COMBINATION OF ORAL KETAMINE AND MIDAZOLAM VERSUS MIDAZOLAM ALONE AS A PREMEDICATION IN CHILDREN UNDERGOING TONSILLECTOMY.

Mohamed E. Rabie MD
Lecturer of Anaesthesia, Faculty of Medicine, Menoufeya University.

ABSTRACT

***Background & Objectives**: Premedication with oral midazolam is a common practice in paediatric anaesthesia. Combining oral ketamine to midazolam has been tried with different dosing regimens and proved to give good results. The aim of this study was to compare the combination of oral ketamine and midazolam to oral midazolam alone as regard sedation and postoperative pain relief.*

***Patients and methods**: A prospective randomized double-blind study was carried out in 60 children who were randomly allocated into two groups. Group M received 0.5 mg.kg^{-1} oral midazolam and group MK received 0.25 mg.kg^{-1} oral midazolam with 4 mg.kg^{-1} oral ketamine as a premedication 20 minutes preoperatively. A five points-sedation score (1 asleep to 5 agitated) on arrival to the operating room and a three points-acceptance score of separation from the parents and a three points-mask cooperation score at induction of anesthesia (1 easy to 3 markedly resistant) were used. The time to recovery from anesthesia and to achieve satisfactory Aldrete score was recorded. Time to supplementary analgesia defined as achieving a pain score of 4 or more was used to compare the two groups. At 30 min, 1, 2, & q4h postoperative, pain score was recorded by a blinded observer. Pain was treated with morphine 25 ug.kg^{-1} intravenously for pain score more than 4, and cumulative morphine consumption in 24hrs was used to compare postoperative analgesic requirements in both groups.*

***Results**: Acceptable sedation scores were seen in both groups, without any serious side effects. However, the combination of Ketamine and Midazolam offered significantly more children in an awake, calm and quiet state, who were easily separated from their parents. The separation and cooperation scores were comparable between the groups. The time to recovery from anaesthesia and time to achieve satisfactory Aldrete score were also comparable between the two groups. Time to supplementary analgesia was significantly prolonged in the KM group than in the M group. Total morphine consumption was significantly less in the KM group than in the M group.*

***Conclusion**: Adding oral Ketamine to midazolam as a premedication in children provides good quality of sedation and decreases post operative analgesic requirements after tonsillectomy.*

***Keywards:** Midazolame, Ketamine, Premedication, Paediatrics, Tonsillectomy.*

INTRODUCTION

Preanaesthetic medication in pediatric anaesthesia should allay anxieties about surgery, parent separation and pain. It should also allow a smooth induction of anaesthesia without delayed recovery. Midazolam, with its favorable pharmacodynamics, (i.e. rapid onset, relatively short duration of action and lack of significant side effects)[1], and pharmacokinetics is among the most popular pediatric premedicant in Europe and USA[2,3]. However good to excellent results are seen in only 60–80% of cases[1,4].

Recently, several investigations demonstrated a significant improvement in sedation and separation scores after premedication with a combination of ketamine and midazolam[5,6].The addition of different doses of ketamine to oral midazolam has been tried and found to have varying results on the success rate of premedication with low but variable side effect profile[5,7].

Tonsillectomy is a common pediatric surgical procedure associated with significant postoperative pain that is a challenge to treat. Inadequate pain management after tonsillectomy may result in poor oral intake, dehydration, sleep disturbances, behavioral changes, and emesis. Although opioids may provide sufficient analgesia, they are associated with respiratory depression, which can be detrimental to the patient with obstructive airway disease. In addition, opioids are associated with an increased incidence of postoperative nausea and vomiting (PONV) in children. Ketamine was shown to be effective against postoperative pain relief

when administered as intravenous agent induction for tonsillectomy[8] and it has the potential to preserve upper airway tone and respiratory drive[9]. However, to date, there have been no investigations examining the influence of ketamine in combination with midazolam as an oral premedication on postoperative pain after tonsillectomy.

