ORIGINAL ARTICLE

Efficacy of Pre-incisional Peritonsillar Infiltration of Ketamine for Post-tonsillectomy Analgesia in Children

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ABSTRACT

Objective: To assess the efficacy of pre-incisional peritonsillar infiltration of two doses of ketamine on postoperative analgesia compared with peritonsillar normal saline in children undergoing tonsillectomy.

Study Design: Double blind, randomized controlled trial.

Place and Duration of Study: Department of Anaesthesiology, Surgical Intensive Care and Pain Management, Civil Hospital, Karachi, Dow University of Health Sciences, from August 2008 to January 2009.

Methodology: Seventy-five ASA physical status one patients, aged 5 – 12 years scheduled for tonsillectomy were enrolled in this study. Patients were divided into three groups of 25 each. Group-A received normal saline, Group-B, ketamine 0.5 mg/kg while group-C ketamine 1 mg/kg respectively. All medications were 2 ml and were applied 1 ml per tonsil; 3 minutes before tonsillectomy incision. Anaesthesia was induced and maintained with standard technique. All patients were monitored throughout surgery. The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) and Wilson sedation scale were used to evaluate pain levels and sedation respectively after operation.

Results: Mean duration of analgesia was significantly higher in group-C (17.28 ± 5.33 hours) as compared to group-B (11.36 ± 4.15 hours) and A (3.2 ± 0.71 hours) as well as group-B was also significantly higher than group-A ($p < 0.05$). Group-A had significantly higher pain scores than group-B and group-C. Both B and C groups had comparable pain scores, which were statistically significant at 6 and 8 hours.

Conclusion: Single 0.5 or 1 mg/kg injection of ketamine given before surgical incision by peritonsillar infiltration provides efficient pain relief during postoperative period without significant side-effects in children undergoing tonsillectomy.

Key Words: *Ketamine. Analgesia. Children. Tonsillectomy.*

INTRODUCTION

Postoperative pain management has become a major concern in paediatric anaesthesia. Although age specific pain evaluation tools are available, postoperative pain is still undertreated in children.[1] Intraoperative and postoperative noxious inputs may cause central sensitization, but analgesic interventions given before the noxious stimulus may alter or block sensitization and hence, reduce acute pain.[2] Because ketamine is an NMDA receptor antagonist, it is hypothesized to prevent or reverse central sensitization and consequently reduce postoperative pain. The local anaesthetic effects are likely from the blocking action of ketamine on sodium channel.[2,3]

Patients undergoing tonsillectomy have high incidence of postoperative pain.[4,5] There are number of studies in which pre-incisional peritonsillar saline infiltration were used as placebo group to establish the effectiveness of peritonsillar infiltrations of other medications in children undergoing tonsillectomy. Honarmand and Reza showed that ketamine given by peritonsillar infiltration provides efficient pain relief after surgery in children undergoing adenotonsillectomy. But they did not show the effectiveness of ketamine infiltration in children undergoing only tonsillectomy.[6]

This study was conducted to assess the effectiveness of pre-incisional peritonsillar infiltration of two doses of ketamine (0.5 and 1 $mg.kg^{-1}$) on postoperative pain relief compared with peritonsillar saline and adverse effects related to ketamine infiltration in children undergoing tonsillectomy.

METHODOLOGY

After the approval of the hospital ethics committee, 75 ASA physical status one patients, aged 5 – 12 years, scheduled for tonsillectomy were included in this study. Written informed consent was obtained from parents of each patient. Exclusion criteria included inability or refusal to consent, systemic or endocrine disease, hypertension, allergy to ketamine, peritonsillar abscess, patient scheduled for adenotonsillectomy and psychiatric disorders.

All patients were fasted for 6 – 8 hours prior to anaesthesia. After taking intravenous line, Lactated Ringer's solution started and monitors (non-invasive blood

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pressure, ECG and pulse oximeter for SpO_2) were applied. Patients were randomly allocated into one of the three study groups with 25 patients in each group by simple balloting method. Anaesthesiologist (primary researcher) prepared syringes containing either normal saline or ketamine for each patient and labeled A (saline), B (ketamine 0.5 $mg.kg^{-1}$) and C (ketamine 1 $mg.kg^{-1}$). Peritonsillar infiltrations were applied by anaesthesiologist, providing anaesthesia to patient (blinded for the study group). All medications were 2 ml and were applied 1 ml per tonsil, 3 minutes before tonsillectomy incision.

