# PREEMPTIVE PERITONSILLAR KETAMINE INFILTRATION: POSTOPERATIVE ANALGESIC EFFICACY VERSUS MEPERIDINE

Mohamed Ibrahim El Sonbaty*, Hisham Abo El Dahab*,
Ahmed Mostafa* and Osama Abo Shanab*

## Abstract

*Objectives:* The current study was planned to assess post-tonsillectomy analgesic efficacy of pre-emptive peritonsillar ketamine infiltration with or without bupivacaine in comparison to meperidine alone or in combination with bupivacaine.

*Patients & Methods:* The study included 100 patients with mean age of 10.5±2.3 years assigned for adenotonsillectomy. Patients were randomly allocated into 4 groups (n=25): Group K1: received peritonsillar infiltration of ketamine (0.5 mg/kg), Group M1: received peritonsillar infiltration of meperidine (1 mg/kg), and groups K2 and M2 received either ketamine (0.5 mg/kg) or meperidine (1 mg/kg) in combination with bupivacaine (5 mg/ml). All medications were prepared as 2 ml in volume and were applied as 1 ml per tonsil 3 min prior to tonsillectomy. On admission to the post-anesthesia care unit (PACU) pain was assessed using the objective pain scale (OPS) score which evaluates 5 parameters each was scored from 0 to 2 for a collective score ranged from 0 = best to 10 = worst. OPS score was assessed at time of admission to PACU and every 15 min for one hour and every 30 minutes till patients were ready for discharge from PACU at an Aldrete score of 9. Rescue analgesia with morphine 0.05 mg/kg i.v. was administered, after operation; for OPS score ≥5 and time elapsed till first request of rescue analgesia was determined. Upon patient discharge, parents were asked to rate their satisfaction with patient analgesia on 7-point scale; 1 = extremely dissatisfied and 7 = extremely satisfied.

*Results:* All enrolled patients passed smooth intraoperative course without complication. Mean duration of PACU stay was significantly shorter in group K2 compared to the other 3 groups and in group K1 compared to groups M1 and M2. Moreover, total hospital stay was significantly shorter in group K2 compared to groups M1 and M2 but was non-significantly shorter compared to group K1. Both duration of PACU and hospital stay showed a non-significant difference between groups M1 and M2. In group K1 number of patients who had short hospital stay was significantly higher compared to groups M1 and M2. Number of patients in group K2 and had short hospital stay was significantly higher compared to groups M1 and M2. Mean recorded OPS scores showed progressive increase in all patients reaching a peak at 90-min after PACU admission in groups K1, M1 and M2 and at 120-min in K2 group. At 60- and 90-minutes after admission to PACU patients enrolled in group K2 had a significantly lower OPS scores compared to groups K1 and M1 but non-significantly lower scores compared to group M2. Mean parents' satisfaction scores reported in group K2 were significantly higher compared to groups K1 and M1 and were non-significantly higher compared to group M2 with non-significant difference among the other three groups despite being in favor of group M2.

*Conclusion:* Peritonsillar injection of a combination of bupivacaine and ketamine

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\* Lecturer of Anesthesia in faculty of Medicine, Cairo University, Cairo, EGYPT.

provided efficient postoperative analgesia after adenotonsillectomy and achieved higher parents' satisfaction for the outcome of surgery. The used drugs' combination and volume could be recommended as a routine preemptive analgesic policy for children assigned for adenotonsillectomy.

## Introduction

Tonsillectomy is a very common pediatric day-case procedure that is associated with significant postoperative pain. This pain has traditionally been treated with opioid analgesics and non-steroidal anti-inflammatory drugs; however, these agents are associated with increased risks of respiratory depression and postoperative bleeding, respectively[1].

Review of literature revealed a great discrepancy regarding the efficacy of peritonsillar infiltration of local anesthetics as a modality for post-tonsillectomy analgesia; *Costas-Gastiaburo et al.*[2] assessed the effect of peritonsillar infiltration of bupivacaine with or without adrenaline versus saline and no infiltration and found peritonsillar infiltrations decrease intra-operative bleeding and pain, independent of the type of solution infiltrated, bupivacaine groups had the highest incidence of nausea and vomiting and pain scores were lowest with non-significant difference in patients received bupivacaine or saline infiltration. Moreover, *Nordahl et al.*[3] in a similar study design found peritonsillar bupivacaine does not provide significant postoperative analgesia after tonsillectomy. *Vasan et al.*[4] found no statistical significant benefit for use of preincisional bupivacaine in tonsillectomy as regards postoperative pain at any time interval in comparison to saline injection.

