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Ketamine for management of re-bleeding due to acute post-tonsillectomy pain in children

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Key points

Infiltration or spray administration of ketamine before, during or after surgery is effective for prevention of acute pain after tonsillectomy with or without adenoidectomy in children. This acute pain management could minimize re-bleeding rate in children.

Abstract

Background

Tonsillectomy with or without adenoidectomy is a common surgical procedure in children. Severe post-operative pain has been reported in 5 to 20% of children undergoing this operation. Hemorrhage due to post-tonsillectomy pain is among the main causes of post-surgical morbidity. This study reviewed the available literature in this regard to determine the efficacy of various doses of ketamine, administration method and its association with other drugs for the management of acute post-tonsillectomy pain and provide a guideline for acute post-surgical pain control.

Methods

In this narrative review study, double blind randomized clinical trials published during 2002-2013 were collected. After primary assessment, 14 studied were included and post-tonsillectomy analgesia due to administration of ketamine was compared with that of other drugs.

Results

Of 14 studies evaluated, 9 confirmed the efficacy of ketamine in doses greater than 0.5 mg/kg for post-tonsillectomy analgesia. Two studies mentioned the superior analgesic effect of other drugs like tramadol and meperidine. In one study, 0.25 mg/kg ketamine could not decrease the post-operative morphine consumption. In our previous study, 0.25 mg/kg ketamine could decrease post tonsillectomy agitation in children. One study reported that lidocaine spray in the first 20 min following surgery was more effective than morphine or ketamine; but at 60 min, morphine and ketamine caused greater analgesia. Only two studies were mentioned the possible effect of ketamine on bleeding amounts after tonsillectomy.

Conclusions

Intravenous, intramuscular, infiltration or spray administration of even a single dose of 0.5 mg/kg ketamine before, during or after surgery could effectively prevent post-operative pain and following bleeding in children who underwent tonsillectomy with or without adenoidectomy.

Keywords: Ketamine, tonsillectomy, acute post-operative pain management, bleeding.

Background

Tonsillectomy with or without adenoidectomy is a common surgical procedure (1). Severe post-operative pain has been reported in 5 to 20 percent of children (2). Uncontrolled post-operative pain can have several physiological effects causing disturbances in cardiovascular system and increasing the metabolism(3). Tonsillar fossa is innervated by trigeminal and glossopharyngeal nerves(4). Post-tonsillectomy pain is a major cause of post-surgical morbidity(5). Pain control and proper selection of analgesic drugs, with consideration of their side effects, is always a challenge for clinicians(2, 3). Post-tonsillectomy pain in children causes crying, agitation, irritability, loss of appetite, dysphagia and dehydration in children and delays full recovery and resuming daily activities(6).

Bleeding is the most important complication of tonsil and adenoid surgeries. Bleeding is more prevalent in tonsillectomy with or without adenoidectomy. There are two types of bleeding after tonsillectomy, primary and secondary. Primary bleeding in the first 24 hours after tonsillectomy occurs in 0.2 to 2.2 percent, and the secondary bleeding occurs in 0.1 to 3.7 percent of patients (7).

This bleeding occurs 0.5 percent in first 12 hours after tonsillectomy, and is more frequent in second 12 hours after surgery when the effects of anesthetics/analgesics does not exist (8). The prevalence of bleeding requiring intervention is 0.2 percent in the first 24 hours (9). The pathophysiology of this bleeding in the first 24 hours is not clear yet (7, 9).

Almost all children after tonsillectomy suffer from a severe acute pain that can lead to gag reflex, agitation, crying, and oral intake restriction, which lead to bleeding. The main compliance after tonsillectomy in children is pain. This pain can lead to gag reflex, agitation, crying and decreasing fluid intake cause more bleeding (10).

By reducing the bleeding amounts after tonsillectomy, the need for emergency operation in children could minimize (9, 10).