Anaesthesia was induced with thiopental sodium (5 $mg.kg^{-1}$) and atracurium (0.5 $mg.kg^{-1}$) and maintained with isoflurane 1% and nitrous oxide 50% in oxygen. Nalbuphine (0.1 $mg.kg^{-1}$) was used as analgesic agent and given before ketamine infiltration to every patient. After endotracheal intubation, positioning and application of mouth gag, peritonsillar infiltration was applied through the tonsillar capsule after careful aspiration to all patients of three study groups that is 2 ml normal saline in group-A, ketamine 0.5 $mg.kg^{-1}$ in group-B and ketamine 1 $mg.kg^{-1}$ In group-C. In all patients, tonsillectomy incision was given three minutes after injection. Paracetamol, 15 $mg.kg^{-1}$ intra-venously was given to every patient intra-operatively.

During operation, patient's heart rate, blood pressure, ECG, end tidal CO_2 and oxygen saturation was monitored every 5 minutes throughout the procedure. After the completion of tonsillectomy operation, neuro-muscular blockade was reversed with neostigmine (0.04 $mg.kg^{-1}$) and atropine (0.02 $mg.kg^{-1}$). Anaesthesia was discontinued and tracheal tube removed in lateral position and then oxygen given via face mask to all patients. After extubation, patients were shifted to post-anaesthesia care unit (PACU).

In post-anaesthesia care unit (PACU), anaesthetist and a nurse who were unaware of the study group observed the patients. In the PACU, non-invasive blood pressure, ECG and oxygen saturation was monitored for one hour and pain scores were assessed by the blinded observer anaesthetist at 5, 15, 30 and 60 minutes using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) established by McGrath *et al*.,[7] by a senior anaesthetist blinded to the study group. Then the patients were shifted to the ward where patients were assessed by doctor on duty who were blinded to the study group at 2 hours intervals for next 12 hours and then 24 hours postoperatively. Patients were usually discharged 24 hours after surgery. Postoperatively, sedation was also assessed by Wilson sedation scale at 5, 15, 30 and 60 minutes in PACU.

Postoperative complications like nausea, vomiting, dysphagia for solid or liquid and hallucination were observed and recorded. Patients with postoperative CHEOPS score of 4 or more were given intravenous nalbuphine (0.1 $mg.kg^{-1}$) as rescue analgesic. Time of first rescue analgesic was recorded for each patient. Metoclopramide (0.1 $mg.kg^{-1}$) intravenously given to patients with nausea or vomiting.

Sample size based on the study by Honarmand and Reza[6] was determined on the basis of the time of first rescue analgesic requirement postoperatively and was calculated by using statistical software NCSS. Sample size of 25 patients per group was needed to detect a difference greater than and equal to 25% in first analgesic requirement among groups with 80% power, using one-way analysis of variance (ANOVA) and post-hoc comparison at various points in time by using Bonferroni's type-I error rate correction for multiple test of significance. Statistical package for social science (SPSS 10) was used to analyze data. Descriptive statistics mean and standard deviation were computed for quantitative variables. Frequency and percentage were computed for qualitative variables. Analysis of variance was applied for mean comparisons for age, weight, duration of analgesia. Chi-square test was applied to compare proportion difference among groups. P-value less than 0.05 was considered significant.

RESULTS

Seventy-five patients, scheduled for tonsillectomy were randomized into the three study groups of 25 each. There were 46 females and 29 males (aged 5 – 12 years). There were no statistically significant difference between the groups for age, weight, gender, duration of anaesthesia and duration of surgery (Table I). There was no statistically significant difference between the groups in heart rate, oxygen saturation, end-tidal CO_2, systolic and diastolic blood pressure during and after operation.

Group-A patients who received saline solution as placebo had higher pain (CHEOPS) scores than group-B and group-C. With multiple comparisons, there

Table I: Demographic characteristics of patients, duration of surgery and anaesthesia.

variables	Group-A n = 25	Group-B n = 25	Group-C n = 25	p-value
Age (years)	11.12 ± 1.7	10.64 ± 2	10.52 ± 1.7	0.54†
Weight (kg)	33.16 ± 6	31.44 ± 10	29.08 ± 6	0.20†
Duration of surgery (min)	36.40 ± 4.55	35 ± 6.29	35.40 ± 7.76	0.98†
Duration of anaesthesia (min)	39.6 ± 4.54	42.4 ± 7.37	43.0 ± 9.01	0.34†
Gender M/F (n)	10 / 15	8 / 17	11 / 14	0.67‡

† Kruskal-Wallis test; ‡ Chi-square test; Quantitative data presented as mean ± SD. Qualitative data presented as frequency.

Table II: Comparison of complications.

