MED ARH. 2012; 66(2): 111-115

doi: 10.5455/medarh.2012.66.111-115
Received: December 28th 2011
Accepted: February 26th 2012

ORIGINAL PAPER

Assessing Intravenous Ketamine and Intravenous Dexamethasone Separately and in Combination for Early Oral Intake, Vomiting and Postoperative Pain Relief in Children Following Tonsillectomy

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Background: The aim of the present study is to evaluate the effect of preoperative 0.5 mg/kg i.v. dexamethasone in combination with 0.5 mg/kg i.v. ketamine on pain, early oral intake and vomiting in pediatric patients undergoing tonsillectomy during the first 24 hours of the postoperative period. **Methods:** One hundred twenty children who were scheduled for tonsillectomy were randomly assigned to receive a single dose of dexamethasone 0.5 mg/kg i.v. as Group D (n = 30), receive ketamine 0.5 mg/kg i.v. as Group K (n = 30), receive dexamethasone 0.5 mg/kg i.v. and ketamine 0.5 mg/kg i.v. as Group KD (n = 30) and an equivalent volume of saline as Group C (n = 30) 15 minutes before the induction of anesthesia. Post-operative pain was evaluated using an observational pain score (OPS) on arrival to the post-anesthesia care unit (PACU), at 15, 30, 45, and 60 minutes after that and at 1, 2, 4, 6, 12, and 24 hours after arrival to the ward. **Results:** OPS scores were significantly lower at the time of arrival to the PACU, and at 15, 30, 45, and 60 minutes in the Group KD compared with Group C ($p < 0.05$). Postoperative OPS scores were significantly lower at 1, 2, 4, 6, 12, and 24 hours after operation in Group KD compared with Group C ($p < 0.05$). **Conclusion:** A prophylactic preoperative single dose of i.v. 0.5 mg/kg dexamethasone in combination with a single dose of i.v. 0.5 mg/kg ketamine significantly decreased post-tonsillectomy pain compare with using i.v. ketamine or i.v. dexamehasone separately. **Key words: Pain, Postoperative, Tonsillectomy, Dexamethasone, Ketamine.**

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1. INTRODUCTION

Postoperative pain is one of the most important problems in children undergoing tonsillectomy (1). Effective postoperative pain management can prevent morbidity, minimize crying that increases the risk of postoperative bleeding, facilitate early oral intake and adequate hydration (1, 2).

Aydin et al. (3) showed that the intravenous use of 0.5 mg/kg of ketamine (i.v.) before a tonsillectomy day-surgery had an analgesic effect and significantly reduced postoperative analgesic requirements. Verbal pain scale score in the ketamine group were significantly lower in the early postoperative period in the fourth and sixth hours.

Kaan et al. (4) showed that using a prophylactic intra-operative single dose of 0.5 mg/kg dexamethasone intravenously significantly reduced early post-tonsillectomy pain, improved oral intake and facilitated meeting the discharge criteria without any significant side effects. Their results showed that the pain score in the first 6 hours after operation was significantly lower in the dexamethasone group compared to the control group. However, they didn't find a significant difference in analgesic requirements between the two groups. Moreover,, there was no difference in the incidence of postoperative vomiting among the two groups.

As above studies showed, using dexamethasone or ketamine intravenously separately limited their efficacy to early post-operative period (till 6 hours) after tonsillectomy. Our hypothesis was that using ketamine plus dexamethasone intravenously before surgical incision will probably prolong the duration of postoperative analgesia after tonsillectomy and reduce analgesic requirements while decreasing adverse effects. To the best of our knowledge, there was no study to examine this hy-

pothesis. Therefore, we designed the present study to investigate effects of 0.5 mg/kg i.v. dexamethasone in combination with 0.5 mg/kg i.v. ketamine, given before induction of anesthesia, on pain, early oral intake and vomiting in pediatric patients undergoing tonsillectomy during the first 24 hours of the postoperative period.

