

The Efficacy of Meperidine for Pain Management in Orthopedic, Dental, and General Surgery in Children: A Review Study

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Abstract

Background: The present study aimed to assess the efficacy of Meperidine for pain relief in children after orthopedic, abdominal surgery, and laceration repair.

Materials and Methods: A systematic search was performed using the following online databases: Medline, Cochrane, Web of Science, Scopus, and Embase to 2 June 2020, with keywords: (Meperidine OR Pethidine) AND (Pain) AND (Child OR Children) with no language restriction.

Results: The Acetaminophen had slightly higher pain scores compared to Meperidine after dental restoration among children. There was better sedation along with more rapid onset and recovery in the combined regimens of Atropine/Midazolam/Ketamine compared to Meperidine/Midazolam. Two studies reported the superiority of Morphine over Meperidine for pain management. A study found a significant increase in the mean pediatric pain scores in the Tramadol group compared to the Meperidine group after 24 hours. There was no difference in the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) between MPC (Meperidine/Promethazine/Chlorpromazine), and OTFC (Oral Transmucosal Fentanyl Citrate) groups during the laceration repair. In the study on the incidence of sleep on the way home or shortly after arriving at home, there were differences in chloral hydrate, Meperidine, and Hydroxyzine regimen compared to Midazolam alone among children being sedated during endodontic procedures.

Conclusion: Meperidine was effective for controlling pain in orthopedic, abdominal surgery, laceration repair, and dental restoration. However, it was only superior to the Tramadol group. Regarding dental surgery, a combination regimen were more effective compared to single Midazolam. The pain intensity during early recovery was slightly lower in Meperidine group. The regimen had better sedation with more rapid onset and recovery compared to Meperidine/Midazolam.

Key Words: Children, Dental, Meperidine, Pain, Orthopedic, Surgery.

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1- INTRODUCTION

Post-operative pain management is one of the significant challenges after surgery. It is estimated that 80% of the world population are receiving adequate pain management, and that is one of the serious problems in more than 150 countries. Most pressures for inadequate pain management have been experienced by old patients, pregnant and breastfeeding women, children, opium addicts, and psychotic patients. Despite the made efforts for the improvement of pain management in children after surgery, numerous children have been suffering from post-operative pain (1). Pain is a mental feeling and a reaction arisen from various nerves perception at different surfaces of the body to the internal or external stimulator, which is created by harmful stimulators in nature (2). It is one of the most frightening symptoms of a disease as humans are always seeking for its alleviation and relief. The *International Association for the Study of Pain (IASP)* has defined it as an unpleasant sensory and emotional experience associated with tissue damage. Pain in children is more at the center of focus since it is a complex phenomenon and difficult to diagnose whether they are crying due to pain, hunger, or fear (3).

After the recurrent experience of pain, permanent changes like the stimulation of the autonomic nervous system will be caused that can lead to disorders in nervous system development, learning ability, and behavioral problems among children. Reaction to the pain in children is derived from the complicated and reciprocal effects of factors like genetics, experience, and developmental factors. The role of people's personal life experiences, which lead to these differences in responses and reactions, cannot be denied. These elements potentially lead to an increased reaction to the pain; therefore, medical staff must pay attention to their important roles. Pain

causes strengthening child reactions and even causes phobia or fear of treatment (2). Unfortunately, due to the lack of awareness and shortage of time for hygiene team members, prescribing sedatives is not always accompanied by adequate sedation. As a result, children do not receive a high quality of care (4). Nevertheless, the lack of surety about the efficacy and safety of analgesic drugs and anxiety about the respiratory repression by the opiate may increase anxiety about the lack of pain treatment after surgery in children. Lack of pain treatment after surgery can lead to a progression of biochemical and physical events that at last culminate in pulmonary system disorder, cardiovascular disorder, an endocrine disorder, immunologic and metabolic disorder (3). Besides, lack of diagnosis and inadequate treatment of pain in children delays the recovery process applies emotional damages and changes in the trajectory of pain processing. Recent studies have shown that the presence of pain culminates in behavioral changes and stress manifestation in children (5).

