of each drug alone.

Conclusion: Intravenous acetaminophen, pethidine, morphine, ketorolac, and paracetamol are effective in reducing postoperative pain in children and adults. Due to the methodological limitations of the included studies, these results should be interpreted with caution.

Key Words: Advantage, Drugs, Pain, Management, Surgery, Medical Providers.

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1- INTRODUCTION

Pain during surgery has been resolved with the help of anesthesiologists. However, the pain is not limited to the time during surgery. After the end of the surgery and wearing off the effect of anesthesia medicine, patients will feel pain at the surgery site which is especially intensive in the first few days after surgery. All patients feel pain for some time after surgery and controlling this pain is very important. Postoperative pain control is mainly mediated by medication. Still, pain relief after surgery remains one of the major medical challenges. If remained untreated, it can delay the patient's discharge, recovery, and ability to participate in rehabilitation. Recent advances include a better understanding of pain mechanisms, physiology, and pharmacology; distribution of guidelines, development of acute pain services (APS), initiatives such as "pain as the Fifth Vital Sign", and the availability of new drugs and devices to control and reduce pain. However, these advances have not led to major improvements, and the insufficient treatment of postoperative pain remains a significant problem worldwide (1, 2).

About 66% of patients experience moderate to severe postsurgical pain at discharge, which might last for two weeks after surgery in 59% of patients who have undergone orthopedic, general, neurological, and gynecologic surgeries (3). The Perioperative Quality Improvement Program (PQIP) report of 2017-18 (4), which includes data from 79 hospital sites across the UK, states that 48% of patients experience moderate and 19% experience severe pain at the surgery site within 24 hours of surgery. This data has been replicated in the most recent report (2018-19) (5). This data is not limited to the UK. A prospective German cohort study on 50,523 patients reported that up to 47.2% of patients, experienced severe pain (with at least a numerical rating scale score of eight) in the first 24 hours after surgery. In addition, moderate to severe pain may continue throughout the postsurgical recovery period (6). The etiology of acute postoperative pain is multifactorial. Surgery causes tissue damage, and surgical injury produces countless responses at the site of pain ranging from sensitization of the peripheral and central pain pathways to feelings of fear, anxiety, and despair (7). Although pain decreases in most patients during the first days after surgery, some patients experience a steady or increasing trend in pain and analgesic needs (6). Postoperative pain is often not limited to the surgical site and might include sore throat following intubation or pain at injection sites (8).

Prevention and relief of postoperative pain is the main responsibility of health care professionals (9). Postoperative pain relief is traditionally done by using opioids. However, overprescription of opioids is associated with a variety of side effects, including respiratory problems, depression, drowsiness, nausea and vomiting, pruritus, ileus, urinary retention, and constipation. Prescribing multimodal analgesic regimens, including non-opioid analgesics (e.g., local anesthetics, non-steroidal anti-inflammatory drugs, cyclooxygenase inhibitors, acetaminophen, ketamine, clonidine, dexmedetomidine, and gabapentin) as a supplement for opioid analgesics may result in better pain control after surgery (10).

Pain management after surgery is a critical issue for most patients. Pain control is essential regardless of the type or method of surgery. Pain relief contributes to earlier patient mobility, reduced hospitalization time, reduced hospital costs, and increased patient satisfaction. Various studies recommend that instead of using a fixed dose of narcotics for all patients, an individualized approach should be used to pain control. Also, the patient's medical,

psychological, and physical condition, age, level of fear or anxiety, type of surgery, personal preferences, and response to pain control methods should be considered (11-13). Opioids have been the mainstay of postoperative pain management, but the Opioid Epidemic, advances in adjuvant therapy, and the development of Enhanced Recovery after Surgery (ERAS) have shifted to adjuvant treatments for postoperative pain (14). Considering the importance of postoperative pain management and its physiological and psychological effects on the patient and the economic effects of successful postoperative pain control for the patient and the hospital, this study aims to review and compare postoperative analgesics in children, adults, and the elderly.

2- MATERIALS AND METHODS

2-1. Study design and population

In this review study, a systemic search of electronic databases of Medline (via PubMed), SCOPUS, Web of Science, Cochrane Library, SID, Magiran, CIVILICA, and Google Scholar search engine was performed with no time limit up to March 2020, using the following keywords alone or in combination: "Pain management", "Pain", "Advantage", "Disadvantage", "Drugs", and "Analgesic". The search was performed independently and in duplication by two reviewers and any disagreement between the reviews was resolved by the supervisor.