2. METHODS

This randomized, double-blind, and placebo-controlled study was performed after obtaining institutional approval from the Ethic Committee of Isfahan University of medical Sciences and taking written informed consent from the parents. One hundred twenty children, 2-12 years old, ASA physical status I or II, who were scheduled for a tonsillectomy, were enrolled in the study. Indications for tonsillectomy were tonsillar hypertrophy with obstructive symptoms and recurrent tonsillitis. Children with pulmonary and/or cardiac disease, history of allergy to the study drugs, peritonsillar abscess, and analgesic usage within 24 hours before surgery were excluded from the study. Moreover, patients who received antiemetic, antihistamine, steroids or psychiatric drugs within 24 hours of surgery were not included in the study.

Children were permitted to eat solid food until 12 a.m. on the day before the operation and drink clear fluids until 3 hours before the surgery. An anesthesiologist prepared syringes containing either the study medications or normal saline for each subject. All medications were 2 ml in volume. All children received intravenous midazolam 0.05 mg/kg for premedication 5-10 minutes before induction of anesthesia.

After establishing standard monitoring, the patients were randomly assigned to receive dexamethasone 0.5 mg/kg i.v. and a maximum dose of 8 mg plus 2 ml normal saline as Group D (n = 30), ketamine 0.5 mg/kg i.v. plus 2 ml normal saline as Group K (n = 30), dexamethasone 0.5 mg/kg i.v. and ketamine 0.5 mg/kg i.v. as Group KD (n = 30) and an two equivalent volume of saline as Group C (n = 30) 15 minutes before induction of anesthesia, in a double-blinded fashion.

General anesthesia was induced by using thiopental sodium 5 mg/kg, fentanyl 2 μg/kg, and atracurium 0.6 mg/kg for facilitation of endotracheal intubation. Anesthesia was maintained with isoflurane 1.2 % and a gas mixture of 50 % nitrous oxide and 50% oxygen adjusted to maintain heart rate and blood pressure values within 20% of the baseline induction value. The amount of intravenous fluid administered was 25-30 ml/kg of lactated Ringer's solution during the intraoperative period. The same surgeon used the dissection and snare technique for all patients. At the end of the surgery neuromuscular blockade was reversed by i.v. neostigmine 0.04 mg/kg and i.v. atropine 0.01 mg/kg. Later, the anesthesia was discontinued and the tracheal tube removed in the operating room when airway reflexes had returned.

Heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), means arterial pressure (MAP), oxygen saturation (SpO_2) were recorded at 15 minute intervals during the operation. After extubation the patients were transferred to the postanesthesia care unit (PACU) where an anesthetist and nurses who were unaware of the study drug observed the patients. The time from anesthesia induction to the discontinuation of anesthetic drugs was considered as duration of anesthesia, and the time between discontinuation of nitrous oxide and extubation was considered extubation time. The time from the first surgical incision to the last mucosal suture was regarded as operation time.

In the PACU, pain was evaluated using a modified Hannallah pain scale[5] an observational pain score (OPS) which tested for validity and reliability in children (Table 1). Pain scores were evaluated by the blinded observer anesthetist on arrival to the PACU, at 15, 30, 45, and 60 minutes after that. If patients had OPS more than 3, acetaminophen suppository 30 mg/kg was administered as a supplementary analgesia.

Vomiting, amount of bleeding (ml), sedation, systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, heart rate and oxygen saturation (SpO_2) were also recorded on arrival in the PACU, at 15, 30 and 60 minutes.

The sedative condition was assessed by using a sedation scale (0, awake; 1, drowsy but responsive to verbal orders; 2, drowsy but responsive to physical stimulus; 3 sleepy but responsive to pain stimulus) at the all above mentioned times. If children vomited two or more times in PACU, they received 50 μg/kg (maximum 8 mg) of ondansetron i.v. We used the Aldrete score, a 10-point post-anesthesia recovery score, for determination of PACU discharge readiness. The time at which the patient reached an Aldrete score of at least 9 was noted as duration of PACU stay.

After the discharge from PACU, nurses were given a prescription for acetaminophen suppository (30 mg/kg) to be given if OPS were higher than 3 as needed for pain. Any supplementary analgesia, nausea and vomiting, bleeding were assessed at the first 24 hours after arrival to the ward. Postoperative pain was evaluated at 1, 2, 4, 6, 12, and 24 hours after arrival to the ward by using OPS.