Various studies have shown that medium to severe pain is the most common complaint of children during the first 24 hours after major or minor surgeries (6). Therefore, post-operative pain treatment in children has attracted the attention of several pediatricians, surgeons, and anesthesiologists. Part of the main duties of the clinical care team is to present high-quality care for the children during a specific period after surgery (7). Administration of opioids, as one of the general principles in post-operative pain management, is the center of focus. However, fear of the serious side effects, particularly respiratory depression, causes a lack of tendency in using an opiate injection in children (8). Despite emphasizing the role of opioid not only as an important element in pain management but also as a main factor in controlling

post-operative complications, unfortunately, there are no useful pieces of evidence for the guidance manual of these medicines usage in the period after children surgery (7). Furthermore, age, race, gender, ability rate in expressing pain, hereditary diseases, amount of physician's awareness, and fear of the complication manifestation are among the factors which impede appropriate pain management in patients (9). Acute pain is one of the most common negative stimulators that children will experience because of lesions, quick and exact evaluation, and effective therapy onset are the main elements in pain management, particularly after surgery. Lack of clinical information in the efficacy of sedative and opioid medications among children can lead to the presentation of incompetent clinical care and lack of pain alleviation (10). Recent advances in post-operative pain management cause an increase in patient satisfaction and their positive effects on the recovery period.

However, using the appropriate technique in post-operative pain management is still one of the controversial discussions in medicine (11). Post-operative pain leads to complications like phlebothrombosis, pulmonary embolism, functional respiratory disorders, and even myocardial infarction (MI) (5). Pain management in orthopedic patients is crucial since inadequate pain management can be associated with bradykinesia and limitation in articular movements (6). Post-operative adequate pain management has various advantages like a decrease in surgical complications and quicker patient discharge from the hospital and, subsequently, a decrease in expenses (7).

Pethidine is a synthetic opioid that has one-tenth of Morphine strength, and its efficacy time is 2-3 hours. Due to its high liposolubility (compared to Morphine, it is more soluble in lipid) and immediate cerebral effects, its abuse possibility is

high, and in the case of emergency pain management, it will be preferable to Morphine. Pethidine is used in slow intravenous injection in 25-50 dosages every 4 hours. The required time for reaching the plasma concentration climax of opioids is 30 minutes after rectal injection and 6-10 minutes after intravenous injection (8). Providing analgesia after surgery in children is significantly different (1); therefore, it is necessary to pay attention to pain management and decrease after surgery among children (9). In this regard, defining the minimum palliative standards for pain after surgery in children can be useful for the appropriate decision-making of physicians for the recovery and prevention of pain after surgery among children (1). Therefore, regarding the difference and variety of treatment and pain management, this study has dealt with considering the efficacy of meperidine medicines on pain management among children after surgery.

2- MATERIALS AND METHODS

2-1. Information Sources

Systemic search on Medline (via PubMed), Cochrane Library, EMBASE, and Scopus were carried out, and articles indexed until 2 Jun 2020 were reviewed using keywords such as (Meperidine OR Pethidine) AND (Pain) AND (Child OR Children) with no language restriction. All the clinical trial papers, which considered the Pethidine effect on pain in all children surgeries, have been studied; the Control group could either be opioid or non-opioid drugs. The search was carried out independently in duplication by two reviewers, and the supervisor dissolved any disagreement between the reviews.

2-2. Exclusion Criteria

Exclusion criteria include irrelevant papers, letters, and letter to the editor, inaccessibility to the complete text or lack of adequate information in the abstract,

presented summary of papers in the conferences, letters, editor notes, and the report of cases. In case of inaccessibility to the complete text, contact the corresponding author or the first author three times through email, and if not receiving any response, they will be excluded from the study.

