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The Comparative Study of Adding Ketamin to Pre-Incional Bupivacaine Infiltration on Pain Relief Post Tonsillectomy

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Abstract: Various types of local anesthetics have been used to achieve more appropriate postoperative consequences as well as to minimize postoperative pain severity in patients undergoing tonsillectomy surgery. It seems that adding ketamine to other local anesthetics may enhance their analgesic effects. The aim of the present study is to evaluate the analgesic effect of ketamine as an additive to bupivacaine in patients undergoing tonsillectomy surgery. This randomized double-blinded clinical trial was conducted on 63 consecutive patients aged between 4 and 30 years, belonging to ASA class I and II who were scheduled for tonsillectomy surgery. Subjects were randomly assigned to receive one of the three following anesthesia protocols: ketamine alone (0.5 mg kg^{-1}) bupivacaine 0.25% alone (5 mL) or ketamine (0.5 mg kg^{-1}) combined with bupivacaine 0.25% (5 mL). At 4 and 24 h after surgery although, no difference was observed between the two groups who received ketamine alone and bupivacaine alone, the pain severity was significantly lower in the group received ketamine combined with bupivacaine. At two time points of 4 and 24 h after surgery, the difference between the patients who received ketamine alone and bupivacaine alone was not significant but mean pulse rate in the group who received ketamine plus bupivacaine was more stable than the other two groups. No significant difference was found across the three groups in prevalence of postoperative nausea and vomiting. Mean number of hospitalization in the group which received bupivacaine alone or the group that received a combination therapy was significantly lower than that receiving only ketamine. Adding ketamine to pre-incional bupivacaine infiltration leads to reduced post operative pain when compared with use of bupivacaine alone. However, this combination therapy may not decrease the prevalence of postoperative nausea and vomiting or the length of hospital stay in the patients undergoing tonsillectomy.

Key words: Ketamine, bupivacaine, tonsillectomy, pain, lead

INTRODUCTION

Though tonsillectomy surgery has been significantly decreased within recent decades due to the change in surgical indications, this operation has remained a common surgery, especially in childhood whole of the world (Millington and Phillips, 2014). The main indications for tonsillectomy include repeated infections of tonsils and adenoids, obstructive causes such as obstructive sleep apnea, adenoid hypertrophy or neoplastic masses (Schymik *et al*., 2015). Due to advances in new generations of antibiotics, occurrence of the recurrent infections has been considerably reduced, however progressive obstructive signs leading to tonsillectomy have become of particular importance. In this regard, about one-third of tonsillectomy surgeries are now performed to remove obstructions (Cielo and Gungor, 2016; Choi *et al*., 2015). More importantly, 60% of the population who undergo tonsillectomy due to obstructive lesions are younger than 8 years of age (Hamada *et al*., 2015). Furthermore, 81% of children younger than 3 years needing tonsillectomy suffer from obstructive lesions (Cohen and Sommer, 2016). Thus, the selection of an appropriate preoperative anesthetic method for children requiring tonsillectomy is now clinically emphasized. Particularly, in children with obstructive sleep apnea, premedication with sedatives should be administered cautiously because of their high sensitivity to these drugs as well as increased risk for respiratory depression (Peng *et al*., 2011). Intubation can be done in patients under deep anesthesia with inhalation agents or following short or intermediate-acting muscle relaxants. Flexible laryngeal airway maskshave been used recently as an alternative to intubation in tonsillectomy surgery (Costantini *et al*., 2011).

Bupivacaine is commonly used for local infiltration in various types of surgeries (Ruetsch *et al*., 2001). Bupivacaine binds to the intracellular portion of voltage-gated sodium channels and blocks sodium influx into nerve cells, preventing depolarization. Without

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depolarization, no initiation or conduction of a pain signal can occur (Geodakian, 2013). However, it has some potential side effects such as cardiotoxicity and adverse drug reactions (Wolfe and Butterworth, 2011). In this regard, the combination of this agent with other cardioprotective anesthetics is now strongly recommended. Ketamine, a phencyclidine derivatineisan N-Methyl-D-Aspartate (NMDA) receptor antagonist. It possesses some definite advantages over the conventional local anesthetic agents as itusually does not cause cardiovascular and respiratory systems depression (Kurdi *et al*., 2014). Now a days, it seems that adding ketamine to other local anesthetics may enhance their analgesic effects. The aim of the present study is to test the effect of adding ketamin to pre-incional bupivacaine infiltration on pain relief after tonsillectomy surgery.

