Comparative Analysis of Preoperative Sedation Modalities: Oral Midazolam and Ketamine Versus Chloral Hydrate and Meperidine in Pediatric Tonsillectomy - A Randomized Clinical Trial

Original Investigation

Nima Naderi, Soodabeh Emami, Mahsa Banifatemi, Maryam Ghadimi, Ensieh Shahriari, Mohammad Ali Sahmeddini

Shiraz University of Medical Sciences, Anesthesiology and Critical Care Research Center, Shiraz, Iran

Abstract

Objective: A pre-anesthetic medication that is ideal for pediatric patients undergoing tonsillectomy should alleviate pediatric anxiety, facilitate the smooth induction of anesthesia, and have an analgesic effect for postoperative care. This study compared the effectiveness of an oral combination of midazolam and ketamine (MK) with an oral combination of chloral hydrate and meperidine (CM) as premedication in pediatric patients undergoing tonsillectomy.

Methods: This double-blind clinical trial study was conducted with 68 pediatric patients scheduled to undergo tonsillectomy. The participants were randomly allocated into two groups: the CM group, which received oral premedication of 50 mg/kg chloral hydrate and 1.5 mg/kg meperidine, and the MK mixture group, which received oral premedication of 0.5 mg/kg midazolam and 5 mg/kg ketamine. Various parameters such as separation anxiety, agitation during emergence from anesthesia, postoperative pain, postoperative nausea, and vomiting, as well as respiratory depression within a 6-hour period following anesthesia, were carefully recorded and observed.

Results: There were no differences between the two groups in terms of separation anxiety (p>0.05) and post-surgery pain scores (p=0.12). Regarding postoperative agitation, there were significantly more patients in an awake but calm state in the CM group than in the MK (44% vs. 17.64%, p=0.01). The incidence of nausea and vomiting was lower in the CM than in the MK group (47% vs. 76.5%, p=0.02).

Conclusion: This study shows that an oral mixture of CM is more suitable as pre-anesthetic medication in pediatric patients undergoing tonsillectomy than a MK.

Keywords: Tonsillectomy, pediatric, anesthesia, premedication, midazolam, ketamine, chloral hydrate, meperidine

ORCID IDs of the authors:

N N 0000-0002-5041-2674
S E 0000-0003-3854-724X
M B 0000-0002-3350-5051
M G 0000-0003-2621-7390
E S 0000-0003-0562-5926
M A S 0000-0003-1510-0103

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Corresponding Author:
Mohammad Ali Sahmeddini;
sahmeddini@sums.ac.ir

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Introduction

Preanesthetic medication in children should aim to alleviate anxiety and promote a smooth and peaceful separation from their parents (1, 2). In addition to its primary objectives, another crucial aim of pre-anesthetic medication before tonsillectomy is to provide effective analgesia post-surgery. Insufficient analgesia following

tonsillectomy can lead to behavioral alterations, restlessness, and vomiting, and may impede the resumption of oral intake (3). A wide range of drugs, administered through various routes such as oral, intramuscular, and intravenous, are presently approved and employed for pre-anesthetic medication in children (4). In context of ambulatory surgeries like tonsillectomy, the optimal choice for premedication in pediatric patients would be a drug that offers prompt and consistent efficacy, minimal adverse effects, and rapid elimination from the body (5, 6). Nevertheless, there is no single drug available that satisfies all of these criteria completely. Furthermore, oral administration is preferred over other routes of administration in pediatric patients as it is non-traumatic and generally more well-received by children (7).

An assortment of drugs, including barbiturates, opioids, benzodiazepines, and ketamine, have been employed as premedication options in pediatric tonsillectomies (8). Certain studies have indicated that a combination of ketamine and midazolam might meet the aforementioned criteria. However, other studies have noted that ketamine could induce prolonged sedation despite its effectiveness in providing satisfactory postoperative analgesia (9-12). In a separate study conducted in pediatric dentistry, a combination of midazolam and meperidine produced favorable outcomes (13). Chloral hydrate is another sedative drug commonly utilized. It is considered safe and exhibits rapid efficacy in alleviating anxiety. However, it lacks analgesic properties, making it less suitable as an ideal premedication option for pediatric tonsillectomy (14, 15). While opioids offer a satisfactory analgesic effect, they pose significant risks, including respiratory depression. Moreover, opioids contribute to an increased occurrence of postoperative nausea and vomiting (PONV), which can be detrimental to pediatric patients undergoing tonsillectomy (16).

The objective of this study was to assess and compare the effectiveness of an oral combination of midazolam and ketamine (MK) versus an oral combination of chloral hydrate and meperidine (CM) as premedication in pediatric patients undergoing tonsillectomy. The primary goals included evaluating the level of sedation before anesthesia and examining postoperative agitation and analgesia. Additionally, the secondary objectives encompassed investigating the potential side effects of the drugs, such as PONV, respiratory depression, and prolonged sedation in the recovery room.

Methods

This randomized clinical trial was designed as a single-center, double-blind, and parallel-group study, utilizing block randomization. The study was duly registered in the Iranian Registry of Clinical Trials (IRCT2015111611662N8) (https://www.irct.ir/trial/11836) and received approval from the Shiraz University of Medical Sciences Ethics Committee (IR.sums.med.rec.1394.351). The research was conducted at Khalili Hospital's operating theater in Shiraz, Iran, from January 2016 to February 2017. The purpose and objectives of the study were thoroughly explained to the parents of the participating children, and written informed consent was obtained from the parents before their inclusion in the trial.