2-3. Study Selection

A database search was carried out for possible studies. The abstracts of the studies were screened for identification of eligible studies, full-text articles were obtained and assessed, and a final list of included studies was prepared. This process was performed independently and in duplication by two reviewers, and the 3rd reviewer resolved any disagreement.

2-4. Data Items

We developed research made form and followed it for each study. Two reviewers collected the data independently; they were combined and compared for accuracy; a third reviewer solved any discrepancies. Data collected from the selected studies included: the first author, study design, year of publication, sample population (sample size in groups), main results, type of intervention, duration of

intervention, criteria, drop out records, and assessment tools.

2-5. Included Studies

Randomized Controlled Trials (RCT), clinical studies, both randomized and nonrandomized, either retrospective or prospective, were included. Due to the limited number of published RCT in the literature, other types of clinical studies were included. Pilot, preliminary, and case report studies were not included due to limited sample size and a higher risk of bias. Studies published in English until Jun 2020.

2-6. Quality of Study

The final version of the Jadad scale, which comprises three important items, was used for evaluating the quality of trials. The Jaded scale ranges from 0 to 5 points (12). These items included: randomization (if randomization was conducted and if it was performed appropriately), blinding (if the trial was blinded and if it was performed appropriately), and reporting withdrawals and dropouts (if rate and reasons for withdrawals and dropouts were reported). The authors independently evaluated these items. **Table.1** shows an assessment of the quality of studies included in the systematic review.

Table-1: Assessment of risk of bias through eligible studies (12).

Author, Year, Country, Reference	Randomization			Blinding			Sample
	Mention randomization	Method: appropriate	Method: inappropriate	Mention blinding	Method: appropriate	Method: inappropriate	Account of all patients
Ekemen et al., 2008, Turkey, (8)	*	*	-	*	-	*	*
Martinez, 2006, USA, (13)	-	-	-	*	-	*	*
McCormack , 2014, USA, (14)	*	-	*	*	-	*	*
Alhashemi et al., 2007, Saudi Arabia, (15)	*	*	-	*	-	*	*
Marx et al., 1997, USA, (16)	*	*	-	*	*	-	*
Vetter,1992, USA, (17)	*	-	*	*	-	*	*
O'Hara et al.,1987, Canada, (18)	*	*	-	*	*	-	*
Schutzman et al.,1996, USA, (19)	*	-	*	*	-	*	*

3- RESULTS

Finally, eight studies were included in the systematic review (**Table.2**) (*Please see the table 2 at the end of this paper*).

3-1. Meperidine for the Management of Pain During Dental Surgery

Martinez et al. examined healthy children (n=30) with 2-5 years old who were to be sedated in a dental clinic for surgery. The patients were prescribed by mere Midazolam at a dose of 0.5-0.75 mg.kg-1 or combined regimen of Chloral Hydrate/Meperidine/Hydroxyzine at different doses of 20-30 mg.kg-1/1-2 mg.kg-1/1-2 mg.kg-1, respectively. Their parents completed a questionnaire on possible events within post-sedation 24 hours. The differences were observed in the incidence rates of sleep on the way home or shortly after arriving at home between the combined regimen and monotherapy, but not in evening sleep, eating, vomiting, post-operative pain, and memory (13).

In a study, the healthy children (n=40) with 3-6 years old were sedated using combined regimens of Midazolam/Meperidine/Hydroxyzine/Nitrous Oxide (MZ/M/H/N₂O; n=21) or Chloral Hydrate/Meperidine/Hydroxyzine/Nitrous Oxide (CH/M/H/N₂O; n=19) for the management of pain during dental surgery. Eight hours after the discharge of the subjects, there was a significant elevation in perioperative hyperactivity and post-operative difficulty of walking and slurring/difficulty of speaking in the MZ/M/H/N₂O regimen; as well, there was a significant elevation in the frequency of sleeping, talking less than normal after arriving home, and the need for more painkiller postoperatively in CH/M/H/N₂O regimen (14). In a double-blind, randomized trial study conducted by Alhashemi et al., children (n=40) received IV Acetaminophen (15 mg/kg) or IM