MATERIALS AND METHODS

This randomized double-blinded clinical trial was conducted on consecutive patients aged between 4-30 years, rated as American Society of Anesthesiology (ASA) I-II who were scheduled for tonsillectomy surgery. Those with the history of hemodynamic instability, sensitivity to the used anesthetic agents and patients with anatomical anomalies in the site of surgery were all excluded. In final, 63 patients were entered into the study. During the pre-operative visit, detailed history of every patient was noted and a routine examination was done. The procedure of pre-incional infiltration of ketamin and bupivacaine was explained to each patient and informed consent of each patient was obtained. The study protocol was approved by the ethics committee at Kermanshah University of Medical Sciences. The patients were randomly assigned to receive one of the three following anesthesia protocols: ketamine alone (0.5 mg kg^{-1}), bupivacaine 0.25% alone (5 mL) or ketamine (0.5 mg kg^{-1}) combined with bupivacaine 0.25% (5 mL). Anesthesia induction was performed by one resident of anesthesiology in with the same method for all patients. Postoperatively, the severity of pain was assessed using the Visual Analogue Scaling (VAS) Method and hemodynamic status was also monitored 1, 4 and 24 h after operation. The occurrence of postoperative nausea and vomiting was also recorded. In final, the need for analgesics within hospitalization was determined.

Results were reported as mean±Standard Deviation (SD) for the quantitative variables and percentages for the categorical variables. The groups were compared using the ANOVA test or non-parametric Kruskal-Wallis test for the continuous variables and the Chi-square test for the categorical variables. The difference in study outcome across 3 groups was assessed using the multivariate logistic regression analysis. Odds Ratio (OR) and 95% Confidence Intervals (CI) were also calculated. The $p<0.05$ were considered statistically significant. All statistical analyses were performed using SPSS Version 16.0 (SPSS Inc., Chicago, IL, USA) and SAS Version 9.1 for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS AND DISCUSSION

All three groups were similar inmean age and gender distribution. In each group, 12 patients were male and 9 were female. Comparing pain severity at 1 h after operation showed no difference across the three groups ($p = 0.785$). At 4 h post-surgery although, no difference was observed between the two groups who received ketamine alone and bupivacaine alone, pain severity was significantly lower in the group who received ketamine combined with bupivacaine infiltration when compared with the group that received ketamine alone ($p = 0.041$) and withthegroup that received bupivacaine alone ($p = 0.016$). Similar results were obtained at 24 h of operation, when patients who received a combination of the two drugs experienced lower pain severity in comparison with patients who received ketamine alone ($p = 0.013$) and those who received bupivacaine alone ($p = 0.049$) (Table 1).

Regarding hemodynamic status, there was a significant difference across the three groups in terms of mean pulse rate 1 h after operation. In this regard, although no difference was found between groups who received ketamine alone and bupivacaine alone ($p = 0.378$), the difference was significant between the group that received ketamine combined with bupivacaine and the group that received ketamine alone ($p = 0.001$) as well as those who received bupivacaine alone ($p = 0.013$). Similarly, at 2 time points of 4 and 24 h after surgery, the difference between the patients that received ketamine alone and bupivacaine alone was not significant but mean

Table 1: Comparing postoperative pain severity between 3 three study groups

Groups	Bupivacaine (n = 21)	Ketamine (n = 21)	Bupivacaine plus Ketamine (n = 21)
1 h after surgery			
Mild	6 (28.6)	8 (38.1)	9 (42.9)
Moderate	12 (57.1)	11 (52.4)	11 (52.4)
Severe	3 (14.3)	2 (9.5)	1 (4.8)
4 h after surgery			
Mild	5 (23.8)	8 (38.1)	13 (61.9)
Moderate	15 (71.4)	12 (57.1)	8 (38.1)
Severe	1 (4.8)	1 (4.8)	0
24 h after surgery			
Mild	17 (81.0)	15 (71.4)	11 (52.4)
Moderate	0	0	0
Severe	0	0	0

pulse rates in the group that received ketamine plus bupivacaine was more stable than the other two groups.