The sample size determination was based on a power calculation which showed that 30 patients per group were necessary to achieve 80% power to detect a 20% difference in the OPS between group C and group KD, with a 0.05. Data presented as mean (SD) or numbers. Differences among the groups' mean were compared using one-way analysis of variance (ANOVA) and post-hoc comparisons at various points in time by using Bonferroni's type I error rate correction for multiple tests of significance. Kruskal-Wallis test was used to compare groups for nonparametric variables. Gender and complication rates were assessed by the Pearson chi-square test and by the Fisher's exact test when the anticipated number was less than 5, $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 16.0 for Windows statistical package.

3. RESULTS

One-hundred twenty patients were included in the study. There was no patient excluded from the study due to any problems. There was no significant difference in the patient characteristics such as gender, ASA, age, weight,

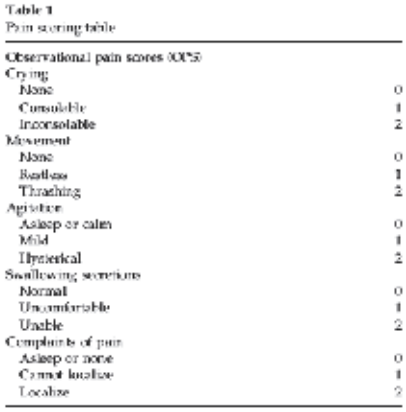

Table 1
Pain scoring table

Observational pain scores (OPS)	
Crying	
None	0
Consolable	1
Inconsolable	2
Movement	
None	0
Restless	1
Thrashing	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 localise	1
Localise	2

Table 1. Pain scoring table

time to tracheal extubation, duration of PACU stay, blood loss, duration of surgery and anesthesia among the four groups (Table 2).

Mean HR, SpO_2 level, SAP, DAP, and MAP values during surgery, in the PACU, and the first 24 hours after operation was not significantly different between the four groups. OPS scores were significantly lower at the time of arrival to the PACU, 15, 30, 45, and 60 minutes in Group KD compared with Group C ($p < 0.05$) (Figure 1). This variable was significantly lower in Group KD compared with Group K and Group D at these intervals ($p < 0.05$) (Figure 1). OPS scores were not significantly different between Group K and Group D.

Postoperative OPS scores were significantly lower at 1, 2, 4, 6, 12, and 24 hours after operation in Group KD compared with Group C ($p < 0.05$) (Figure 2). This variable was significantly lower in Group KD compared with Group K and Group D at these intervals ($p < 0.05$) (Figure 2). OPS scores were not significantly different between Group K and Group D.

There was no significant difference in median sedation values at any postoperative period among the four groups. Postoperative analgesic requirement was significantly less in Group KD compared with Group C ($p < 0.05$) (Table 3). This variable was not significantly different between Group D and Group K with Group C (Table 3). Postoperative antiemetic requirement was significantly less in Group K, Group D, and Group KD compared with Group C ($p < 0.05$) (Table 3).

The time duration until the first oral intake was significantly lower in Group KD compared with Group K, Group D, and Group C ($p < 0.05$) (Table 3). This variable was not significantly different between Group D and Group K. The incidence of early vomiting (at the first 2 hours stay in PACU) and late vomiting (at 2nd to 24th hours of stay in the ward) were significantly less in Group KD compared with Group K and Group C ($p < 0.05$) (Table 3).

Variable	Group K	Group D	Group KD	Group C
	(n = 30)	(n = 30)	(n = 30)	(n = 30)
Age (Year)	8.7 ± 1.9	8.6 ± 1.7	7.8 ± 2.2	7.9 ± 2.1
Gender (F/M)	18/12	13/17	16/14	17/13
Weight (Kg)	22.1 ± 5.1	20.6 ± 5.1	19.3 ± 4.9	19.7 ± 4.6
Duration of surgery (min)	44.8 ± 6.5	44.5 ± 6.7	45.7 ± 6.3	47.3 ± 6.4
Duration of anesthesia (min)	61.8 ± 9.4	62.8 ± 8.4	58.4 ± 6.7	52.2 ± 6.5
Extubation time (min)	7.3 ± 1.2	9.4 ± 2.6	7.7 ± 1.3	8.2 ± 1.1
PACU stay time (min)	62.3 ± 4.8	64.7 ± 5.7	63.3 ± 4.5	65.1 ± 4.2
Blood loss (ml)	68.3 ± 20.2	64.6 ± 23.4	65.5 ± 21.6	66.3 ± 24.1