Meperidine (1 mg/kg) to manage pain after dental restoration. According to the results, the pain intensity during early recovery was slightly lower in the Meperidine group compared to the Acetaminophen group (15). Marx et al. prescribed Meperidine/Midazolam (MM) at the doses of 2 mg.kg-1/0.1 mg.kg-1 or Atropine/Midazolam/Ketamine (KM) at the doses of 0.01 mg.kg-1/0.05 mg.kg-1/1.5 mg.kg-1, respectively, for twenty-two children, aged 24 to 178 months. The results showed that the KM regimen had better sedation with more rapid onset and recovery and fewer complications (16).

3-2. Meperidine for the Management of Pain during Orthopedic Surgery

Vetter et al. examined children (n=50) undergoing orthopedic procedure within two groups of receiving post-operative Patient-Controlled Analgesia (PCA) with Meperidine (n=25) and Morphine (n=25). The pain intensity was significantly reduced in the Morphine group compared to the Meperidine group (P=0.001) (17). O'Hara et al. evaluated children (n=25) with 7-17 years old for pain management at first 48 hours after orthopedic surgery using the injection of Morphine every 4 hours and Meperidine every 3-4 hours, and rated the pain intensity every 1-3 hours for 24 hours. The Morphine group experienced no pain significantly more compared to the Meperidine group on both days 1 and 2 (18). Overall, there have been mild to moderate genitourinary or orthopedic procedures. The interventions were intramuscular administration of Meperidine (1 mg/kg), ketorolac (0.75 mg/kg), or normal saline (placebo) was (IM) at the beginning of surgery. The earlier rescue was found for the placebo patients (P<0.0001) who needed twice the rescue dosage (P=0.013) compared to both ketorolac and meperidine groups. The ketorolac and meperidine groups showed the same time until the first rescue, the

rescue-requiring cumulative proportion of the number of needed rescue doses (18).

3-3. Meperidine for the Management of Pain during Abdominal Surgery

The healthy children (n=110) with 2-12 years old underwent elective lower abdominal surgery within two groups of Pethidine (1 mg.kg⁻¹, n = 60) or Tramadol (2 mg.kg⁻¹, n = 50) to manage the post-operative pain after anesthesia induction. The mean post-operative pain intensity was significantly higher in the Tramadol group compared to the Pethidine group on 24 hours. No significant difference was observed in sedation scores between the groups (8).

3-4. Meperidine for the Management of Pain during Laceration Repair

In a study by Schutzman, the children (n=40) with 3-8 years old were examined for laceration repair. The premedication was performed for the patients by OTFC (10-15 l-mg/kg), and a mock injection or intramuscular MPC (Meperidine, 2 mg.kg⁻¹/Promethazine 0.5 mg.kg⁻¹/Chlorpromazine 0.5 mg.kg⁻¹) followed by a placebo. Although more sedation was observed in the MPC group, there was no difference in the CHEOPS between groups during the laceration repair (19).

4- DISCUSSION

The Acetaminophen showed slightly higher pain scores compared to Meperidine after dental restoration in children. There was better sedation, more rapid onset, and recovery, and fewer complications in the combined regimens of Atropine/Midazolam/Ketamine (KM) compared to Meperidine/Midazolam (MM). Two studies reported the superiority of Morphine over Meperidine for pain management. A study found a significant increase in the mean pediatric pain scores in the Tramadol group compared to the Meperidine group after 24