2-2. Included studies

Randomized controlled trials (RCT), clinical studies both randomized and nonrandomized, either retrospective or prospective were included. Pilot, preliminary, and case report studies were not included due to limited sample size and higher risk of bias. Studies were published in English up to March 2020.

2-3. Exclusion criteria

Studies that included adults in their sample and studies that evaluate the use of other modalities in pain management were excluded.

2-4. Study selection

Database search was done for suitable studies. Abstracts of the studies were screened for identification of eligible studies, full-text articles were obtained and assessed, and a final list of eligible studies was created. This process was done independently and in duplication by two reviewers and any disagreement was resolved by a third reviewer. References were organized and managed using EndNote software (version X8).

3- RESULTS

1. Comparison of pethidine (Demerol or meperidine) with Paracetamol

In their study, Jarineshin et al. compared the effect of paracetamol and meperidine on pain control after elective cesarean section in patients under general anesthesia in Shariati Hospital in Bandar Abbas, Iran. The paracetamol group received 1 gram paracetamol per 100 ml of normal saline, and the meperidine group received 25 mg of meperidine per 100 ml of normal salt. The findings demonstrated that the pain score after 30 minutes in the paracetamol group was significantly higher than the meperidine group ($p>0.05$). The pain score in the surgical ward after six hours in the meperidine group was significantly less than the paracetamol group. The score of vomiting in the recovery room and 24 hours later in the surgical ward in the meperidine group was significantly higher than the paracetamol group ($p<0.05$) (15).

2. Comparison of Postoperative Analgesia using Muscular Methadone and Morphine

The study of Hasani et al. was performed to compare the effect of intramuscular morphine and methadone on postoperative

analgesia in patients with tibial fractures. This study was performed on 60 participating patients with tibial fractures in Zahedan, Iran. Patients were divided into two groups receiving either muscle methadone or morphine, and each group had a case and a control group. The results showed that the mean number of diclofenac suppositories in the methadone group was significantly lower than the morphine group (p=0.011), and the mean Scuere consumption in the methadone group was significantly lower than the morphine group (P = 0.024). The results also showed that the pain intensity in the case group was significantly lower than the control group at all times (p <0.05) (16).

3. Intravenous Acetaminophen with Intravenous Morphine Sulfate

A study was conducted by Talebi Deloee et al. to compare the analgesic effect of intravenous acetaminophen with intravenous morphine sulfate on patients with traumatic long bone diaphysis fractures. Patients were randomly assigned to two groups, either receiving 15 mg/kg acetaminophen or 0.1 mg/kg morphine sulfate. The findings demonstrated a significant difference between the two groups five minutes after taking the drug so that the morphine sulfate group reported a greater decrease in pain intensity after 5 minutes (p <0.001). However, there was no significant difference between the two groups in terms of pain intensity 30 minutes after taking the drug (p=0.85). After 30 minutes, intravenous acetaminophen appeared to be as effective as intravenous morphine sulfate in relieving the pain of isolated long bone diaphyseal fractures. However, it should be noted that the analgesic effect of acetaminophen is delayed. Therefore, intravenous acetaminophen is recommended when morphine is contraindicated (17).

4. Analgesic Acetaminophen and Fentanyl

Haghighi et al. compared the analgesic effects of acetaminophen and fentanyl on the treatment of pain after intramedullary lower limb surgery on 114 men aged 25-50 years who had lower limb fracture nailing surgery. One group (56 patients) received intravenous acetaminophen 1000 mg in 150 mm normal saline for 15 minutes every six hours for 24 hours. The other group (47 patients) received fentanyl as a controlled analgesic for 24 hours. The results showed that acetaminophen was more effective than fentanyl and had fewer side effects (18).

