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Comparison of Ketamine and Fentanyl for Postoperative Pain Relief in Children Following Adenotonsillectomy

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Abstract: Adenotonsillectomy has a high incidence of postoperative pain. Therefore, the purpose of this study was to evaluate the effectiveness and safety of either ketamine or fentanyl for postoperative pain relief in children following adenotonsillectomy. Sixty children aged 3-12 years, scheduled for adenotonsillectomy, were enrolled in this randomized, double-blind study. Patients were divided into two groups of 30 cases and received intravenous ketamine (0.5 mg kg^{-1}) or fentanyl (1 μg kg^{-1}). Modified Hannallah pain scale or Observational Pain Scores (OPS), nausea, vomiting, bleeding, rescue analgesia, sedation and post-anesthesia recovery scores were recorded both at first and 15th minute postoperatively. Moreover, patients receiving ketamine (group 1) or fentanyl (group 2) had comparable OPS and sedation score both on arrival and at 15th minute in the recovery room ($p>0.05$). Although rescue analgesics were similarly required in both groups ($p>0.05$), the time to reach rescue analgesia was shorter in group 1 ($p = 0.001$). Only one patient in fentanyl group had nausea and vomiting in the first 15 min that needed antiemetic in the recovery room. In conclusion, intravenous fentanyl (1 μg kg^{-1}) compared with intravenous ketamine (0.5 mg kg^{-1}) might provide extended time to first analgesic in children undergoing adenotonsillectomy. Interestingly, fentanyl and ketamine did not differ in post-operative vomiting.

Key words: Tonsillectomy, anesthesia, ketamine, fentanyl, pain, children

INTRODUCTION

Tonsillectomy is a common and painful procedure in children, often performed on an outpatient basis. In addition to patient comfort, efficient post-tonsillectomy analgesia is desirable to encourage oral intake in order to maintain the child's hydration status and to minimize crying that increases the risk of postoperative bleeding (Dal *et al*., 2007; O'Flaherty and Lin, 2003). There are many analgesics used for post-tonsillectomy pain such as opioids, Non-steroidal Anti-inflammatory Drugs (NSAIDs) and local anesthetics. However, the former may decrease upper airway tone, suppress the cough reflex, lead to sedation and respiratory depression and contribute to postoperative nausea and vomiting. Although earlier studies were indicative of an increased risk of reoperation for bleeding due to use NSAIDs after tonsillectomy (Marret *et al*., 2003; Moiniche *et al*., 2003), recent reviews highlighted that NSAIDs did not significantly alter the number of perioperative bleeding events requiring surgical intervention (Cardwell *et al*., 2005; Heaney *et al*., 2007).

Ketamine is a non-competitive antagonist at the N-methyl-D-aspartate (NMDA) receptor and has analgesic properties at sub-anesthetic doses (Marcus *et al*., 2000; DA Conceicao *et al*., 2006; Kamal, 2008; Mostafa *et al*., 2008). Administration of ketamine as a general anesthetic agent is limited due to a number of side effects, especially unpleasant emergence delirium and cardiovascular stimulation. The links between the NMDA receptor and pain processing have led to the investigation of the use of ketamine as a postoperative analgesic, either alone or in combination with opioids (Dix *et al*., 2003; Kamal, 2008; Nourozi *et al*., 2010). However, the efficacy of ketamine used in preventative analgesia is controversial (Honarmand *et al*., 2008; Papaziogas *et al*., 2001). The aim of the present study was to investigate whether the use of low dose intravenous ketamine compared to fentanyl, prior to the

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surgery, would significantly improve short-time pain control after tonsillectomy in pediatric patients.

MATERIALS AND METHODS

Sixty children (ASA I or II), aged 3-12 years, were enrolled in this randomized, double-blind study. Institutional ethics committee approval and parental written consent were taken for all subjects. Children with systemic disease, metabolic and endocrine disorders, growth developmental, motor-mental retardation, a history of allergy to any of the study drugs, peritonsillar abscess, psychiatric disorders, chronic pain syndrome and those who had received analgesics were excluded from the study (Naderpour *et al*., 2011). Patients were fasted for 8 h prior to the surgery and received premedication of midazolam (0.05 mg kg^{-1}, IV) 5 min before anesthesia induction. Preoperative fluid administration was given with lactated Ringer's solution (5 mL kg^{-1}) (Holte *et al*., 2003). Systolic Arterial Pressure (SAP), Diastolic Arterial Pressure (DAP), Heart Rate (HR) and peripheral oxygen saturation (SpO2) levels were monitored in the operation room.