hours. There was no difference in CHEOPS scores between MPC (Meperidine/ Promethazine/ Chlorpromazine) group and the OTFC group during the laceration repair. In the study of the incidence of sleep on the way home or shortly after arriving at home, there were differences in Chloral Hydrate, Meperidine, and Hydroxyzine regimen compared to Midazolam alone among children being sedated during endodontic procedures. Systemic opioid sedative medicines are the touchstone for post-operative pain management. However, various reasons like fear of serious side effects lead to a lack of tendency to the prescription of opioid sedative injection among children (20). Ideal sedative after surgery must have widespread therapeutic range, at least cardiovascular and pulmonary repressive effects, and in case of emergency, its effects are reversible (21). Pethidine is a synthetic opioid (21), and is derived from opium (22). Pethidine acts through receptors of ascending and descending pathways, and hypothalamic basal ganglia neurons, limbic system, and cerebral cortex (21). This medication has about one-tenth of Morphine strength, and its efficacy time is 2-3 hours. Due to the high liposolubility (compared to Morphine, it is more soluble in lipid), and immediate cerebral effects, its abuse possibility is high (20). This medication is associated with significant side-effects like respiratory depression, nausea, vomiting, and hypotension. The most serious complication is respiratory depression that can threaten life. Anaphylactic reactions, as well as convulsion, are mentioned as the side effects of this medicine (23). Pethidine is used in slow intravenous injection in 25-50 dosages every 4 hours. The required time for reaching the plasma concentration climax of opioids is 30 minutes after rectal injection and 6-10 minutes after intravenous injection. Pethidine may cause an increase of hospitalization in the recovery room, the

slow movement of the gastrointestinal system, and delay in normal gastrointestinal nutrition in patients (23). Nevertheless, compared to Morphine, Pethidine is a less hazardous medicine, its addiction probability is low, proper for rapid pain management. Nowadays, Pethidine is only recommended for very short-term treatment and in the patients who have shown sensitivity or intolerance to opioid medicines like Morphine, as it is associated with the higher alternation of side effects compared to other opioid medicines. However, infinite complications of inadequate pain alleviation, medicine interactions, and the manifestation of common side effects of Pethidine are reported, which makes it challenging for children (22).

According to several studies, Tramadol is effective and tolerable compared to other opioid sedative medicines in post-operative pain management for one-year-old children. Moreover, its subtle side effect on respiration is tangible compared to the Pethidine sedative. Moreover, Tramadol has advantages compared to traditional opioid medicines like Morphine and Pethidine for pain alleviation after surgery in children (24). Tramadol has a significant effect on decreasing medium to severe pains. Besides the systemic effect, its local analgesic and anesthetic effects in the periphery nervous system and spinal cord have been proved in the clinical and laboratory studies. Tramadol is well-tolerated in patients, and cardiac depression occurs less frequently compared to Morphine and Pethidine. Moreover, vertigo, dizziness, addiction, and abuse of Tramadol are significantly less compared to Morphine. The prominent side effect is nausea and vomiting that can be prevented by antiemetic medicines like Metoclopramide (25). Ekemen et al. (2008) have dealt with the comparison of Pethidine and Tramadol effect in pain management after abdominal surgery in

patients. They showed that those children who were received Pethidine had less pain remarkably compared to Tramadol in the first 6 hours after surgery. However, the pain severity in both groups had no significant difference in the 6 and 24 hours after surgery (8). Barsoum (1995) compared Pethidine and Tramadol effect in children and showed that patients in the Pethidine group had no pain only 30 minutes after medicine usage. Moreover, they had less pain, and this level of analgesia was preserved for 24 hours. Pain has been measured 24 hours after surgery, and no significant difference was observed between these two groups. Besides, the Tramadol group had adequate analgesia compared to the Pethidine group (26).

Furthermore, side effects of Pethidine and Tramadol were compared in Ekemen et al. study (2008). In the Tramadol group, respiratory repression was not observed. Nausea and vomiting in the two groups had no significant changes after surgery (26). Umuroglu et al. used Tramadol of 1.5mg/ kg intravenously for the children under adenotonsillectomy. They observed nausea and vomiting in 20% of the cases, which were similar to the group of patients who had received Morphine of 0.1 mg/kg (27). Ekemen et al. (2008) concluded that there is a possibility that Pethidine has less efficacy time compared to Tramadol. As a result, it seems that 0.2 mg/kg of Tramadol and 0.1 mg/kg of Pethidine are associated with the anesthesia inculcation, effective and tolerable analgesia in children with the post-operative pain. Analgesia preservation in the last post-operative stages was similar between Tramadol and Pethidine, but it seems that Pethidine in the early stages after surgery is subtly preferable to Tramadol (8). In a study conducted by Abdolkarimi et al. (2016), the Pethidine and Ketamine were compared in the decrease of pain after bone marrow biopsy in children with cancer, and they have concluded that