The purpose of the current study was to compare combination of oral ketamine and midazolam to oral midazolam alone as regard sedation and postoperative pain relief after tonsillectomy.

PATIENTS & METHODS

After approval from the hospital ethics committee, and informed parental consent, 60 children of physical status ASA I and II, aged between 3 and 8 years, scheduled to undergo tonsillectomy with or without adenoidectomy were enrolled in this prospective randomized double blinded study. The exclusion criteria included children with neurological dysfunction, increased intracranial pressure, anomalies of cardiovascular system, and long-term therapy with hepatic enzyme-inducing drugs. Children were allocated to one of the two equal groups, using a closed envelop technique. Group M received 0.5 $mg.kg^{-1}$ oral midazolam and group KM received 4 $mg.kg^{-1}$ oral ketamine with 0.25 $mg.kg^{-1}$ oral midazolam. Both the medications were mixed in 5ml cherry or orange juice according to the child preference by a pharmacist not involved in the study and administered to the children by their parents approximately 20 minutes prior to the induction under supervision. The pre-operative sedation score, the ease of parental separation, and the ease of mask acceptance were each evaluated (Table 1).[10]. Scores 2 and 3 in the sedation score were defined as 'effective', and score 3 for separation from the parents and mask cooperation at the induction of anaesthesia was defined as 'poor'. Patients with sedation score 5, separation score 3, or mask cooperation score 3 were given 3$mg.kg^{-1}$ intramuscular ketamine and excluded from the study for postoperative pain relief.

Anaesthesia was induced with sevoflurane in 100% oxygen administered via the mask and breathing circuit. Appropriate sized intravenous catheter was then inserted and muscle relaxation was achieved with atracurium besylate 0.5 $mg.kg^{-1}$. The trachea was intubated with an appropriate sized tracheal tube. Fentanyl 1 $ug.kg^{-1}$ was given for analgesia. Anaesthesia was maintained with sevoflurane (1-3%) in oxygen 40% titrated to clinical response. All patients received dextrose 5% in 0.2% NaCl intravenously 2-4 $ml.kg^{-1}$. Monitoring consisted of electrocardiogram, automated noninvasive blood pressure measurement, pulse oximetry, and endtidal carbon dioxide analysis. Surgery was carried out by the same surgeon using the same surgical technique. At the end of surgery sevoflurane was discontinued and residual neuromuscular blockade reversed with neostigmine 0.05 $mg.kg^{-1}$ and glycopyrolate 0.01 $mg.kg^{-1}$. The trachea was extubated when the child had resumed spontaneous ventilation and the gag reflex had returned. The length of the surgical procedure and anaesthesia, and the time interval between discontinuation of anaesthesia and arousal (spontaneous ventilation, extubation) were recorded. The time interval between end of surgery and discharge from the recovery room were also recorded. Postanaesthetic recovery was assessed using the Aldrete score[11], with discharge from the recovery unit requiring an Aldrete score of 9.

Time to supplementary analgesia defined as achieving a pain score of 4 or more was used to compare the two groups. Paracetamol 15 $mg.kg^{-1}$ rectally was given to all patients q4hrs. At 30 min, 1, 2, &q4hrs for 24hrs postoperative pain score was recorded by a blinded observer. A modification of the pain score scale originally described by Hannallah et al. was utilized[12]. This allowed for a maximum score of 10 and a minimum 0. The modification was to allow observation and scoring of pain on swallowing water as opposed to pain on movement (Tables 2). Pain was treated with morphine 25 $ug.kg^{-1}$ intravenously for pain score more than 4 every time pain score was measured, and cumulative morphine consumption in 24hrs was used to compare postoperative analgesic requirements in both groups. The presence of vomiting and any emergence phenomena were also noted.