Patients were randomized into one of two test groups by means of a computer-generated random number table with 30 patients in each group. An anesthesiologist prepared syringes containing either ketamine or fentanyl for each subject. Patients received dexamethasone (0.5 mg kg^{-1}) and either ketamine 0.5 mg kg^{-1} (group 1) or fentanyl 1 μg kg^{-1} (Ali and Maryam, 2007) (group 2) before induction.

Anesthesia was induced with propofol (2-3 mg kg^{-1}) (Mohammadi *et al*., 2006) and atracurium (0.5 mg kg^{-1}) (Mohammadi and Ghafari, 2007) and maintained with 1.2% isoflurane and 50% nitrous oxide in oxygen (Mohammadi *et al*., 2009). The same surgeon used the dissection and snare technique for every subject. Heart rate, SAP, DAP and SpO2 were recorded at 10 min intervals during the operation. At the end of the surgery, neuromuscular blockade was reversed by neostigmine (0.04 mg kg^{-1}, IV) and atropine (0.02 mg kg^{-1}, IV). Anesthesia was discontinued and the tracheal tube was removed in the operating room when airway reflexes had returned. After extubation, the patients were taken to the recovery room where an anesthetist and nurses who were unaware of the study drug, observed the patients. In the recovery room, pain assessment was performed using a modified Hannallah pain scale (Dal *et al*., 2007), an Observational Pain Score (OPS) developed and tested for validity and reliability in children. Different items of the modified Hannallah pain score are shown in Table 1. Pain scores were assessed by the blinded observer anesthetist on arrival and at 15th min. As supplementary analgesia, acetaminophen (40 mg kg^{-1}) was given for patients with OPS>4, on the patients' request for pain medication, or in case of continuous crying for a 5 min period (Taheri *et al*., 2010). Nausea, vomiting, bleeding, sedation, SAP, HR, SpO2 were also recorded both on arrival in recovery room and at 15th min. Items and scores used to evaluate sedation, nausea and vomiting and bleeding are shown in Table 2 (Dal *et al*., 2007). Metoclopramide (0.1 mg kg^{-1}, IV) was administered to patients with nausea. Items of the post anesthesia recovery score (Aldrete score) (Aldrete, 1995), a 10-point post-anesthesia recovery score used to determine recovery room discharge readiness, are shown in Table 3.

Table 1: Pain scoring table (modified hannallah score)

Item		Score
Crying	None	0
	Consolable	1
	Inconsolable	2
Movement	None	0
	Restless	1
	Trashing	2
Agitation	Asleep or calm	0
	Mild	1
	Hysterical	2
Swallowing secretions	Normal	0
	Uncomfortable	1
	Unable	2
Complaints of pain	Asleep or none	0
	Cannot localize	1
	Localize	2

Table 2: Nausea/vomiting scale, bleeding scale and sedation scale

Item		Score
Nausea/vomiting, score	None	0
	dry heaves	1
	Nausea	
	Vomiting	2
Bleeding score	Minimal	0
	Moderate	1
	Severe (return to operating room)	2
	Awake and alert	0
Sedation score	Occasionally drowsy, easy to arouse	1
	Drowsy most of the time, arousable	2
	Somnolent, difficult to arouse	3

Table 3: The post anesthesia recovery score (Aldrete score)

Item		Score
Activity	Able to move four extremities on command	2
	Able to move two extremities on command	1
	Able to move no extremities on command	0
Breathing	Able to breathe deeply and cough freely	2
	Dyspnea	1
	Apnea	0
Circulation	Systemic blood pressure ≠ 20% of the preanesthetic level2	
	Systemic blood pressure is 20% to 49% of the preanesthetic level	1
	Systemic blood pressure ≠ 50% of the preanesthetic level0	
Consciousness	Fully awake	2
	Arousable	1
	Not responding	0
Oxygen saturation (pulse oximetry)	>92% while breathing room air	2
	Needs supplemental oxygen to maintain saturation >90%	1
	<90% even with supplemental oxygen	0

The time at which the patient reached a post-anesthesia recovery score of at least 9 was noted. The time between anesthesia induction and extubation, between discontinuation of nitrous oxide and extubation and from tonsillectomy operation to the end of bleeding control was regarded as anesthesia duration, extubation time and operation time, respectively.