Table 2 Patients demographic data, extubation time, PACU stay time and blood loss in the four groups Values are presented as mean ± SD or number. Group K = ketamine treated patients; Group D = dexamethasone treated patients;Group KD = ketamine-dexamethasone treated patients; Group C = control group. PACU = post-anesthesia care unit. There were no significant differences between the four groups.

Variable	Group K	Group D	Group KD	Group C	P value
	(n = 30)	(n = 30)	(n = 30)	(n = 30)	
Postoperative analgesic requirement (mg)	116.2 ± 48.6	128.1 ± 43.3	00.0 ± 00.0*	243.5 ± 50.8	< 0.001
Postoperative antiemetic requirement (mg)	0.93 ± 0.2*	01.0 ± 0.2*	00.0 ± 00. *	6.2 ± 1.2	< 0.001
The time to first oral intake (hours)	4.6 ± 0.8*	4.6 ± 1.4*	3.6 ± 0.8*†‡	5.3 ± 0.8	< 0.001
Early vomiting (during 2 h) [n (%)]	5 (16.6)	1 (3.3)	0 (0) *†	8 (26.6)	0.035
Late vomiting (during 2-24 h) [n (%)]	4 (13.3)	1 (3.3)	0 (0) *†	7 (23.3)	0.098

Table 3. Postoperative analgesics and antiemetic use in four groups Values are presented as mean ± SD. Group K = ketamine treated patients; Group D = dexamethasone treated patients; Group KD = ketamine-dexamethasone treated patients; Group C = control group. * $P < 0.05$ vs. Group C. † $P < 0.05$ vs. Group K. ‡ $P < 0.05$ vs Group D.

4. DISCUSSION

The children candidates for tonsillectomy are at risk of significant airway obstruction and respiratory depression in the postoperative period (6). As Negus et al. (7) reported, posttonsillectomy upper airway obstruction occurred more frequently in children who receive oral midazolam as premedication in combination with morphine for analgesia.

Although paracetamol is a safe and effective analgesic, if used alone it often provides insufficient analgesia (8, 9). NSAIDs are an effective alternative to opioids because they have no adverse effect on the airway, however they increase the risk of posttonsillectomy bleeding and reoperation (10). Therefore, choosing the effective treatment of pain after tonsillectomy in children still remains challenging for physicians.

As our results showed, ketamine 0.5 mg/kg i.v. significantly reduced postoperative pain score compared with placebo in PACU. This is in accordance with the study of Aspinall et al. (11) which showed i.v. ketamine 0.5 mg/kg provides effective analgesia for the immediate postoperative period after adenotonsillectomy without increasing the risk of side-effects. The study by Dal et al. (2) had a similar conclusion.

Our data also showed that dexamethasone 0.5 mg/kg IV didn't decrease postoperative pain compared with the placebo in the PACU. Our finding is similar to the study by Kaan et al. (4) that showed the postoperative first hour pain score before transferring to floor were similar between the group which received a single dose of 0.5 mg/kg i.v. dexamethasone preoperatively with the group which received the placebo.

Our results showed that the administrating 0.5 mg/kg i.v. dexamethasone in combination with i.v. ketamine 0.5