The most commonly administered analgesics after tonsillectomy include NSAIDs, opioids, antihistamines, anti-inflammatory drugs, local anesthetic agents and ketamine that has recently been suggested(2).

Ketamine hydrochloride is a phencyclidine and a non-competitive N-methyl-D-Aspartate (NMDA) antagonist. The main difference between ketamine and other anesthetic agents is its significant analgesic property. Ketamine has analgesic effects in subanesthetic doses and causes dose-related unconsciousness. It does not cause respiratory depression like other opioids and does not have gastrointestinal complications like NSAIDs(11). Its anesthetic dosage is 2-2.5 mg/kg. If 0.2 to 0.8 mg/kg is administered intravenously or 2 to 4 mg/kg intramuscularly, it has both sedative and analgesic properties (12).

Ketamine has intravenous, intramuscular, subcutaneous, oral, intranasal, rectal, epidural and intrathecal administration. It is contraindicated in patients with high brain pressure or open ocular trauma and also as a sedative in patients with ischemic heart disease(13).

Children undergoing tonsillectomy usually experience severe post-operative pain and selection of the drug of choice for pain management considering drug side effects is very important for patient's family and hospital staff (2). This narrative review evaluated the effect of different doses of ketamine, administration method and association with other drugs on management of acute post-tonsillectomy pain to suggest a guideline in this respect.

Methods

In this narrative review, a search of electronic literature was carried out in Medline, Google Scholar and Scopus using the keywords "ketamine", "postoperative pain", "acute pain", "bleeding" and "tonsillectomy" and relevant randomized double blind clinical trials published during 2002 to 2013 were collected. After initial evaluation, 14 articles were selected evaluating the analgesia caused by ketamine after tonsillectomy and comparing it with other drugs.

Results

Da Concei et al, in 2006 evaluated 90 ASA class I and II children aged 5-7 yrs. who underwent tonsillectomy in three groups. The first group was the control group and received conventional analgesics, the second group received 0.5 mg/kg ketamine pre-operatively and the third group received 0.5 mg/kg ketamine IV after the completion of operation. They concluded that administration of a single dose of ketamine before or after tonsillectomy in children reduced the use of rescue analgesia (morphine) post-surgery (14).

Ertugrul et al. evaluated 45 ASA class I and II children aged 1 to 7 yrs. scheduled for elective tonsillectomy. Subjects were assigned into 3 groups. The first group received 0.5 mg/kg ketamine IM, the second group received 1 mg/kg tramadol IV and the third group received 1 mg/kg meperidine IV before the intubation. They concluded that the mentioned three drugs caused equal analgesia but the agitation score in ketamine group was higher than in other drugs (15).

Erhan et al. studied 60 ASA class I and II children aged 3 to 7 yrs. who underwent tonsillectomy. The children were divided into two groups. The first group received administration of 2 cc of 0.9% normal saline into the tonsillar region after tonsillectomy and the second group received 0.5 mg/kg ketamine and 2 cc normal saline in each tonsillar fossa post-operatively (1 cc in each tonsillar fossa). Ketamine administration into the tonsillar region decreased acute post-tonsillectomy pain and caused no side effects (3).

Aydin et al, in 2005 evaluated 90 ASA class I and II patients aged 5 to 15 yrs. scheduled for tonsillectomy in three groups. The first group received 0.5 mg/kg ketamine IV before the surgery with a maintenance dose of 6 mcg/kg/min until bleeding control. The second group received 0.8 mg/kg ketamine IV and 2 cc infiltration of saline solution in each tonsillar fossa before surgery. The third group received 2 ml saline in the tonsillar fossa before surgery and 3 ml/kg saline infusion during bleeding control. The total dose of tramadol required in the first 6 hours after surgery (for management of post-operative pain) in the first group was less than in other groups (16).