*Likar et al.*[5], compared pre-emptive versus postoperative analgesic effect of ropivacaine infiltration in adults undergoing tonsillectomy and demonstrated no significant pre-emptive analgesic effect with ropivacaine and recommend the administration of ropivacaine post-operatively after tonsillectomy, since a reduction of pain scores can thereby be achieved, but with supplements of a combination of a non-opioid analgesic with a weak opioid.

*Kaygusuz & Susaman*[6], compared the topical administration of bupivacaine hydrochloride, dexamethasone and lidocaine hydrochloride in decreasing post-tonsillectomy pain and found the three medicines applied as nasal aerosol decreased the pain significantly in the first postoperative day compared with the placebo group with a non-significant difference in-between. Also, *Kadar & Obaid*[7], found topical application of bupivacaine to the tonsillar fossa can reduce post-operative pain and facilitate early eating and drinking during the post-operative period.

On contrary; *Naja et al.*[8], tried to determine the potential effect of pre-incision infiltration of local anesthesia mixture on post-operative pain after tonsillectomy in comparison to saline infiltration or no infiltration at all and reported that pre-incision infiltration of anesthetic mixture combined with general anesthesia reduces significantly post-tonsillectomy pain in children and provides a more rapid return to normal activity compared to general anesthesia alone or in combination with a placebo infiltration.

Combining local anesthetic agents with other drugs such as adrenaline, clonidine, ketamine or various opioids have met with varied degrees of success[9]. Ketamine, a derivative of phencyclidine, works at a number of different target sites which could explain its analegisc effects irrespective of route of administration. It is an antagonist at N-methyl-D-aspartate (NMDA) receptors, with a stereoselectivity[10]. NMDA receptors are found throughout the central nervous system, and play an important role in nociceptive processing[11]. Analgesic effects of ketamine may also result from agonist activity at mu-opioid receptors[12], and interaction with voltage-sensitive sodium channels[13].

The current study was planned to assess post-tonsillectomy analgesic efficacy of pre-emptive peritonsillar ketamine infiltration with or without bupivacaine in comparison to meperidine alone or in combination with bupivacaine.

## Patients & Methods

The study was conducted at Otorhinolaryngology in conjunction with Anesthesiology Departments, University hospital. After obtaining parents' written consents, 100 children aged 5 to 15 years presented with symptoms of obstruction including persistent snoring with tonsillar or adenotonsillar hypertrophy

*Table 1*
*Constituents Parameters of OPS score*

| Score | Blood pressure | Crying | Movement | Agitation | Posture |
|---|---|---|---|---|---|
| 0 | ±10% pre-operative value | Not crying | None | Asleep or calm | No special posture |
| 1 | >20% pre-operative value | Crying but responds to loving care | Restless | mild | Flexing legs and thighs |
| 2 | >30% pre-operative value | Crying and does not respond to loving care | Thrashing | Hysterical | Holding scrotum or groin |

were recruited in the study.

All study patients were premedicated with oral midazolam 0.5 mg/kg 30 min before the procedure and received fentanyl 1 µg/kg i.v. immediately after induction of general anesthesia with sevoflurane inhalation. Anesthesia was maintained, in all groups with sevoflurane in an oxygen/nitrous oxide mixture at a total fresh gas flow of 1 litre and patients were allowed to breathe spontaneously. No additional opioids or non-steroidal analgesics were administered intraoperatively. Intraoperatively, each child received an antibiotic ampicillin sodium intravenously at a dose of 25 mg/kg up to a maximum of 100 mg/kg or clindamycin intravenously, 10 mg/kg, up to a maximum of 600 mg/kg if penicillin-allergic and dexamethasone in dose of 1 mg/kg up to a maximum of 20 mg/kg.