hemodynamic stability and pain management in the patients who have received Ketamine were significantly better. Nausea and vomiting in the Ketamine-assisted therapy were more than the Pethidine group, but no significant differences between these two therapies have been observed (28). Saleh et al. (2019) compared Pethidine and rectal Diclofenac effect in the pain decrease after tonsillectomy in children. They concluded that pain scores in different groups at a different time was significantly lower and required fewer sedatives. Tranquility and vomiting after surgery in the Pethidine group were significantly higher. Respiratory depression only occurred in the Pethidine group (29). In another study, Yeung et al. (2007) compared the effect of Pethidine and Midazolam in the pain decrease after renal biopsy in children and concluded that the dosage of Midazolam compared to Pethidine was less in the decrease of pain. However, the compound of intravenous Pethidine and Midazolam 1 was a tranquil, effective, and safe protocol for subcutaneous renal biopsy in children (30). Pethidine is an appropriate medication in pain decrease. The results of this study in anesthesiologists and orthopedists' decision-making can assist them in pain management among children.

4-1. Limitation

Quantitative limitations in the recent review study have been observed. One of the main limitations is related to the applied methodology in this review study, including a short time of sampling, which has limited the overgeneralization of the results of current studies. Methodology limitation is related to blinding; for proper blinding, it is required that medicines be used with stable dosages and in equal intervals. More studies with longer follow-up for the confirmation of the reported results are recommended. The results are mainly focused on dental, orthopedic surgery, and probably it does not apply to

all other surgeries. Furthermore, the results of this study were based upon children, and perhaps it does not apply to adults. One of the strengths of the current study the use of the pain scale as an appropriate instrument for pain measurement. It is recommended that the long-term effects of Pethidine on pain in further studies be considered. It is recommended that pethidine effects with other opioid medicines alone or as a compound be evaluated. Because of shortage or inappropriate report, the sequence of random dedication, shortage or inappropriate report of blinding, lack of intention to treat analysis, it is recommended that further studies be drawn and be reported according to consort. Moreover, rarely related studies and low sample sizes, which are indicative of the need for more studies with more sample size in this field. Some of the studies with a low sample size will have varied results when the sample size is increased. Some of the published studies have not been included in this study due to lack of a placebo group, and some of the studies have been designed as a test, post-test without a control group, are excluded from the study, and it is recommended that further study be designed with the placebo-controlled group.

5- CONCLUSIONS

Meperidine was effective for controlling pain in orthopedic, abdominal surgery, laceration repair, and dental restoration. However, it was only superior to the Tramadol group. Regarding surgery, dental, combination regimen (chloral hydrate/meperidine/hydroxyzine) were more effective compared to Midazolam alone. The pain intensity during early recovery was slightly lower in Meperidine, which was superior to the Acetaminophen group. Regimen had better sedation with more rapid onset and recovery and fewer complications than Meperidine/

Midazolam. Generally, findings of this study have shown that Pethidine was an opioid drug in post-operative pain management in children. However, regarding the methodologic limitations, the results of this study have to be interpreted with discretion.

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7- CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest.

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Table-1: General characteristics of included studies.