Table (1): The scoring system for assessments of premedication in children

Five points-sedation score	
Asleep, not readily arousable	1
Asleep, but arousable	2
Calm but awake	3
Restless	4
Agitated	5
Score for acceptance (separation from parents	1
Easy	2
Slightly resistant	3
Markedly resistant	
Mask acceptance score	
Easy	1
Slightly resistant	2
Markedly resistant	3

Table (2): Pain scoring system

Crying	
Non	0
Consolable	1
Inconsolable	2
Movement	
Non	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 non	0
Can not localize	1
Localizes	2

Statistical analysis

Results were expressed as mean ± SD, analyzed using tests of significance to identify the variables significantly to differences in different groups: Student t-test, and Chi square test were used. Statistical significance was considered at the level of $p<0.05$

RESULTS

There were no statistically significant differences between both groups as regards age, weight, gender, duration of surgery, duration of anesthesia, time to extubation, and time to discharge from the recovery room (Table 3).

On arrival to the operation room two patients (6.7%) in group M were asleep, not arrousable, while only one patient (3.3%) was asleep in group KM with no statistically significant difference between both groups.27 patients (90%) in group M had a score of 2 or 3 considered as effective sedation, while 28 patients (93.3%) in group KM had a score of 2 or 3 with no statistically significant difference between both groups. 12 patients (40%) of group KM were awake, calm (sedation score 3), and easy separable from their parents While only 5 patients (16.7%) in group M had a sedation score of 3 with a statistically significant intergroup difference.

There were no statistically significant differences between both groups as regards parental separation, and mask cooperation scores. Only one patient in each group (3.3%) was considered poor separation score while two patients were considered poor mask cooperation score in group M compared to one patient in group KM.

Time to supplementary analgesia was 18.67±7.42, and 31.33±10.42 minutes in group M, and KM respectively, which was significantly prolonged in the KM group (Figure 1), and cumulative morphine consumption was 143.33±28.57, and 111.67±35.19 ug in group M, and KM respectively, it was significantly less in KM group (Figure 2).

There were two cases of vomiting in each, they were self limited required no pharmacological interference. There were no reported cases of emergence agitation in both studied groups.

DISCUSSION

Premedication is widely used in paediatric anaesthesia in order to provide sedation, anxiolysis, and reduction in emotional trauma and to facilitate smooth induction. Reports have indicated that both oral midazolam[1,4,13,14] and oral ketamine fulfill many of the desirable characteristics of an ideal premedicant[15,16]

To overcome the drawbacks and disadvantages when midazolam or ketamine is used alone, combinations of both drugs in different doses have been

tried to improve sedation, and success rate of premedication, but the results had shown marked variations[5,17]. In this study the plan was to compare the efficacy of oral midazolam 0.5 $mg.kg^{-1}$**,** which is commonly used in our hospital, with a combination of oral ketamine 4$mg.kg^{-1}$and 0.25 $mg.kg^{-1}$ midazolam**.** Ketamine-alone group was not included in the study as oral ketamine, when used alone may produce variable anxiolytic results when used in low dosages and associated with psychomimetic[6,17,18], and sympathomimetic side effects[6,18] as well as vertigo and emesis at higher dosages[16].

Table (3): Demographic data, duration of anesthesia, and surgery, and time to extubation ,and to discharge from the recovery room of the two studied groups.

	Group M	Group KM	P
Age (years)			
Mean±S.D.	4.65±1.92	4.05±1.70	0.102
Weight (KG)			
Mean±S.D.	16.92±3.85	15.85±3.67	0.13
Gender			
Male	11 (36.37%)	12 (40.0%)	0.32
Female	19 (63.3%)	18 (60.0%)	
Duration of anesthesia (min)			
Mean±S.D.	50.23±11.73	54.03±13.33	0.12
Duration of Surgery (min)			
Mean±S.D.	24.80±9.95	27.00±9.97	0.19
Time to extubation (min)			
Mean±S.D.	12.03±3.55	11.60±3.42	0.35
Time to Discharge from RR (min)			
Mean±S.D.	50.67±20.03	46.67±18.59	0.212

*****significant (p<0.05)

Table (4): Sedation score, parental separation score and mask cooperation score in the two studied groups.