Abu-Shahwan et al, in their study evaluated 84 patients aged 2 to 12 yrs. in two groups. The first group received 0.25 mg/kg ketamine along with morphine and the second group received a single dose of morphine at the time of anesthetic induction. The pain score was equal in both groups. They also stated that althoucgh the administration of morphine in the first days following tonsillectomy was less in the ketamine group, the two groups were not significantly different in overall administration of morphine post-operation. Furthermore, fewer people in the ketamine group required oral pain relievers in the post-operative period. They also found that administration of 0.25 mg/kg ketamine along with morphine at the time of anesthesia induction could not decrease post-operative morphine consumption (17).

Canbay studied 60 ASA class I and II children aged 3 to 12 years who underwent tonsillectomy. Patients were divided into 4 groups. The first group received an injection of 20 mg ketamine in 10cc artificial saliva (5 cc in each tonsillar fossa) administered by a surgeon. The second group received 20 mg ketamine and 20 mg morphine aqueous solution in 5 cc artificial saliva in each fossa. The third group received 20 mg morphine aqueous solution in 5 cc artificial saliva in each fossa and the 4th group received 5 cc artificial saliva in each fossa post-operatively. Pain scores in the ketamine

group were lower than in other groups and combination of ketamine and morphine had no superiority (2).

In a study by Honarmand, 75 ASA class I and II patients aged 3 to 12 years undergoing tonsillectomy were evaluated in 3 groups. The first group received 1 cc of 0.9% normal saline, the second group received 0.5 mg/kg ketamine in 2 cc normal saline and the third group received 1 mg/kg ketamine in 2 cc normal saline 3 minutes before the incision equally in both tonsillar fossae. The pain score was significantly lower in the first 24 hours in both groups receiving ketamine and no significant difference was noted in analgesia caused by two doses of 0.5 and 1 mg/kg ketamine (18).

Öksüz studied 40 ASA class I and II children aged 3 to 10 years who were candidates for tonsillectomy surgery. Subjects were divided into two groups. The first group received 0.5 mg/kg ketamine and the second group received 1 mcg/kg fentanyl IM pre-operatively. The results showed that although ketamine and fentanyl were not significantly different in management of post-tonsillectomy pain, ketamine caused a longer analgesia than fentanyl. IM administration of fentanyl was found to be a good substitute for ketamine in the first hours following tonsillectomy (19).

Khademi assessed 78 ASA class I and II subjects aged 5 to 18 yrs. scheduled for tonsillectomy. The first group received 0.5 mg/kg IV administration of ketamine, the second group received 2cc IV administration of normal saline, the third group received 0.5 mg/kg ketamine injected through the tonsillar capsule and the 4th group 2 cc normal saline in the same location after the induction of anesthesia and 3 minutes before tonsillectomy. The post-operative pain was significantly lower in the two groups of IV and peri-tonsillar infiltration of ketamine than the control groups. Also, the need for post-operative administration of opioids significantly decreased in the mentioned two groups. The peri-tonsillar infiltration of ketamine was more effective for post-tonsillectomy pain management (20).

Taheri in his study evaluated 60 ASA class I and II children aged 3 to 12 years undergoing tonsillectomy in two groups. The first group received 0.5 mg/kg ketamine IV while the second group received 1 mcg/kg fentanyl IV after the termination of anesthesia. Fentanyl provided extended time to first analgesic compared to ketamine (21).

Elshammaa in his study evaluated 60 ASA status I and II children aged 2 to 7 years undergoing tonsillectomy in 4 groups. The first group received 1 mcg/kg fentanyl, the second group received 2 mcg/kg fentanyl, the third group received 0.5 mg/kg ketamine and the 4th group received 1 mcg/kg fentanyl and 0.5 mg/kg ketamine IV pre-incision. Simultaneous administration of ketamine and fentanyl IV preoperatively improved analgesia and accelerated discharge of patients from the hospital (22).