5. Intravenous Acetaminophen and Pethidine

Kolahdouzan et al. compared the analgesic effect of intravenous acetaminophen and intravenous pethidine on postoperative pain in 100 patients aged 18-62 years who had undergone urology surgery in Imam Reza Hospital in Tabriz, Iran. Patients in the acetaminophen group received 1 g of acetaminophen per 100 ml of saline for 15 minutes, and patients in the meperidine group received an intravenous injection of 0.5 mg/kg meperidine 15 minutes before the operation. The results showed that pain intensity in patients treated with intravenous acetaminophen was significantly lower than the meperidine group (p <0.001) six hours after surgery at one-hour intervals. Patients in the meperidine group needed additional doses of analgesics compared to the acetaminophen group. Nausea occurrence was significantly lower in the acetaminophen group than in the meperidine group (19).

6. Paracetamol

Two studies investigated the effect of acetaminophen on pain relief. Sanie et al. (2015) studied the pain relief effect of paracetamol during and after surgery of

upper limbs on 44 patients aged 15-55 years, who all were ASA 1 and candidates for orthopedic surgery of upper limbs. The first group received 15 mg/kg paracetamol and the second group (control) did not receive any medication. The results showed that paracetamol is not enough for reducing severe pain after orthopedic surgery of the upper limb, but its analgesic effect can reduce the use of the drug by 40% one hour after surgery. Hence, paracetamol can be used as an adjunct drug to reduce pain (20). Parish et al. conducted a study on the effect of infusion of intravenous paracetamol on the hemodynamic variables and pain score at post-anesthesia care unit after major surgery. In the first group, 15 mg/kg acetaminophen dissolved in 100 ml of normal saline serum was infused as a single dose over 20 minutes. Patients in the second group received only 100 ml of normal saline for 20 minutes. The results showed that intravenous acetaminophen is a useful and safe analgesic for postoperative pain relief and an effective drug without any specific side effects (21).

7. Ketorolac and Pethidine

Saryazdi et al. conducted a comparative study of the analgesic effect of intravenous pethidine vs. Ketorolac after inguinal hernia surgery on children under general anesthesia in Al-Zahra and Imam Hossein hospitals of Isfahan University of Medical Sciences in Isfahan, Iran. The first group received 0.5 mg/kg ketorolac and the second group received 1 mg/kg pethidine during extubation. The findings demonstrated that ketorolac is more effective than intravenous pethidine in reducing the pain score and has fewer complications after inguinal hernia surgery (22).

8. Intravenous Dexketoprofen and Paracetamol

Yilmaz et al. compared the effectiveness of intravenous dexketoprofen and paracetamol on the treatment of traumatic musculoskeletal pain. Patients were randomly divided into two groups, one receiving 50 mg of dexketoprofen and the other receiving 1000 mg of paracetamol intravenously by rapid infusion in 150 mL of normal saline. The results showed that administration of paracetamol and dexketoprofen reduced VAS pain scores over time ($p= 0.0001$). There was no significant difference between paracetamol and dexketoprofen in reducing VAS ($p = 0.613$). Intravenous paracetamol and dexketoprofen appear to alleviate acute musculoskeletal pain to the same extent in the emergency department (23).

9. Combination Injection of Ropivacaine, Epinephrine, and Morphine

In a study conducted by Koehler et al., 102 patients undergoing operative interventions (plate fixation, intramedullary device insertion, or arthroplasty) for a broad range of femoral fracture patterns who were prospectively randomized either to receive an intraoperative, surgical-site injection containing ropivacaine, epinephrine, and morphine into the superficial and deep tissues or receive no injection. The injection group demonstrated significantly lower VAS scores ($p< 0.05$) than the control cohort in the recovery room and at 4-, 8-, and 12-hour postoperative time points. Additionally, narcotic consumption was significantly lower ($p = 0.007$) in the injection group (5.0 mg [1.3 to 8.0 mg]) compared with the control group (9.7 mg [3.9 to 15.6 mg]) over the first 8 hours following the surgical procedure. No cardiac or central nervous system toxicity was observed secondary to infiltration of the local anesthetic (24).

10. Brachial Plexus block and general anesthesia

In a study conducted by Koehler et al. on patients who presented with acute closed

distal radius fractures (Orthopedic Trauma Association 23A-C), oxycodone and acetaminophen 5/325 mg were prescribed for pain control and VAS forms were provided. The results showed that patients under general anesthesia had worse pain scores than those with brachial plexus block two hours after surgery ($p<0.001$) while the pain in patients with brachial plexus block was worse after 12 hours ($p=0.002$), and 24 hours ($p= 0.031$) than patients with general anesthesia (25).