Patients were randomly allocated into 4 equal groups (n=25) according to medication used for peritonsillar infiltration; Group K1: received local peritonsillar infiltration of ketamine in dose of 0.5 mg/kg, Group M1: received local peritonsillar infiltration of meperidine in dose of 1 mg/kg, and groups K2 and M2 received either ketamine (0.5 mg/kg) or meperidine (1 mg/kg) in combination with bupivacaine (5 mg/ml). All medications prepared as 2 ml in volume and were applied as 1 ml per tonsil 3 min prior to tonsillectomy.

On admission to the post-anesthesia care unit (PACU) pain was assessed using the objective pain scale (OPS) score which evaluates 5 parameters; blood pressure, crying, movement, agitation and posture, (Table 1). Each parameter was scored from 0 to 2 and a collective score ranged from 0 = best to 10 = worst[14]. OPS score was assessed at time of admission to PACU and every 15 min for one hour and every 30 minutes till patients were ready for discharge from the unit. Readiness for discharge from PACU was determined using Aldrete score which evaluated 5 parameters namely; respiration, blood pressure, activity, consciousness and $O_2$ saturation. Each parameter scored from 0 to 2 and readiness for PACU discharge was decided by achieving an Aldrete score of 9[15]. At ward, OPS scores were determined hourly till home discharge. Rescue analgesia with morphine 0.05 mg/kg i.v. was administered, after operation; for OPS score ≥5 or if the patient requested analgesia during pain assessment and time elapsed till first request of rescue analgesia was determined.

Upon patient discharge, parents were asked to rate their satisfaction with patient analgesia on a 7-point scale; 1 being extremely dissatisfied and 7 being extremely satisfied[16]. All adverse events

*Table 2*
*Constituents Parameters of Aldrete score*

| Score | Respiration | Blood pressure | Activity | Consciousness | $O_2$ saturation |
|---|---|---|---|---|---|
| 2 | Able to breath deeply & cough freely | ±20% pre-operative value | Able to move 4 limbs voluntarily or on commond | Fully awake | >92% on air |
| 1 | Dyspnea or limited breathing | ±20-49% pre-operative value | Able to move 2 limbs voluntarily or on commond | Arousable on calling | >90% with $O_2$ supplement |
| 0 | Apnea | ±50% pre-operative value | Unable to move limbs voluntarily or on command | Not responding | <90% even with $O_2$ supplement |

*Table 3*
*Patients' demographic and operative data*

| Data | Group K1 | Group K2 | Group M1 | Group M2 | Total |
|---|---|---|---|---|---|
| Age (years) | 9.9±2.8 | 10.6±2.3 | 11±1.9 | 10.5±2.1 | 10.5±2.3 |
| Sex; M:F | 16:9 | 13:12 | 15:10 | 13:12 | 57:43 |
| Weight (kg) | 29.2±7.4 | 30.4±6.4 | 31.3±6.6 | 32±9.2 | 30.7±7.4 |
| Duration of surgery (min) | 35.2±9.4 | 39.2±10 | 33.7±8.1 | 36.1±8.8 | 36.1±9.2 |

Data are presented as mean±SD & ratios

including respiratory depression defined as ventilatory frequency of <10 breaths/min, $O_2$ saturation <90%, nausea or vomiting, and bleeding requiring assessment by the surgeon, were documented. Duration of hospital stay was determined and on discharge all patients were prescribed acetaminophen syrup 15 mg/kg orally 6 hourly as needed for analgesia at home.