	Group M		Group KM		p
	No.	%	No.	%	
Sedation score					
1	2	6.7	1	3.3	-
2	22	73.3	16	53.3	0.06
3	5	16.7	12	40.0	0.02*
4&5	1	3.3	1	3.3	
Parental separation score					
1	24	80.0	22	73.3	0.52
2	5	16.7	7	23.3	0.109
3	1	3.3	1	3.3	-
Mask cooperation score					
1	22	73.3	21	70.0	0.3
2	6	20.0	8	26.7	0.21
3	2	6.7	1	3.3	-

*****significant (p<0.05)

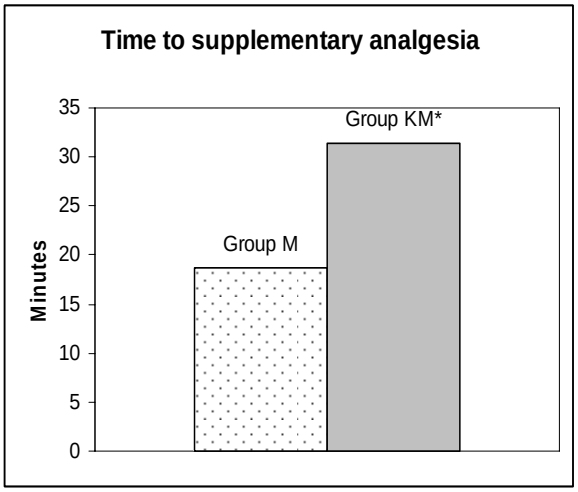

Figure 1. Time to supplementary analgesia (Minutes)
*****significant (p<0.05)

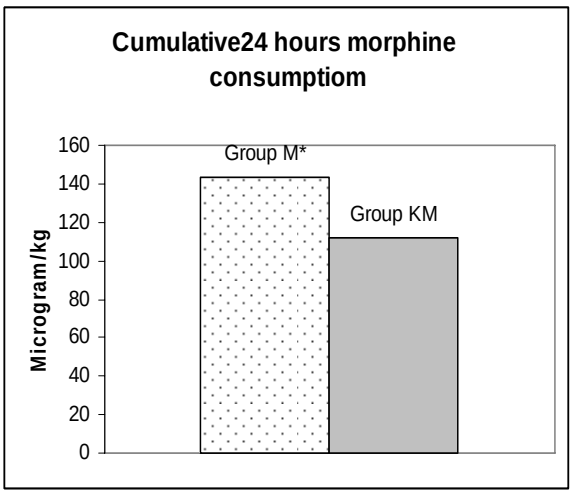

Figure 2. Cumulative 24 hours morphine consumption (ug/ kg)
*****significant (p<0.05)

Beebe et al.[5] compared a combination of rectal midazolam 0.5 mg.kg^{-1} and rectal ketamine 3 mg.kg^{-1} with either drug alone. They reported satisfactory parental separation in 92%cases with midazolam and in 100% with combination but in only 60% with the ketamine-alone group. Complications were low and similar between the groups. Similar results were obtained by Warner et al.[19] who found that a mixture of midazolam 0.4 mg.kg^{-1} and ketamine 4 mg.kg^{-1}, is more effective than midazolam 0.5 mg.kg^{-1} or ketamine 6 mg.kg^{-1} when used alone. Babita et al,[20] compared oral midazolam 0.5 mg.kg^{-1} and a low dose combination of midazolam 0.25 mg.kg^{-1} with ketamine 2.5 mg.kg^{-1} acceptable sedation scores were seen in both groups (95.9% in midazolam group, 97.96% in the combination group). More children (46.93%) in the combination group compared with midazolam group (20%) were awake, calm, and quiet. Both groups were equally effective in relation to parental separation, mask acceptance and recovery room characteristics. In the current study there were acceptable sedation scores in both groups (90% in M group, and 93.3% in KM group), while 40% of children were calm and awake(score 3) easily separable from their parents in the KM group, only 16.7% of children in group M were calm and awake which is similar to Babita et al results then can be of great value to children with airway obstructive symptoms where complication of deep sedation such as loss of airway control, hypoxia, etc. should be avoided. Parental separation, and mask cooperation scores, time to extubation, and time to discharge from the recovery room were also acceptable without significant difference between both groups.