11. Intravenous Paracetamol and Intravenous Morphine

Craig et al. conducted a study to compare the clinical effectiveness of intravenous paracetamol with intravenous morphine in patients with moderate to severe traumatic limb pain. A total of 55 patients received either 1 g intravenous paracetamol or 10 mg intravenous morphine sulfate over 15 min. Results showed that intravenous paracetamol provides a level of analgesia comparable to intravenous morphine in isolated limb trauma. However, due to the limited sample size, more studies are needed (26).

12. Intravenous Pethidine and Intravenous Ketorolac

In another study the University of Isfahan, Saryazdi et al. compared the analgesic effect of intravenous pethidine and intravenous ketorolac on 66 children aged 12-12 years who underwent inguinal hernia surgery. The results showed that ketorolac was more effective in reducing pain scores as well as complications after inguinal hernia surgery than intravenous pethidine (22).

13. Pethidine and morphine

O'Hara et al. evaluated the effectiveness of two drugs pethidine and morphine in controlling pain in children in the first 48 hours after orthopedic surgery. The first group received oral morphine every four hours, and the second group received injectable meperidine (Demerol) every 3-4 hours. Patients received either morphine (bolus dose 2 mg, lockout time 10 min) or pethidine (bolus dose 20 mg, lockout time 10 min) for postoperative pain relief. Results showed that the morphine group had a significantly higher number of pain-free children on both day 1 and day 2 (27).

In a in a double-blind study by Stanley et al., patients were allocated randomly into two groups either receiving morphine (bolus dose 2 mg, lockout time 10 min) or pethidine (bolus dose 20 mg, lockout time 10 min) for postoperative pain relief. Mean 24-h morphine and pethidine consumption were 70 (SEM 6.2) mg, and 660 (67.8) mg, respectively (ratio 1:9.4). There were no significant differences in postoperative sedation, nausea, pain relief, patient satisfaction (VAS 0-100 mm), and requirements for antiemetics (28). In a study by Stanley et al., 50 patients, aged 8-16 years, were randomly assigned to receive postoperative patient-controlled analgesia (PCA) using either morphine or meperidine. Results showed that pain scores during morphine PCA were significantly less than those during meperidine PCA ($p<0.001$). These results suggested that morphine is the better opioid for pediatric PCA (29).

14. Diclofenac and Pethidine

Noroozinia et al. assessed the effects of suppository diclofenac on post-herniorrhaphy pain management. They divided 60 patients who were candidates for the surgical repair of inguinal hernia were divided into two groups; group A received 100 mg of suppository diclofenac and group received B 50 mg of pethidine after the induction of anesthesia and before surgical incision. Results showed that pain relief was similar in the two groups ($p=0.3$). Patients in group B required more analgesia two hours post-operatively ($p=0.03$), while patients in group A had

more favorable results regarding pain control ($p<0.05$) (30).

4- DISCUSSION

Postoperative pain is highly prevalent and the use of efficient pain management methods in the postoperative period is essential (31). This review study was performed to review analgesics and their effectiveness in pain management after surgery. The main finding of this study was the effectiveness of pethidine, morphine and paracetamol in reducing postoperative pain in children and adults. However, there were conflicting findings regarding the comparative efficacy of pethidine, morphine, pethidine, and paracetamol. The results of two studies on comparing the effect of pethidine and morphine on postoperative pain in children demonstrated that the pain intensity in the morphine group was significantly lower than the meperidine group in pediatric surgery (29, 32). In contrast to the above studies, the findings of one study did not find a significant difference in postoperative sedation and patient satisfaction under cesarean section (29).