## Results

All enrolled patients passed smooth intraoperative course without complication. The study included 100 patients; 57 males and 43 females with mean age of 10.5±2.3; range: 5-14 years and a mean weight of 30.7±7.4; range: 19-54 kg. Mean duration of surgery was 36.1±9.2; range: 19-56 minutes. There was a non-significant difference between studied groups regarding age, sex, weight or duration of surgery, (Table 3).
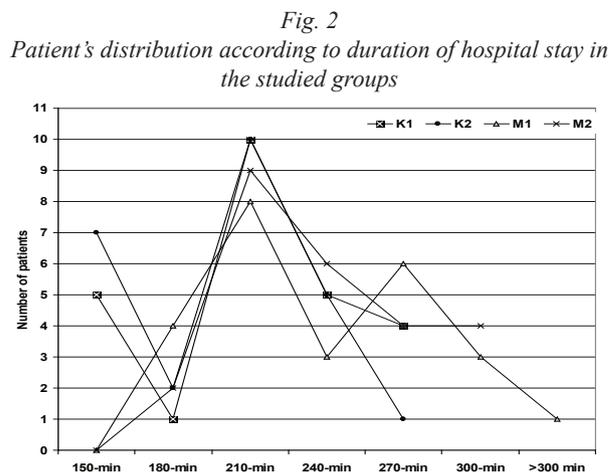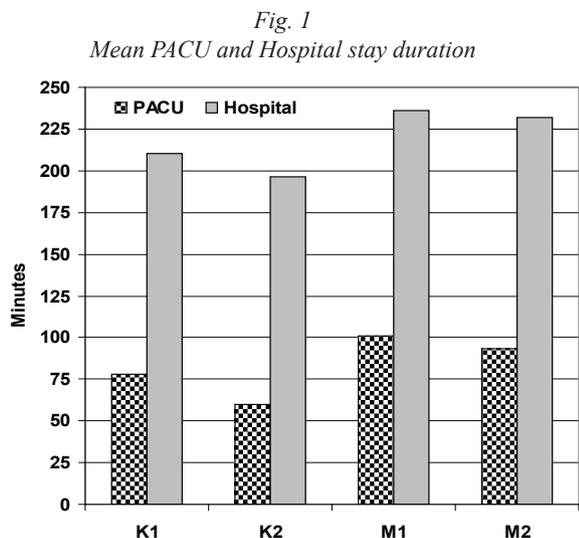
Mean duration of PACU stay was significantly shorter in group K2 compared to the other 3 groups and in group K1 compared to groups M1 and M2 with a non-significant difference between groups M1 and M2. Moreover, total hospital stay was significantly shorter in group K2 compared to groups M1 and M2 but was non-significantly shorter compared to group K1 and was significantly shorter in group K1 compared to group M1 and non-significantly shorter compared to group M2 with a non-significant difference between groups M1 and M2, (Table 4, Fig. 1).

*Table 4*
*PACU and Hospital stay data*

| | | Group K1 | Group K2 | Group M1 | Group M2 |
|---|---|---|---|---|---|
| PACU (minutes) | Mean±SD | 78.6±15.6 | 60±12 | 101.1±20 | 93.1±19.7 |
| | Z | | 3.997 | 3.808 | 2.354 |
| | $p_1$ | | <0.001 | <0.001 | =0.019 |
| | Z | | | 4.346 | 4.225 |
| | $p_2$ | | | <0.001 | <0.001 |
| | Z | | | | 1.583 |
| | $p_3$ | | | | >0.05 |
| Hospital (minutes) | Mean±SD | 210.2±41.3 | 196.2±37.9 | 236.3±49 | 231.6±43.6 |
| | Z | | 0.989 | 2.044 | 1.657 |
| | $p_1$ | | >0.05 | =0.041 | >0.05 |
| | Z | | | 2.859 | 2.694 |
| | $p_2$ | | | =0.004 | =0.007 |
| | Z | | | | 0.470 |
| | $p_3$ | | | | >0.05 |

Data are presented as mean±SD
$P_2$: significance versus group K2

$p_1$: significance versus group K1
$p_3$: significance versus group M1

*Fig. 1*
*Mean PACU and Hospital stay duration*



*Fig. 2*
*Patient's distribution according to duration of hospital stay in the studied groups*

Number of patients received ketamine injection only and had short hospital stay was significantly higher compared to those received meperidine with or without bupivacaine ($X^2$=5.928 & 5.244, respectively, p<0.01), but showed non-significant decrease compared to those received ketamine with bupivacaine, ($X^2$=1.22, p>0.05). Also, number of patients received injection of ketamine with bupivacaine and had short hospital stay was significantly higher compared to those received meperidine with or without bupivacaine ($X^2$=6.151 & 3.194, p<0.01 & <0.05, respectively). On contrary, number of patients received injection of meperidine with bupivacaine and had short hospital stay was non-significantly higher ($X^2$=0.528, p>0.05) compared to those received meperidine without bupivacaine, (Table 5, Fig. 2).

Mean OPS scores recorded throughout the observation period since PACU admission till discharge from the hospital showed progressive increase in all patients reaching a peak at 90-min after PACU

admission in groups K1, M1 and M2 and at 120-min after admission to PACU in K2 group, (Fig. 3).