No difference was revealed between the three groups in prevalence of postoperative nausea ($p = 0.560$) and vomiting ($p = 0.768$).

The mean number of hospitalization in the group that received bupivacaine alone and the group that received combination therapy was significantly lower than the group that received only ketamine (mean hospitalization days: ketamine alone group = 1.19 days, bupivacaine alone group = 1 day, ketamine plus bupivacaine group = 1 day, $p = 0.013$). In this regard, all patients in the two former groups were hospitalized only 1 day while 19.0% of those who received ketamine alone were hospitalized for 2 days.

According to the study findings, adding ketamine to pre-incional bupivacaine infiltration led to reduced postoperative pain when compared with the use of bupivacaine alone. However, this combination therapy could not decrease the prevalence of postoperative nausea and vomiting or the length of hospital stay for the patients undergoing tonsillectomy. According to this fact the patients' satisfaction is directly affected by early postoperative recovery as well as lowering postoperative pain severity. It seems that by adding ketamine to pre-incional bupivacaine infiltration, an improvement inpatient's satisfaction can be well obtained. No similar previous studies focused on the effect of adding ketamine to bupivacaine infiltration to improve post-tonsillectomy outcome, however its beneficial effects in other types of surgeries has been examined. In a study by Khezri *et al.* (2013) on patients who underwent cesarean section, intrathecal ketamine co-administered with spinal bupivacaine elongated the time to the first analgesic request and lessened the total analgesic consumption in the first 24 postoperative hours in comparison with bupivacaine alone in the control group indicating its beneficial effect on requiring less analgesic use due to significantly lowered postoperative pain in the patients. A similar result was obtained by Akbas *et al.* (2005) study showing that ketamine added to either bupivacaine or ropivacaine for caudal analgesia gave a longer duration of analgesia than bupivacaine alone. Togal *et al.* (2004) also indicated that the duration of complete motor block and spinal analgesia was shorter in the bupivacaine plus ketamine group with more hemodynamic stability and without increasing drug-related side effects. As shown by Batra *et al.* (2005), using a combination of bupivacaine plus ketamine resulted in providing better pain relief than intra-articular ketamine in arthroscopic knee surgery.

In the field of pain relief following tonsillectomy, previous studies have shown only the effects of eitherketamine or bupivacaine drugs on postoperative pain relief. In study by Umuroglu *et al.* (2004), effect of ketamine in children who underwent tonsillectomy was comparable with morphine in postoperative pain relieving. Chaturvedil and Domkondwar (2005) also showed that the use of bupivacaine alone in tonsillectomy surgery led to effectively reduced postoperative pain. However, those studies could notshow beneficial effect of adding ketamine to pre-incional local anesthetics for relieving postoperative pain. As shown by Barta *et al.* (2007), adding ketamine to remifentanil could not reduce post-tonsillectomy pain because of the small dose of ketamine used in their study.

In total, although analgesic effect of combination infiltration of ketamine and bupivacaine may be begun with a short delaying, significant pain relief effect of this combination can be appeared at 4 h after operation and can be maintained for at least 24 h facilitating patient's postoperative recovery. More interestingly, adding ketamine to bupivacaine can lead to more hemodynamic stability, especially lowering pulse rate during tonsillectomy without increasing drugs side effects. Moreover, although we obtained favorable outcome following the use of ketamine with a dose of 0.5 mg kg^{-1}, other drug dosages can be examined to maximize its beneficial pain relieving effects.

CONCLUSION

Adding ketamine to pre-incional bupivacaine infiltration can reduce postoperative pain as well as maintain hemodynamic stability compared with using bupivacaine alone in patients undergoing tonsillectomy.

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