The reason for this contradiction can be differences in the type of surgery, the extent of the researchers' relationship with the patient, differences in dose, dose interval and duration of administration, and possibly also differences in the age group of patients. Pethidine and morphine drugs may have different analgesic effects in children and adults, and future studies should be large enough in terms of the sample size to compare the effects of pethidine in adult and pediatric groups. On the other hand, according to the results of some studies, pethidine is a safer drug than morphine (33) and might be preferred to morphine when rapid control of acute pain is necessary (34). Two studies compared the effect of pethidine and paracetamol on surgical pain. Pethidine is a synthetic opioid (34), and a derivative of opium (35). Intravenous acetaminophen (paracetamol) is an effective and safe drug with known analgesic effects (36). In some studies, there was no significant difference between pain intensity 24 and 6 hours after surgery. However, the difference in pain intensity between the two groups was significant after 6 hours; in other words, pethidine more than paracetamol reduced the pain score, but led to increased vomiting in patients (15). The results of another study also showed that pain intensity in patients treated with intravenous acetaminophen was significantly lower than meperidine group 6 hours after surgery in one hour intervals ($p<0.001$) (19). The reason for the difference between studies can be differences in the type of surgery, the extent of the researchers' relationship with the patient, differences in dose, dose interval, and duration of drug administration. The difference between the two studies may also be related to the mechanisms of action. Pethidine acts as an analgesic through ascending and descending receptors and neurons of the hypothalamic basal ganglia, limbic structure, and cerebral cortex (37).

Paracetamol inhibits the synthesis of prostaglandin. The first enzyme in the synthesis cycle of prostaglandin is cyclooxygenase. When paracetamol enters the cycle, it prevents the production of the enzyme and produces its analgesic effect (38). A comparative study on pethidine and ketorolac in postoperative pain control showed that ketorolac was effective in reducing the pain score and was also associated with fewer complications than intravenous pethidine after inguinal hernia surgery (22). Also, in the study of Zangoue et al., no significant difference was observed in the mean pain intensity between the two groups receiving either pethidine or ketorolac after cesarean section surgery according to VAS criteria. However, based on the Faces pain scale,

the pain intensity in the ketorolac group was significantly lower than the pethidine group (39). However, in another study to compare the efficacy of ketorolac and pethidine, there was no significant difference in postoperative pain scores between the two groups (40). Ketorolac is a non-steroidal anti-inflammatory drug (NSAID) that reduces pain and inflammation by inhibiting prostaglandin synthesis (41). Differences observed between studies may be due to differences in drug dose as well as pain score measurement methods.

4-1. Study Limitations

One of the main limitations of this study is the low number of studies performed on this topic. Other limitations include study methodology. The small sample size and short sampling time, limit the generalizability of the findings of this study. Further research with longer follow-ups and larger sample sizes is recommended to confirm the reported findings. The second methodological limitation is related to blindness. In order to properly blind, drugs need to be given at a fixed dose and at equal intervals, which is not the case in any of the studies. Participants with a variety of surgical methods (cesarean section, fracture, etc.) were included in the present review study, which caused heterogeneity of data. On the other hand, in the studies included in this study, a review of various tools (the Faces pain scale and VAS) was used to assess pain, which may be another factor for data heterogeneity. Also, relief and analgesia should be done based on the cost, effectiveness, and safety of the drugs. None of the studies included in this review evaluated the cost-effectiveness of analgesics.

5- CONCLUSION

Intravenous acetaminophen, pethidine, morphine, ketorolac, and paracetamol are effective in reducing postoperative pain in children and adults. There are conflicting findings regarding the comparative efficacy of pethidine, acetaminophen, morphine, ketorolac, and paracetamol. Due to the methodological limitations of the included studies, these results should be interpreted with caution. Further studies with larger sample sizes are recommended.

6- AUTHORS' CONTRIBUTIONS

Study conception or design: MM, MJ, and FR; Data analyzing and draft manuscript preparation: SI, RR, and SS; Critical revision of the paper: MM, MJ; Supervision of the research: MM and FR; Final approval of the version to be published: MM, MJ, SI, SS, RR, and FR.

7- CONFLICT OF INTEREST: None.

8- REFERENCES

1. Wu CL, Raja SN. Treatment of acute postoperative pain. The lancet. 2011;377(9784):2215-25.

2. Werner MU, Søholm L, Rotbøll-Nielsen P, Kehlet H. Does an acute pain service improve postoperative outcome? Anesthesia & Analgesia. 2002;95(5):1361-72.

3. Buvanendran A, Fiala J, Patel KA, Golden AD, Moric M, Kroin JS. The incidence and severity of postoperative pain following inpatient surgery. Pain Medicine. 2015;16(12):2277-83.

4. National Institute of Academic Anaesthesia (NIAA) Health Services Research Centre. Perioperative Quality Improvement Programme Annual Report 2017–18. NIAA: London; 2018.