Patients received ketamine with or without bupivacaine injection had non-significantly lower OPS scores compared to those received meperidine injection
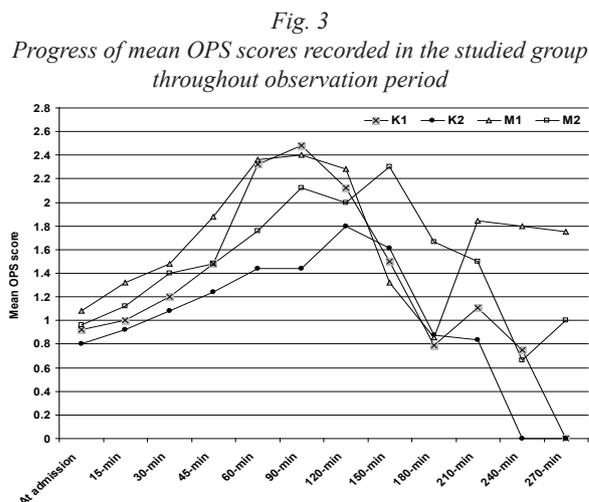
*Fig. 3*
*Progress of mean OPS scores recorded in the studied group throughout observation period*



*Table 5*
*Patients' distribution according to duration of hospital stay in the studied groups*

|          | 150-min  | 180-min  | 210-min   | 240-min  | 270-min  | 300-min  | >300 min |
|----------|----------|----------|-----------|----------|----------|----------|----------|
| Group K1 | 5 (20%)  | 1 (4%)   | 10 (40%)  | 5 (20%)  | 4 (16%)  | 0        | 0        |
| Group K2 | 7 (28%)  | 2 (8%)   | 10 (40%)  | 5 (20%)  | 1 (4%)   | 0        | 0        |
| Group M1 | 0        | 4 (16%)  | 8 (32%)   | 3 (12%)  | 6 (24%)  | 3 (12%)  | 1 (4%)   |
| Group M2 | 0        | 2 (8%)   | 9 (36%)   | 6 (24%)  | 4 (16%)  | 4 (16%)  | 0        |

*Table 6*
*OPS score data recorded throughout the observation period*

|  | Group K1 | Group K2 | Group M1 | Group M2 |
|---|---|---|---|---|
| At admission | 0.92±0.5 | 0.8±0.8 | 1.1±0.7 | 1±0.7 |
| 15-min | 1±0.6 | 0.9±0.9 | 1.32±1.1 | 1.1±0.9 |
| 30-min | 1.2±0.7 | 1.1±1 | 1.5±1.1 | 1.4±1.1 |
| 45-min | 1.5±1 | 1.2±1.2 | 1.9±1.2 | 1.5±1.2 |
| 60-min | 2.3±1.4† | 1.4±1.4 | 2.4±1.7† | 1.8±1.6 |
| 90-min | 2.5±1.6† | 1.4±1.3 | 2.4±1.9† | 2.1±1.8 |
| 120-min | 2.1±1.9 | 1.8±1.8 | 2.3±2.1 | 2±1.7 |
| 150-min | 1.5±1.8 | 1.6±1.9 | 1.3±2 | 2.3±2.1 |
| 180-min | 0.8±1 | 0.9±1.1 | 0.9±1.7 | 1.7±1.9 |
| 210-min | 1.1±1.2 | 0.8±1.3 | 1.8±1.3 | 1.5±1.7 |
| 240-min | 0.8±1 | 0 | 1.8±1.5 | 0.7±1 |
| 270-min | 0 | 0 | 1.8±1.2 | 0.8±1.4 |

Data are presented as mean±SD  
†: significant versus group K2  

$p_1$: significance versus group K1  
$p_3$: significance versus group M1

till 45-minutes after admission to PACU. At 60- and 90-minutes after admission to PACU patients received peritonsillar injection of ketamine with bupivacaine had a significantly lower OPS scores compared to those received ketamine or meperidine alone and non-significantly lower scores compared to those received meperidine with bupivacaine, (Table 6).