Complications	Group-A n = 25	Group-B n = 25	Group-C n = 25	p-value
Nausea	7 (28%)	7 (28%)	4 (16%)	0.52
Vomiting	4 (16%)	2 (8%)	2 (8%)	0.57
Dysphagia	10 (40%)	7 (28%)	7 (28%)	0.03*

** Significantly higher in group-A (chi-square test)*

was a statistically significant difference between group-A and B ($p < 0.05$), as well as group-A and C ($p < 0.05$) regarding the CHEOPS scores observed at all times. Group-B and group-C had comparable pain scores, which were statistically significant at 6 and 8 hours (Figure 1).

Average duration of analgesia in group-A was 3.2 ± 0.71 hours, in group-B 11.36 ± 4.15 hours while in group-C 17.28 ± 5.33 hours. Mean duration of analgesia was significantly higher in group-C as compared to group-B and A as well as group-B was also significantly higher than group-A ($p < 0.05$, Figure 2). Supplemental analgesia was required early in group-A (3.2 ± 0.71 hours) as compared to group-B and group-C. Two patients (8%) in group-B and 8 patients (32%) in group-C did not require any rescue analgesia during 24 hours postoperatively. Sedation was assessed postoperatively by Wilson sedation scale. All patients in the three study groups achieved score 1 (awake and oriented) within one hour in PACU.

There was no statistically significant difference among three groups regarding incidence of nausea and vomiting while dysphagia was significantly higher in group-A as compared to group-B and C ($p = 0.03$, Table II). During first postoperative night, none of the patients or parents reported bad dreams or anything like hallucination. No patient included in this study suffered from any serious complication and none of the patients required re-operation for bleeding.

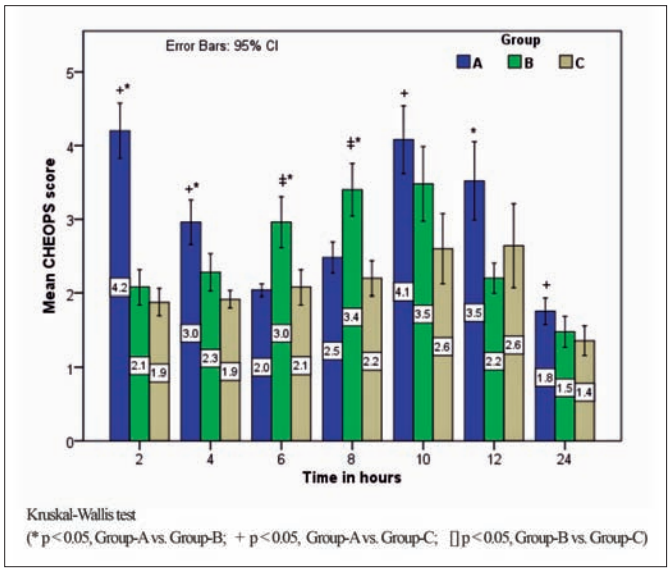

Figure 1: Comparison of mean CHEOPS scores among groups post-operatively.

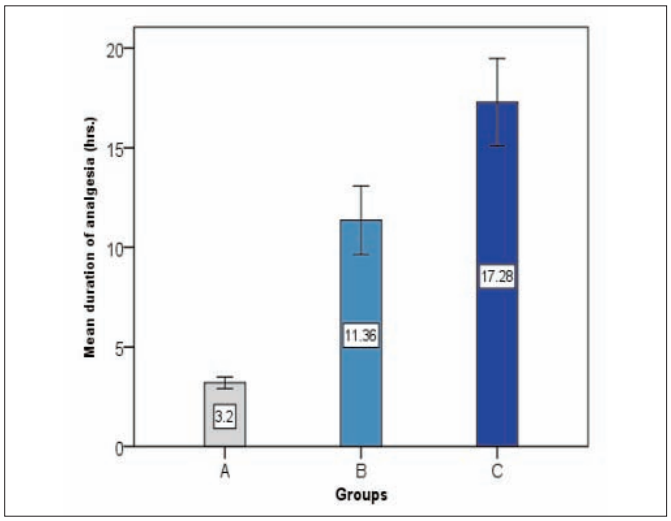

Figure 2: Comparison of mean duration of analgesia among groups.

DISCUSSION

Pain control after tonsillectomy in children always remain a challenge for anaesthesiologists, especially for those who are at higher risk of airway obstruction and respiratory depression.[8] Post-tonsillectomy airway complications varying from significant oxygen desaturation to respiratory depression requiring intubation and ventilation occurred in 30% of patients with obstructive sleep apnea syndrome in a series stated by Rosen *et al*.[9] Moreover, post-tonsillectomy, upper airway obstruction was reported where oral midazolam was used as pre-medication in combination with morphine for postoperative analgesia.[10] Paracetamol is a safe and effective analgesic except if used alone often provides unsatisfactory analgesia.[11] Non-steroidal anti-inflammatory drugs (NSAIDs) are an attractive alter-native to opioids because they have no adverse effects on the airway but drugs such as ketorolac, ibuprofen or ketoprofen increase the risk of re-operation for hemostasis after tonsillectomy.[12] Because of these reasons, effective treatment of post-tonsillectomy pain in children still provide unique challenge to physicians.