Funk et al. compared a combination of oral ketamine 3 mg.kg^{-1} and midazolam 0.5 mg.kg^{-1} with oral midazolam 0.5 mg.kg^{-1} or ketamine 6 mg.kg^{-1} alone[6]. In their study they separated sedation, and separation scores into success (score 3 and 4) and no success (score 1 and 2). Success rates for sedation and separation were >90% with the combination, approximately 70% with midazolam and only 51% with ketamine alone. The success rate for sedation was low in all the groups. However, the sedation score used in their study classified an awake state (score 2) as no success. The awake state should not be considered as a disadvantage as long as successful separation coincides with good anxiolysis. In fact, an awake state is an additional advantage. They reported low incidence of side effects in all the groups; however, vertigo and emesis before induction was significantly higher in the ketamine-alone (6 mg.kg^{-1}) group.

Aspinall and Mayor[21] found that Ketamine 0.5 mg.kg^{-1} given at induction provided similar postoperative analgesia as i.v morphine 0.1 mg.kg^{-1}. In another, similarly designed study, Marcus et al.[22] compared the effects of intramuscular ketamine with morphine for postoperative

analgesia in children undergoing tonsillectomy and they found that there were no differences in supplemental analgesia requirements or side effects between the groups. Elhakim et al.[23] showed a in a randomized, placebo controlled trial that premedication with low dose ketamine 0.1 $mg.kg^{-1}$ intramuscularly before tonsillectomy improved postoperative analgesia, swallowing and oral intake during the first postoperative day. This analgesic effect can be explained as ketamine is known to be N-methyl-D-Aspartate (NMDA) receptor antagonist[24]. NMDA receptors have been postulated to play a crucial role in the development of central sensitization after noxious peripheral stimulation[25]. Afferent noxious stimuli stimulate the release of excitatory amino acids in the dorsal horn of the spinal cord, in particular glutamate, which activates NMDA receptors. Activation of NMDA receptors leads to opening of voltage-dependent calcium channels, allowing calcium entry into the cell. This mechanism is thought to be significant in the development of 'wind-up' of the CNS such that there is subsequent hyperalgesia at the original site of peripheral stimulation[25]. Sensitization of the CNS is thought to play an important role in determining the degree of postoperative pain. Effective blockade of this CNS 'wind-up' could be tremendously valuable to postoperative pain management in surgical patients[26]. Ketamine also reported to be targeting other receptors, but are probably not greatly relevant at plasma levels attained in the clinical setting[9].

O'Flaherty & Lin[27] did not demonstrate a decrease in pain or analgesic consumption in pediatric patients undergoing tonsillectomy when pretreated with a single does of 0.15 $mg.kg^{-1}$ ketamine and/or 30 $mg.kg^{-1}$ magnesium sulfate. The authors attributed these results to multiple factors, the most important of which were, insufficient dose of ketamine, and the difficulty of pain assessment in children particularly young children.

In conclusion the combination of Ketamine 4 $mg.kg^{-1}$ to midazolam 0.25 $mg.kg^{-1}$as a premedication in chilidren undergoing tonsillectomy is equally effective and safe as midazolam 0.5 $mg.kg^{-1}$ in relation to sedation, parental separation, mask cooperation, and recovery room characteristics. However, the combination produces more children in a calm, awake, and quiet state who are easily separated from parents and have good mask acceptance. Further, the addition of ketamine provides postoperative analgesia and decreases the 24 hours postoperative morphine consumption.

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