Mean parents' satisfaction scores reported in group K2 were significantly higher compared to that reported in groups K1 ($p_1$=0.021) and M1, ($p_2$=0.010) and were non-significantly higher compared to group M2, ($p_3$>0.05). On the other hand, the reported scores were non-significant among the other three groups despite being in favor of group M2, (Table 7, Fig. 4).

*Fig. 4*
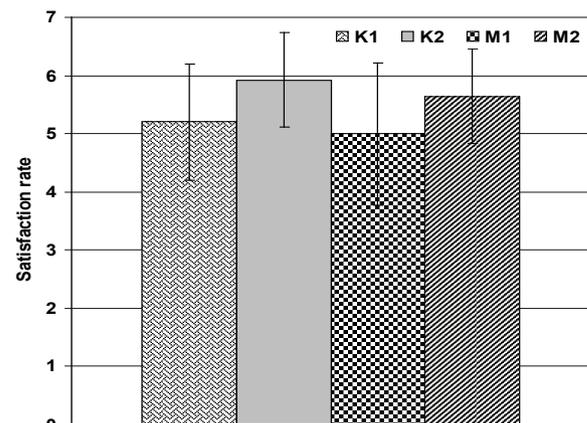*Mean (±SD Parent's satisfaction rates*



*Table 7*
*Mean (±SD) parents' satisfaction rates*

|  | Group K1 | Group K2 | Group M1 | Group M2 |
|---|---|---|---|---|
| Mean±SD | 5.2±1 | 5.92±0.8 | 5±1.22 | 5.6±0.8 |
| Z |  | 2.311 | 0.433 | 1.563 |
| $p_1$ |  | =0.021 | >0.05 | >0.05 |
| Z |  |  | 2.581 | 1.389 |
| $p_2$ |  |  | =0.010 | >0.165 |
| Z |  |  |  | 1.744 |
| $p_3$ |  |  |  | >0.05 |

Data are presented as mean±SD  
$P_2$: significance versus group K2  

$p_1$: significance versus group K1  
$p_3$: significance versus group M1

## Discussion

Tonsillectomy with or without adenoidectomy is one of the most commonly performed surgical procedures and the technique for performing tonsillectomy, dissection of all tonsillar tissue free of the underlying pharyngeal constrictor muscle, has not changed significantly in more than 60 years[17].

The most common serious complication of tonsillectomy is delayed hemorrhage, which occurs in 2% to 4% of all patients. In addition, an expected sequela of the procedure is pain, which typically lasts from 7 to 10 days and can be moderate to severe in intensity. This pain can affect the patient's nutrition, ability to return to work or school, discharge from the hospital, and overall satisfaction with the procedure[18]. Moreover, *Alhamarneh et al.*[19], reported a significantly greater than normal secondary haemorrhage rate in patients who had undergone tonsillectomy or adenotonsillectomy and did not receive adequate analgesia and concluded that adequate analgesia, for the first week post-tonsillectomy, is essential in order to keep the secondary haemorrhage rate within an acceptable range.

Pain intensity was found to be unrelated to used technique for tonsillectomy; *D'Agostino et al.*[20], compared operative time, intraoperative and postoperative bleeding and pain using two different techniques for tonsillectomy: electronic molecular resonance bipolar tonsillectomy and blunt dissection tonsillectomy and this study showed that concerning postoperative pain, the two techniques did not present significant differences in the use of analgesics.

Several techniques have been described for the alleviation of this pain, including the use of opioids, steroids, and nonsteroidal antiinflammatory drugs, as well as local anesthetic sprays and infiltration with local anesthetics around the tonsillar bed[21], and the current was designed to assess post-tonsillectomy analgesic efficacy of pre-emptive peritonsillar ketamine infiltration with or without bupivacaine in comparison to meperidine alone or in combination with bupivacaine.

Preemptive peritonsillar ketamine injection improved tonsillectomy outcome as manifested by significantly shorter duration of PACU and hospital stay and significantly lower OPS scores coupled with significantly higher parents' satisfaction rate compared to meperidine. Such effect was significantly manifested in patients administered ketamine-bupivacaine than in those received ketamine alone.