Studies showed that oral ketamine provide ineffective analgesia postoperatively and causes more salivation while intramuscular ketamine produces sedation and reduce pain on swallowing but provide ineffective analgesia postoperatively.[13] Heidari *et al*. showed rectal ketamine also has analgesic effects, especially in the first hours after surgery in comparison with acetaminophen, and it can be an alternative analgesic with easy administration in children after tonsillectomy.[14]

Dal and Elven showed that low dose ketamine (0.5 $mg.kg^{-1}$) given i.v. or peritonsillar infiltration perioperatively provides efficient pain relief without significant side effects in children undergoing adenotonsillectomy but children in i.v. ketamine group had significantly higher sedation scores than peri-tonsillar ketamine group in immediate postoperative period.[15]

Honarmand and Reza performed a study which showed that low dose ketamine (0.5 $mg.kg^{-1}$ or 1 $mg.kg^{-1}$) given 3 minutes before incision by peritonsillar infiltration provides efficient pain relief during 24 hours after surgery without significant side effects in children undergoing adenotonsillectomy.[6]

Molliex *et al*. showed that pain scores were lower in peritonsillar bupivacaine infiltrated groups compared with peritonsillar saline infiltrations.[16] In another study, peritonsillar infiltration with bupivacaine was found moderately useful for analgesia compared with peritonsillar saline infiltration in children undergoing tonsillectomy.[17]

Ketamine has its peripheral and central effects. During peritonsillar infiltration, ketamine shows its local analgesic effect by blockade of sodium and potassium channels in the peripheral nerve (tonsillar nerve).[18] In pre-clinical studies, peripheral local ketamine was shown to have an anti-hyperalgesic effect.[19] Tverskoy *et al*. showed that analgesic efficacy of bupivacaine with ketamine infiltration through an inguinal hernia incision and the length of local anaesthesia are doubled through peripheral mechanisms. The local anaesthetic effect of ketamine is more than 90 minutes and it lasts for 1 week after infiltration.[20]

Results of this study showed that ketamine applied by peritonsillar infiltration reduces postoperative pain scores compared with peritonsillar infiltration of normal saline solution in children whereas it has minimal side-effects. It was also found that the higher dose of ketamine infiltration (1 $mg.kg^{-1}$) significantly lower postoperative pain scores compared with peritonsillar infiltration of normal saline with reduced incidence of complications.

Aspinall and Mayor administered intravenous ketamine (0.5 $mg.kg^{-1}$) showing this dose provides effective analgesia for the immediate postoperative period after adenotonsillectomy with no increased risk of side-effects. In their series, there was one incidence of deep sedation in the recovery room and 88% of children in the ketamine group still suffered pain at home.[21]

Swallowed blood, pain, opioid administration and direct oropharyngeal irritation may contribute to postoperative nausea and vomiting following tonsillectomy. In this study, there was no statistically significant difference observed in the incidence of nausea or vomiting between groups while dysphagia was significantly higher in group-A as compared to group-B and C ($p = 0.03$). In this study, postoperative CHEOPS scores remained higher in group-A as compared to group-B which was still higher than group-C. All patients were fully awake within one hour after operation in PACU. No patient in this study suffered from any serious complication and none of the patients required re-operation for bleeding.

Aydin *et al*. showed that intravenous ketamine produces efficient analgesia with its preventive properties in paediatric patients. Ketamine decreases postoperative analgesic requirements and has an analgesic effect when used before day-surgery tonsillectomy / adeno-tonsillectomy.[22] Saeed *et al*. showed that peritonsillar infiltration of ketamine was more effective in reducing the postoperative pain severity, need for rescue analgesics and antiemetic. Thus, peritonsillar infiltration of ketamine is suggested for postoperative pain control in children undergoing adenotonsillectomy.[23]

Dahmani *et al*. conducted a meta analysis of 35 randomized control studies to investigate postoperative analgesic properties of ketamine in paediatric patients demonstrated the safety of ketamine. Ketamine administered locally during tonsillectomy, reduces PACU and early (6 – 24 hours) pain intensity and PACU analgesic requirements. During systemic, local or caudal administration of ketamine, the analgesic effect of this compound was observed in the PACU period and was not associated with an opioid-sparing effect.[24]

CONCLUSION

Single 0.5 or 1 $mg.kg^{-1}$ injection of ketamine given before surgical incision by peritonsillar infiltration provides efficient pain relief during postoperative period without significant side-effects in children undergoing tonsillectomy.

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