Authors, Year, Country, Reference	Study Design	Number of Subjects Intervention/ Control	Type of Intervention	Type of Control	Drop out	Assessment tool	Results
Ekemen et al., 2008, Turkey, (8)	Prospective, randomized, controlled study	Pethidine (n = 60) Tramadol (n = 50)	Pethidine 1 mg/kg	Tramadol 2 mg/kg.	0	Four-point restlessness–pain protocol	The mean postoperative pain intensity was significantly higher in tramadol group than in pethidine group on 24 h. No significant difference was observed in sedation scores between the groups.
Schutzman et al., 1996, USA, (19)	Randomized single blinded study	OTFC, (n=20) MPC, (n=19)	OTFC at a dose of 10 to 15 micrograms/kg and a mock injection	Injected MPC (2 mg/kg Meperidine, .5 mg/kg Promethazine, and .5 mg/kg Chlorpromazine; maximum doses 50, 12.5, and 12.5 mg, respectively).	1 later excluded 20 children in the OTFC group and 19 in the MPC group	The degree of sedation 5-point activity scale, Children's Hospital of Eastern Ontario Pain Scale (CHEOPS).	Although more sedation was seen in the MPC group, there was no difference in Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) scores between groups during the laceration repair.
O'Hara et al., 1987, Canada, (18)	Randomized clinical trial	Morphine, n=13, Meperidine, n=12	Oral morphine, every 4 h	Injected meperidine (Demerol).	7	Visual Analogue Scale	The morphine group experienced no pain significantly more than meperidine group on both days 1 and 2.
Vetter et al. 1992, USA, (17)	Randomized clinical trial	Morphine, n=25, Meperidine, n=25	PCA therapy Morphine	PCA therapy Meperidine	-	Numerical rating pain scale.	The pain intensity was significantly reduced in morphine group than in meperidine group (P = 0.001)
Alhashemi, et al., 2007, Saudi Arabia, (15)	Randomized clinical trial double-blind study	40/40	Acetaminophen 15 mg kg, Meperidine 1 mg kg	Meperidine 1 mg kg.	10	Objective pain scale, Ramsay sedation score, and Aldrete score.	According to the results, the pain intensity during early recovery was slightly lower in meperidine group than in acetaminophen group to be further explored.
McCormack, et al. 2014, USA, (14)	Prospective cohort study	(CH/M/H/N2O; n=19) (MZ/M/H/N2O; n=21).	Chloral hydrate, meperidine, and hydroxyzine with nitrous oxide	Regimen of midazolam, meperidine, and hydroxyzine with nitrous oxide.	-	Answered a questionnaire regarding the perioperative period.	According to the results, the pain intensity during early recovery was slightly lower in meperidine group than in acetaminophen group.

Martinez, D. ,et al., 2006, USA, (13)	Prospective study	30 healthy patients	Triple combination of chloral hydrate, meperidine, and hydroxyzine/	Midazolam alone.		Questionnaire concerning events that may occur during the 24 hours after the sedation and were told they would be interviewed via telephone regarding these events.	The differences were observed in the incidence rates of sleep on the way home or shortly after arriving at home between the combined regimen and monotherapy, but not in evening sleep, eating, vomiting, postoperative pain and memory.
Marx et al., 1997, USA, (16)	Randomized, double-blind crossover trial	40 children 18 KM 18 MM	Meperidine Midozolam Midozolam	Atropine with Midazolam Ketamine Ketamine.	22	Observational Scale of Behavioral Distress-Revised (OSBD-R), visual analog scale (VAS).	Marx et al. prescribed meperidine/midazolam (MM) at the doses of 2 mg.kg ⁻¹ /0.1 mg.kg ⁻¹ or atropine/midazolam/ketamine (KM) at the doses of 0.01 mg.kg ⁻¹ /0.05 mg.kg ⁻¹ /1.5 mg.kg ⁻¹ , respectively, for children, the results of which showed that the KM regimen had better sedation with more rapid onset and recovery and fewer complications.

OTFC: Oral transmucosal fentanyl citrate, MPC: Meperidine, promethazine, and chlorpromazine, PCA: Patient-controlled analgesia, H/M/H/N2O: Chloral hydrate, meperidine, and hydroxyzine with nitrous oxide, MZ/M/H/N2O: Midazolam, meperidine, and hydroxyzine with nitrous oxide, KM: Ketamine-midazolam.