5. Centre. NIoAANHSR. Perioperative Quality Improvement Programme Annual Report 2017–18. NIAA: London; 2019 .

6. Chapman CR, Donaldson GW, Davis JJ, Bradshaw DH. Improving individual measurement of postoperative pain: the pain trajectory. The Journal of Pain. 2011;12(2):257-62.

7. McMahon SB, Koltzenburg M, Tracey I, Turk D. Wall & melzack's textbook of pain e-book: Elsevier Health Sciences; 2013.

8. Walker E, Bell M, Cook T, Grocott M, Moonesinghe S. Patient reported outcome of adult perioperative anaesthesia in the United Kingdom: a cross-sectional observational study. BJA: British Journal of Anaesthesia. 2016;117(6):758-66.

9. Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. Anesthesia & Analgesia. 2007;105(1):205-21.

10. White PF. The changing role of non-opioid analgesic techniques in the management of postoperative pain. Anesthesia & Analgesia. 2005;101(5S):S5-S22.

11. Liu SS, Wu CL .Effect of postoperative analgesia on major postoperative complications: a systematic update of the evidence. Anesthesia & Analgesia. 2007;104(3):689-702.

12. Kehlet H, Holte K. Effect of postoperative analgesia on surgical outcome. British journal of anaesthesia. 2001;87(1):62-72.

13. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery: a review of predictive factors. The Journal of the American Society of Anesthesiologists. 2000;93(4):1123-33.

14. Mitra S, Carlyle D, Kodumudi G, Kodumudi V, Vadivelu N. New advances in acute postoperative pain management. Current pain and headache reports. 2018;22(5):1-11.

15. Jarineshin H, Fekrat F, Kashani S. The effect of paracetamol versus meperidine on postoperative pain of cesarean section. Anesthesia, essays and researches. 2017;11(1):165.

16. Hasani V, Farahmand RR, AAli AH. Comparison of intramuscular morphine and methadone on postoperative analgesia in patients with tibial fracture. Journal of Iranian Society Anaesthesiology and Intensive Care. 2018;40: 63-72.

17. Talebi Deloee, M., Zarmehri, B., Pishbin, E., Najaf Najafi, M., Salehi, M. Intravenous Acetaminophen Versus Intravenous Morphine Sulfate for Isolated Diaphyseal Long Bone Fractures: A Randomized Clinical Trial. Trauma Monthly, 2017; 22(4). doi: 10.5812/traumamon.57680.

18. Haghighi M, Sedighinejad A, Ettehad H, Mirbolook A, Nabi BN, Rad MR, et al. Acetaminophen versus fentanyl for post-operative pain after lower limb surgery: a randomized controlled trial. J Pioneer Med Sci. 2016;6:38-41.

19. Kolahdouzan K, Eydi M, Anvari HM, Golzari SE, Abri R, Ghojazadeh M, et al. Comparing the efficacy of intravenous acetaminophen and intravenous meperidine in pain relief after outpatient urological surgery. Anesthesiology and pain medicine. 2014;4(5):1-5.

20. Sanie M, Kalani N, Radmehr M, Zabetiyan H, Dowlatkhah H. The effect of paracetamol on the level of drug use during and after orthopedic surgery of the upper limb. Journal of Jahrom University of Medical Sciences. 2015;13(2):33-8.

21. Parish M, Shimia M, Abedini N, Ghanbari M, Farzin H, Sakha H .The Effect of Infusion of Intravenous paracetamol on the hemodynamic variables and pain score at post anesthesia care unit after major surgery. Journal of Iranian Society Anaesthesiology and Intensive Care. 2017;39(4):2-9.

22. Saryazdi HH, Aghadavoudi O ,Shafa A, Masoumi A, Saberian P. A comparative study of the analgesic effect of intravenous pethidine vs. Ketorolac after inguinal hernia surgery in children under general anesthesia. Middle East J Anaesthesiol. 2016;23(5):527-33.

23. Yilmaz A, Sabirli R ,Ozen M, Turkcuer I, Erdur B, Arikan C, et al. Intravenous paracetamol versus dexketoprofen in acute musculoskeletal trauma in the emergency department: A randomised clinical trial. The American journal of emergency medicine. 2019;37(5):902-8.