These findings agreed with *Dal et al.*[22], evaluated the effects of peritonsillar infiltration versus intravenous injection of ketamine in children undergoing adenotonsillectomy and reported that low dose (0.5 mg/kg) ketamine given i.v. or by peritonsillar infiltration perioperatively provides efficient pain relief without side-effects in children undergoing adenotonsillectomy and with *Erhan et al.*[23], who reported that the used dose of ketamin (0.5 mg/kg) caused no sedation or nausea and provided a high level of analgesia and concluded that ketamine infiltration into the tonsillar region after tonsillectomy was found to be easy and effective.

Also, *Honarmand et al.*[24], who assessed the efficacy of preincisional peritonsillar infiltration of two doses of ketamine on postoperative pain relief compared with peritonsillar saline in children undergoing adenotonsillectomy and reported that 0.5 or 1 mg/kg dose of ketamine provides efficient pain relief during 24 h after surgery without side-effects in children undergoing adenotonsillectomy. Also, the obtained results goes in hand with *Canbay et al.*[25], who tried to evaluate the potential effects of topically administered ketamine and morphine by an oral rinse into the tonsillar fossae and reported higher pain scores in the control group at arrival in the recovery ward with longer effective analgesia in morphine-ketamine group compared to either drug alone and to control group and concluded that topical ketamine and morphine seems to be a safe and easy analgesic approach for decreasing adenotonsillectomy pain.

However, the obtained results in the current study were superior to that reported by both *Honarmand et al.*[24], and *Canbay et al.*[25], in that both authors compared their study group versus placebo and surely the study drugs will be more effective, while in the present study the comparison was versus a well-settled analgesic drugs; bupivacaine and meperidine. Moreover, the obtained results in the present study were superior to that reported by *Canbay et al.*[25] in that both ketamine and morphine had central analgesic effect, while

bupivacaine had no central effect so the effect of the combination of ketamine-bupivacaine lacks this central effect and points to the local effect of such combination.

The obtained data illustrate a fact that the beneficial effects of ketamine are multi-factors; firstly, the preemptive injection which the concept of providing analgesia before surgical incision resulting in less postoperative pain, such attribution agreed with *Kwok et al.*[26], who reported that a small preoperative dose of ketamine produced preemptive analgesia with no significant hemodynamic and psychological side effects after gynecologic laparoscopic surgery and with *Kitamura et al.*[27], who found preoperative ketamine may elicit preemptive analgesic effects, and can be an efficient adjuvant to postoperative pain management for patients undergoing laparotomy.

The reported preemptive analgesic effect of peritonsillar ketamine injection could be attributed to its modulatory effect on the local release of nocieptive pro-inflammatory cytokines during incision and dissection. This explanation goes in hand with results of the experimental work of *Yu et al.*[28], who reported that ketamine suppressed injury induced TNF-alpha and IL-6 production, NF-kappaB activity, Toll-like receptor 2 (TLF 2) and TLF 4 expression in rat. Also, *Zhu et al.*[29], found local delivery of aerosolized ketamine markedly suppressed allergen-mediated airway hyperreactivity, airway inflammation and airway inflammatory cell infiltration into the BALF,

and significantly decreased the levels of interleukin-4 and expression of iNOS and the concentration of NO in the inflamed airways from OVA-treated rats. Moreover, *Wu et al.*[30], found that a clinically relevant concentration of ketamine can inhibit TNF-alpha and IL-6 gene expressions in activated macrophages and the suppressive mechanisms occur through suppression of TLR4-mediated sequential activations of c-Jun N-terminal kinase and activator protein-1.

Secondly, the reported significantly improved outcome with ketamine-bupivacaine combination versus ketamine alone points to a synergistic or additive effect of both drugs to achieve such superior outcome. In support of this assumption, *Unal et al.*[31], found peritonsillar bupivacaine infiltration is, however, insufficient to control postoperative pain. Also, *Locatelli et al.*[32], reported that the addition of 0.5 mg/kg ketamine to levobupivacaine 0.175% for caudal analgesia for lower abdominal and urological surgery is significantly more effective in providing postoperative analgesia than levobupivacaine 0.2%.

It could be concluded that peritonsillar injection of a combination of bupivacaine and ketamine provided efficient postoperative analgesia after adenotonsillectomy and achieved higher parents' satisfaction for the outcome of surgery. The used drugs' combination and volume could be recommended as a routine preemptive analgesic policy for children assigned for adenotonsillectomy.

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