The postoperative OPS at 15th minute was considered the primary endpoint and was used to determine the sample size. It was calculated that sample size of 30 in each group would have an 80% power to detect a 20% difference in the OPS between two groups.

Statistical analysis: Data were presented as Mean±SD or as median (interquartile range). Statistical analysis was performed with SPSS for windows version 16.0 (Chicago, IL, USA) by using Chi-square test, Fisher's exact test, Mann-whitney U test and Independent-Samples T test wherever appropriate. The Kolmogorov-Smirnov statistics was used for testing normality for continuous variables. A p-value less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Thirty four females and 26 males (age 3-12 years) were studied. No patient was excluded from the study. The demographic data as well as the analyses of the variables are shown in Table 4. There were no differences in gender, age, weight, duration of surgery and duration of anesthesia between the groups (Table 4, p>0.05). Furthermore, no statistically significant difference was observed between the groups in HR, SAP, DAP and SpO2 during the first 30 min of the surgery (p>0.05). Moreover, patients receiving ketamine (group 1) or fentanyl (group 2) had comparable OPS and sedation score both on arrival and at 15th minute in the recovery room (Table 4, p>0.05). Although rescue analgesics were similarly required in both groups (Table 4, p = 0.47), the time to reach rescue analgesia was shorter in group 1 (Table 4, p = 0.001). Post-anesthesia recovery scores (Aldrete scores) at 15th minute were not statistically different between the groups (9.13±0.68 in group 1 vs. 8.99±0.45 in group 2, Table 4, p>0.05). Only one patient in group 2 had nausea and vomiting in the first 15 minutes that needed antiemetic in the recovery room. In the first 15th minute in the recovery room, all patients had minimal or no bleeding; none of the patients required reoperation for bleeding.

The present study revealed that children receiving intravenous fentanyl (1 μg kg^{-1}) before adenotonsillectomy had prolonged time to first request for

Table 4: Patient's demographic data and intra- and post-operative characteristics (Mean±SD) (n = number of patients)

Parameter	Ketamine group (n = 30)	Fentanyl group (n = 30)	p value
Gender (male:female)	18:12	14:16	0.29
Age (years)	6.23±2.19	5.66±2.19	0.41
Weight (kg)	21.23±5.80	19.73±4.35	0.51
Duration of surgery (min)	20 (5)	20 (15)	0.30
Duration of anesthesia (min)	33.52±3.42	32.33±8.20	0.30
Analgesia required (%)	17 (56.7%)	12 (40%)	0.47
Time to first analgesia (min)	15 (20)	30 (0)	0.001*
OPS in the recovery room (on arrival)	1 (2)	1 (2)	0.96
OPS in the recovery room (at 15th min)	4.47±2.21	3.53±2.16	0.21
Post-anesthesia recovery score (Aldrete score) (at 15th min)	9.13±0.68	8.99±0.45	0.62
Sedation score in the recovery room (on arrival)	3 (0.5)	3 (0)	0.17
Sedation scores in the recovery room (at 15th min)	1 (2)	1 (1)	0.56

OPS: Observational Pain Score. *Statistically significant (p<0.05)

analgesia when compared to those receiving intravenous ketamine (0.5 mg kg^{-1}). However, no difference was found between ketamine and fentanyl groups with respect to OPS, sedation score, post-anesthesia recovery score and rescue analgesics. In contrast to our findings, Kennedy *et al.* (1998) found that children on ketamine/midazolam had lower pain scores than those on fentanyl/midazolam in pediatric orthopedic emergency room. To the best of our knowledge, the present study is the first investigation to compare ketamine and fentanyl for postoperative pain relief in children following adenotonsillectomy.