Ayatollahi et al. studied 126 ASA class I and II children aged 5 to 12 years who were candidates for tonsillectomy in 3 groups. The first group received 0.5 mg/kg ketamine, the second group received 2 mg/kg tramadol and the third group received 2cc normal saline as peritonsillar infiltration pre-incision. They found that peritonsillar infiltration of tramadol was more effective in reducing acute post-tonsillectomy pain than ketamine and was associated with no side effects (23).

Jahromi studied 120 ASA class I and II patients aged 3 to 12 yrs. undergoing tonsillectomy in 4 groups. The first group received 2 mg/kg lidocaine spray, the second group received 0.05 mg/kg morphine spray, the third group received 0.5 mg/kg ketamine spray and the 4th group received normal saline spray after surgery in the tonsillar fossa. In the recovery period, lidocaine was the most and morphine was the least effective analgesic drug. In the first 20 min post-operatively, lidocaine was the most effective drug while ketamine and morphine had similar analgesic effects. At 40 minutes, all three drugs had the same analgesic effect and at 60 minutes, morphine and ketamine had a greater analgesic effect than lidocaine (24).

In our previous study, only 0.25 mg/kg intravenous ketamine at induction, decreased post tonsillectomy pain and agitation of children. (25)

In our literature, only two studies, evaluated the effect of ketamine on re-bleeding after tonsillectomy in children (2, 18);

Canbay et al. and Honarmand et al. did not mention any significant difference between groups in bleeding amounts after tonsillectomy. Bleeding was controlled in all patients and not need any additive surgeries (2, 18).

tonsillar infiltration of ketamine compared to the control groups and significantly reduced the need for post-operative opioids. Between the two, peri-tonsillar infiltration of ketamine was more effective for the management of post-tonsillectomy pain (20). These results were confirmed by some other studies as well. For instance, Aydin et al. reported that the required amount of tramadol in the first 6 hours post-surgery (for management of post-operative pain) was lower in groups that received ketamine (16). Also, ketamine

Study	Year	Age	Samples	Dosage	Administration Method	Control	Time of Administration
Da ConceiÇÃO	2006	5-7	78	0.5 mg/kg	Peritonsillar	-	Pre/ Post-Operative
Ertugrul	2006	1-7	45	0.5 mg/kg	Intramuscular	Tramadol/ Meperidine	Pre-intubation
Erhan	2007	3-7	60	0.5 mg/kg	Peritonsillar	Placebo (N/S)	Post-Tonsillectomy
Aydin	2007	5-15	90	0.5, 0.8 mg/kg	Intravenous	Placebo (N/S)	Pre-Incision
Abu-Shahwan	2008	2-12	84	0.25 mg/kg	Intravenous	Morphine	Induction
Canbay	2008	3-12	60	20 mg	Peritonsillar	Morphine/ Placebo	Post-Tonsillectomy
Honarmand	2008	3-12	75	0.5 mg/kg	Peritonsillar	Placebo (N/S)	Pre-Incision
Öksüz	2009	3-10	40	1 mg/kg	Intramuscular	Fentanyl	Pre-Incision
Khademi	2011	5-18	78	0.5 mg/kg	Intravenous/ Peritonsillar	Placebo (N/S)	Post- Induction
Taheri	2011	3-12	60	0.5 mg/kg	Intravenous	Fentanyl	Post- Induction
Elshammaa	2011	2-7	60	0.5 mg/kg	Intravenous	Fentanyl	Pre-Incision
Ayatollahi	2012	5-12	126	1 mg/kg	Peritonsillar	Tramadol/ Saline	Pre-Incision
Jahromi	2012	3-12	120	0.5 mg/kg	Topical spray	Lidocaine/ Morphine/ Saline	Induction
Eghbal	2013	5-15	66	0.5 mg/kg	Intravenous	Placebo (N/S)	Induction

Table 1. Ketamine studies, description of case group, number of cases, prescription method, prescription doses and time and control group