24. Koehler D, Marsh JL, Karam M, Fruehling C, Willey M. Efficacy of surgical-site, multimodal drug injection following operative management of femoral fractures: a randomized controlled trial. JBJS. 2017;99(6):512-9.

25. Galos DK, Taormina DP, Crespo A, Ding DY, Sapienza A, Jain S, et al. Does

brachial plexus blockade result in improved pain scores after distal radius fracture fixation? A randomized trial. Clinical Orthopaedics and Related Research®. 2016;474(5):1247-54.

26. Craig M, Jeavons R, Probert J, Benger J .Randomised comparison of intravenous paracetamol and intravenous morphine for acute traumatic limb pain in the emergency department. Emergency Medicine Journal. 2012;29(1):37-9.

27. O'Hara M, McGrath PJ, D'Astous J, Vair C. Oral morphine versus injected meperidine (Demerol) for pain relief in children after orthopedic surgery. Journal of Pediatric Orthopaedics. 1987;7(1):78-82.

28. Stanley G, Appadu B, Mead M, Rowbotham D. Dose requirements, efficacy and side effects of morphine and pethidine delivered by patient-controlled analgesia after gynaecological surgery. British journal of anaesthesia. 1996;76(4):484-6.

29. Vetter TR. Pediatric patient-controlled analgesia with morphine versus meperidine. Journal of pain and symptom management. 1992;7(4):204-8.

30. Noroozinia H, Mahoori A, Hassani E, Akhbari P. Diclofenac suppository versus intramuscular pethidine in post herniorrhaphy pain relief. Tehran University Medical Journal. 2011;69(3):198-203.

31. Gregory J, McGowan L. An examination of the prevalence of acute pain for hospitalised adult patients: a systematic review. Journal of clinical nursing. 2016;25(5-6):583-98.

32. O'Hara M, McGrath PJ, D'Astous J, Vair C. Oral morphine versus injected meperidine (Demerol) for pain relief in children after orthopedic surgery. Journal of pediatric orthopedics. 1987;7(1):78-82.

33. Pouyan M, Ozmaie S, Sakha M, Asghari A. Evaluation of the Analgesic and Sedative Effects of Pethidine (meperidine) with Xylazine in the Horse. Journal of Comparative Pathobiology. 2017;14(1):209.

34. Sattari H, Haghbin M, Etminan M, Dehghani A. Survey of the Effect of Intraoperative Intravenous Lidocaine Infusion on Postoperative Pain in Laparoscopic Cholecystectomy Surgery. Journal of Rafsanjan University of Medical Sciences. 2015;13(10):937.

35. Pouyan M, Ozmaie S, Sakha M, Asghari A. Evaluation Of The Analgesic and Sedative Effects of Pethidine (Meperidine) With Xylazine In The Horse. 2017.

36. Amrimaleh P, Alijanpour E, Zabihi A, Attarzadeh H, Shirkhani Z, Rezaee B, et al. Comparison of analgesic effect of intravenous paracetamol plus meperidine and meperedine alone on postoperative pain after elective cesarean. Anesthesiology and Pain. 2013;4(3):1-7.

37. Sereshti M, Asefi F, Shabanian M, Banaeian-Borujeni S. Comparing the effects of massage and intra intramuscular pethidine on pain relief in the stages of labor and the length of labor. Iranian Journal of Obstetrics, Gynecology and Infertility. 2013;16(80):6-16.

38. 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. Journal of Jahrom University of Medical Sciences. 2015;13(2):33-8.

39. Zangoue M, Bijari B, Abasspour Z, Tolyat M. Comparison of the Effect of Ketorolac and Pethidine on Pain Control after Cesarean Section Surgery. Journal of North Khorasan University of Medical Sciences. 2019;11(2):73-7.

40. Khezri MB, Mosallaei MA-s, Ebtehaj M, Mohammadi N. Comparison of preemptive effect of intravenous ketorolac versus meperidine on postoperative shivering and pain in patients undergoing cesarean section under spinal anesthesia: A prospective, randomized, double-blind study. Caspian journal of internal medicine. 2018;9(2):151.

41. Lowder JL, Shackelford DP, Holbert D, Beste TM. A randomized, controlled trial to compare ketorolac tromethamine versus placebo after cesarean section to reduce pain and narcotic usage. American journal of obstetrics and gynecology. 2003;189(6):1559-62.