Recent studies on ketamine have reported contrasting results regarding its analgesic characteristics in adenotonsillectomy. A number of previous studies indicated that intravenous ketamine could reduce postoperative pain scores in children undergoing adenotonsillectomy without significant side effects (Dal *et al.*, 2007; Marcus *et al.*, 2000; Aydin *et al.*, 2007; Murray *et al.*, 1987). Furthermore, Marcus *et al.* (2000) and Aspinall and Mayor (2001) found that intravenous ketamine (0.5 mg kg^{-1}) might be a safe and effective alternative to morphine in providing postoperative analgesia after adenotonsillectomy. In contrast, Umuroglu *et al.* (2004) concluded that due to its positive chronotropic effect, high sedative and low analgesic effects, ketamine might not be a good analgesic in adenotonsillectomy when compared to morphine and tramadol. Moreover, O'Flaherty and Lin (2003) failed to demonstrate a decrease in pain and analgesic consumption in children undergoing tonsillectomy when pretreated with intravenous ketamine (0.15 mg kg^{-1}). Although our dosage was three times higher (0.5 mg kg^{-1}), we found no difference in analgesic effect between ketamine and fentanyl in our subjects. Ketamine is believed to be accompanied with undesirable psychological reactions occurring during awakening from ketamine anesthesia (emergence reactions; vivid dreaming, extracorporeal experiences and illusions) (Mistry and Nahata, 2005; Chen *et al*., 2010). Nevertheless, Treston and colleagues concluded that emergency physicians should not be deterred from using ketamine for pediatric procedural sedation (Treston *et al*., 2009).

A few studies have been targeted at analgesic characteristics of fentanyl in pediatric adenotonsillectomy. Davis *et al*. (2000) investigated the effect of remifentanil, an ultra-short acting synthetic opioid (Mohammadi *et al*., 2006), versus fentanyl on post-operative pain in children undergoing tonsillectomy and adenoidectomy (Davis *et al*., 2000). They concluded that remifentanil was associated with higher postoperative pain scores (Davis *et al*., 2000). In addition, pain scores in recovery and over the next 24 h were similar between fentanyl and morphine groups following pediatric adenotonsillectomy in the study by Mukherjee *et al*. (2001). In the present report, children in fentanyl group had prolonged time to first analgesia.

Postoperative nausea and vomiting following adenotonsillectomy may be due to swallowed blood, pain, opioid administration and direct oropharyngeal irritation (Dal *et al*., 2007). Although intravenous ketamine has been shown to accompany with significant postoperative vomiting in the study by Kennedy *et al*. (1998), rectally administered fentanyl-droperidol in children resulted in higher rate of postoperative nausea and vomiting than ketamine group (Zanette *et al*., 2010). In our study, there was no difference in the incidence of vomiting between two groups. We believe that administration of propofol, dexamethasone and fluid at the start of anesthesia might have decreased the incidence of vomiting in our study.

This study has certain limitations. We did not have a placebo group in the present study. We believed that providing no pain relief following adenotonsillectomy would be unethical. In addition, an intravenous Non-opioid analgesic drug such as paracetamol was not available as a rescue analgesic at our center. This clarifies why acetaminophen suppository was used for rescue analgesic in the recovery room. Furthermore, difficulties of pain assessment in children and refinement of follow-up period to 15-30 min should be considered as limitations of the present report. Moreover, the present investigation has focused on the effect of ketamine without considering the timing of the drug administration. The effect of the ketamine dose used at the start of the surgical procedure could diminish as time elapses. This would allow noxious stimuli from surgical area to reach the central nervous neurons. However, tonsillectomy is considered as a relatively short procedure in which, we believe, the diminishing effect of drug with time could not be of significance. In addition, the use of midazolam as a premedication could add to postoperative sedation and complicate scoring (Fakheri *et al*., 2010). On the other hand, the Hannallah pain score was originally described for use in unpremedicated patients (Hannallah *et al*., 1987), however we used modified Hannallah score which has been applied to premedicated patients in a number of previous studies (Dal *et al*., 2007; Pappas *et al*., 2003).

In conclusion, intravenous fentanyl (1 μg kg^{-1}) compared with intravenous ketamine (0.5 mg kg^{-1}) might provide extended time to first analgesic in children undergoing adenotonsillectomy. Interestingly, fentanyl and ketamine did not differ in post-operative vomiting.

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