Discussion and conclusions

After the review of literature published in the past 10 years regarding the efficacy of ketamine for tonsillectomy with or without adenoidectomy pain management, the following conclusions were drawn:

Da Concei CAO stated that administration of a single dose of ketamine before or after tonsillectomy in children decreased the required amount of morphine post-operation (14). In the study by Khademi, post-operative analgesia was greater in the two groups of IV and peri-infiltration in tonsillar region was effective in reducing acute post-tonsillectomy pain and caused no side effect (3). Administration of ketamine provided higher level of analgesia than morphine or artificial saliva and combination of ketamine and morphine had no superiority over ketamine alone (2). Pain scores in the first 24 hours significantly decreased in both groups receiving ketamine compared to the placebo. No significant difference was noted in analgesia caused by two doses of 0.5 and 1 mg/kg ketamine (18). Ketamine and fentanyl were not

significantly different in management of post-tonsillectomy pain but ketaminecaused a longer lasting analgesia compared to fentanyl (19). Fentanyl provided extended time to first analgesic compared to ketamine (21).

Also, in Elshammaa study, simultaneous pre-surgical administration of ketamine and fentanyl IV resulted in greater analgesia and accelerated discharge of patients (22). At 60 minutes post-operatively, morphine and ketamine had greater analgesic effects than lidocaine (24).

In some previous studies, other drugs showed similar or superior effects to that of ketamine. Ertugrul et al. demonstrated that ketamine, tramadol and meperidine had similar analgesic properties but the agitation score was higher in the ketamine group (15).

Abu-Shahwan showed that 0.25 mg/kg ketamine at the time of anesthesia induction did not decrease the need for post-op morphine administration (17).

Ayatollahi reported that peri-tonsillar infiltration of tramadol was more effective than ketamine in reducing acute post-tonsillectomy pain and had no side effects (23).

In the first 20 minutes post-surgery, lidocaine spray had the greatest analgesic effect compared to ketamine and morphine sprays. The analgesic effects of ketamine and morphine were the same. At 40 minutes post-operation, all three sprays of ketamine, morphine and lidocaine had equal analgesic properties (24).

Important complications after tonsillectomy are bleeding, pain with dysphagia, laryngospasm, airway obstruction and nausea and vomiting (10).

The cause of secondary bleeding in the first 24 hours after tonsillectomy is not well defined, but the pain especially in the second 12 hours, can cause bleeding (7, 9).

Dysphagia and pain can lead to fluid intake restriction in children, causing infection and bleeding due to fibrin plaque formation in surgical site (9, 10).

Furthermore, crying and gag reflex due to pain can cause or exacerbate bleeding, so good management of acute pain after tonsillectomy in children can reduce bleeding and the need for further surgeries to control bleeding (9).

In the other hand, pain management using non steroid anti-inflammatory drugs (NSAIDS) could lead to more bleeding, thus ketamine seems to be a good analgesic considering bleeding (26, 27).

Few studies evaluated the effect of ketamine in bleeding reduction after tonsillectomy (2, 18). Although these studies did not report any bleeding control effect of ketamine after tonsillectomy in children, but it seems to be a good management for acute post tonsillectomy pain and can lead to significant reduction of bleeding in children. Proving this hypothesis requires further well designed randomized clinical trials with adequate sample size focusing on bleeding after tonsillectomy in children. In Canbay et al. and Honarmand et al. studies only the primary bleeding (seems to be related to surgical technique and in the first 6 hours after tonsillectomy) were evaluated. Researchers suggest the evaluation of ketamine effect and pain management on primary and secondary bleeding in the first 24 hours after tonsillectomy for future studies.

Considering all the above, we may conclude that IV, IM, infiltration or spray administration of even a single dose of ketamine (higher than 0.5 mg/kg) before, during or after surgery is effective for prevention of acute pain after tonsillectomy with or without adenoidectomy in children. This acute pain management could minimize re-bleeding rate in children.

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