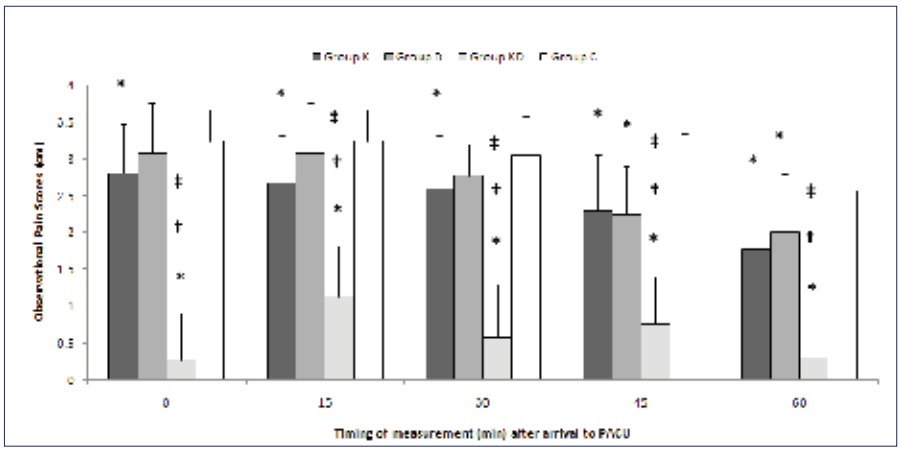

Figure 1. Postoperative observational pain scores at 0, 15, 30, 45 and 60 minutes after arrival to the post anesthesia care unit (PACU). Data are presented as mean (SD). Group K = ketamine treated patients; Group D = dexamethasone treated patients;Group; KD = ketamine-dexamethasone treated patients; Group C = control group. *P < 0.05 vs. Group C.†P < 0.05 vs. Group K. ‡P < 0.05 vs. Group D. There was no significant difference between Group K and Group D.

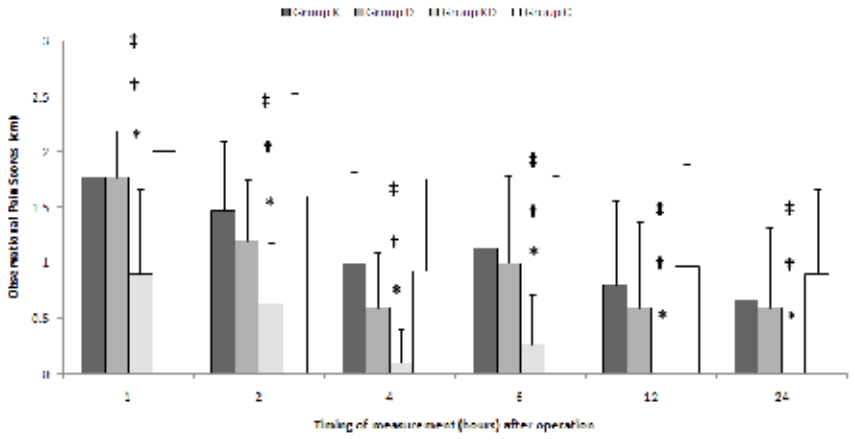

Figure 2. Postoperative observational pain scores at 1, 2, 4, 6, 12, and 24hours after operation. Data are presented as mean (SD). Group K = ketamine treated patients; Group D = dexamethasone treated patients;Group KD = ketamine-dexamethasone treated patients; Group C = control group.*P < 0.05 vs. Group C.†P < 0.05 vs. Group K. ‡P < 0.05 vs. Group D.

mg/kg significantly reduced postoperative pain in PACU in comparison with groups using placebo, or ketamine or dexamethasone separately without increasing adverse effects. This conclusion is also true when postoperative pain evaluation is extended for 24 hours.

Tonsillectomy can cause damage to the underlying muscle tissue and surrounding tissues mechanically, thermally or both. This causes the activation of an acute inflammatory response in the surrounding tissues and consequently causes spasm of pharyngeal muscles, irritation of nerve endings and in some cases disruption of the mucosa (12). Finally, the tissue damage results in an imbalance in the mechanisms of swallowing, incoordination, dysphagia and pain. Review of the above events shows that if the tissue damage was prevented, the normal physiologic mechanisms could be reestablished (13).

Glucocorticoids decrease the degree of inflammation by inhibition of bradykinin, prostaglandin and leukotrienes. Decrease in inflammatory response results in lessening of accompanying signs and symptoms including pain (13). The efficacy of using 0.5 mg/kg i.v. dexamethasone in combination with i.v. ketamine 0.5 mg/kg ketamine in reducing postoperative pain may be attributed to the anti-inflammatory effect of dexamethasone which may decrease local edema and pain (14). Moreover, dexamethasone can modulate inducible COX-2 (15). The complication following corticosteroid administration such as increased rate of infection, adrenal suppression and peptic ulcer are usually related to its long term use. The adverse effect of steroid therapy less than 24 hours is insignificant (16). In our study we didn't have any complications related to the dexamethasone administration.

Perioperative ketamine, an NMDA antagonist, has been shown to decrease rescue analgesic requirements, pain severity, or both (17). Woolf et al. (18) showed that NMDA receptors are located in the dorsal horn of the spinal cord. Activation of these receptors can cause alterations in the central nervous system's (CNS) response to pain and subsequent postoperative hyperalgesia**.** Local and regional anesthesia can prevent the transmission of peripheral nociceptive stimuli from the surgical incision to the dorsal horn of the spinal cord (1). This conclusion cannot be attributed to the general anesthesia. As Woolf et al. (19) suggested, blockade of the NMDA receptors may inhibit central sensitization. Using NMDA receptor antagonist at subanesthetic doses can prevent or block central hypersensitivity (3).

Ketamine has side effects such as hallucinations, bad dreams, dysphoria, nausea and vomiting, sedation, and diplopia. These adverse effects of ketamine are usually seen when higher doses (more than 1 mg/kg) are used (20). No case of hallucination was seen in our study. It seems that the anti-inflammatory effect of dexamethasone combined with the anti-nociceptive effect of ketamine caused more analgesic effects compared with using each drug separately.

Two of the most important side effects following tonsillectomy are nausea and vomiting. This can be due to opioid administration, swallowed blood, pain, and direct oropharyngeal irritation**.** As our findings showed, the use of ketamine in combination with dexamethasone decreased the incidence of nausea and vomiting at the early and late postoperative periods. This can be attributed to antiemetic effect of dexamethasone as described by the study of Fazel et al. (21).

Dexamethasone exerts its antiemetic effect through inhibition of

serotonin (22), release of endorphins (23), and antagonism of prostaglandin (24). Potentiating of opioid analgesia by dexamethasone may be another mechanism for antiemetic effect of dexamethasone (25). One of the important risk factors for the occurrence of PONV is opioid administration (26). We used opioids infrequently in our study. The relatively low incidence of vomiting in the present study can also be due to this factor. Potentiating of opioid analgesia by dexamethasone may be another mechanism for antiemetic effect of dexamethasone (25).

According to our findings the combined use of dexamethasone and ketamine significantly reduced the time to the first oral intake compared with Group K, Group D, and Group C. These results can be related to the anti-inflammatory effect of dexamethasone which reduced local edema and pain. It is possible that the analgesic effect of ketamine contributed to the results was obtained.

Our study had some limitations. We only recorded total consumption of rescue analgesics on first postoperative days. Therefore, our results cannot document whether the acetaminophen sparing effect of combined use of dexamethasone with ketamine was prolonged beyond the expected duration of action or it was limited merely to the early postoperative period. Another limitation of the study was that we did not repeat dexamethasone-ketamine combination in postoperative period. Therefore, the effect of continuing the medication could not be evaluated.

In conclusion, our study showed that a prophylactic preoperative single dose of i.v. 0.5 mg/kg dexamethasone in combination with a single dose of i.v. 0.5 mg/kg ketamine in patients undergoing tonsillectomy decreases postoperative pain and improves oral intake without significant side effects compared with using i.v. ketamine or i.v. dexamehasone separately. Our results also showed a significant decrease in postoperative vomiting incidence in patients who received a combination of ketamine and dexamethasone. Our findings are interesting in light of the potential clinical application to other types of surgeries.

Acknowledgment

The authors wish to sincerely thank the support of all the colleagues in Kashani Hospital Medical Center affiliated to Isfahan University of Medical Sciences in Isfahan, Iran. Furthermore, our special thanks go to the patients, who wholeheartedly and actively assisted us to carry out this research. No conflict of interest existed. This prospective randomized observational study was approved by the Ethics Committee of our university, (Isfahan University of Medical Sciences) and all patients gave their written, informed consent.

Conflict of interests: authors have no conflict of interests.

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