The participants in this study comprised pediatric patients aged 3-7 years, classified as American Society of Anesthesiologists were scheduled for elective tonsillectomy surgery under general anesthesia. Exclusion criteria were applied, and patients were ineligible if they had a history of congenital cardiopulmonary disorders, known allergic reactions to the study drugs, a history of convulsions, brain tumors, high intracranial pressure, hepatic or renal disorders, gastritis, recent use of anxiolytic medications within the past 48 hours, acute upper respiratory tract infection, or if they were undergoing adenotonsillectomy.

In a preoperative holding area, patients received preoperative anesthesia 30 minutes before going into the operating theater. The CM group received chloral hydrate (100 mg/mL) 50 mg/kg and meperidine1.5 mg/kg (10 mg/mL) diluted in cherry juice to a total volume of 5 mL, and the MK mixture group received midazolam (5mg/mL) 0.5 mg/kg and ketamine (50mg/mL) 5 mg/kg diluted in cherry juice to a total volume of 5 ml. These mixtures were administered in syringes identical in appearance that had been labeled either A or B and were prepared by a nurse anesthetist not participating in the study. The patients and the research assessor were not aware of the contents of either syringe.

When the children were separated from their parents to prepare for entering the operating theater, separation anxiety of the children was assessed by a resident of anesthesia who was blinded to study groups, according to a scale of 1=Violent movement, 2=Crying, 3=Full awake-calm, 4=Asleep (17). Separation anxiety was the primary outcome of this study.

When the child was laid down in the operating room, and after the attachment of standard monitors (EKG, noninvasive blood pressure monitor, and pulse oximetry), an angiocatheter No. 22 was inserted. Anesthesia of midazolam 0.03 mg/kg, fentanyl (10mcg/mL) 2 mcg/kg, propofol (10mg/mL) 2 mg/kg, and atracurium (10mg/mL) 0.6 mg/kg was administered through the angiocatheter, then tracheal intubation was performed with a suitable size tracheal tube. Anesthesia was maintained with O_2/N_2O (50%/50%) and isoflurane with controlled ventilation. At the end of the operation, the muscle relaxant was reversed with an appropriate dose of neostigmine 0.15mg/kg with atropine 20 mic/Kg, when the patient had spontaneous eye-opening and good muscle strength, tracheal extubation was performed. Then the child was transported to the post anesthesia care unit (PACU).

Five minutes after arriving in the PACU, the emergence of agitation was evaluated by a blinded examiner to the study groups with this scale: 1=severely agitated and difficult to comfort, 2=agitated, 3=asleep, 4=awake but calm (17). Emergence agitation was a secondary outcome of the study.

Other secondary outcomes included: postoperative pain assessed with the Baker-FACES pain scale (18) (Figure 1); PONV recorded according to a scale of 0=no nausea or vomiting, 1=nausea only, and 2=retching and vomiting (19). Also, respiratory rate was recorded, and respiratory depression was defined as a respiratory rate of less than eight breaths per minute. These second outcomes were recorded up to six hours after surgery. Also, if a VAS score higher than 4 was observed, 0.1 mg/kg of morphine was injected.

Sample Size

The sample size was estimated by setting postoperative agitation as the primary outcome. Assuming the routine premedication (midazolam) success rate was 50%, we calculated that 34 patients in each group would be sufficient to detect an achieved 90% success rate on the postoperative agitation at an alpha threshold of 0.05 with 90% power and 30% dropouts. Eligible patients using the block randomization method (www.sealedenvelope.com) were allocated to the groups in 11 blocks of size 4 and 8. The name of each patient's group was written and prepared in sealed envelopes by a single staff member who had access to the randomization list.

Statistical Analysis

Data were analyzed using SPSS 21 (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and GraphPad Prism version 9.00 for Windows, (GraphPad Software, Boston, Massachusetts USA), Continuous variables were reported as mean±SD, and independent sample t-test and Mann-Whitney U test were used for analyzing continuous variables. Categorical variables were reported as numbers and percentages, and the chi-square test and Fisher's exact test were used to test the difference in categorical outcome variables. A repeated measure ANOVA test was used for the data obtained over time. P-values less than 0.05 were considered statistically significant and the Bonferroni correction was used for p-values if needed.

Results

Of the 90 pediatric patients aged 3 to 7 years old scheduled for just tonsillectomy surgery from January 2016 to February 2017, a total of 22 patients were excluded from the study due to pulmonary disorders (n=2), a definite diagnosis of convulsion disorder (n=5), presence of congenital heart disease (n=3) and acute upper respiratory tract infection (n=9), or declined to participate (n=3). Thus, a total of 68 patients were enrolled in the study and were randomly allocated into two intervention groups (Figure 2).

Table 1 shows the demographic characteristics data of patients. There were no significant differences in age (p=0.18), weight (p=0.34), sex (p=0.55), duration of anesthesia (p=0.21), and surgery duration (p=0.32) between the two groups (p>0.05).

The comparison of separation anxiety scores in Table 2 shows that there was no significant difference in separation anxiety scores between the groups (p>0.05). For clarity, each condition is accompanied by its corresponding p-value: sleep (p=0.42), fully awake and calm (p=0.80), crying (p=0.49), and violent movement (p>0.99).

Furthermore, there were no significant differences in the postoperative agitation scores for asleep (p=0.80), agitated (p=0.33), and severely agitated difficult-to-comfort (p>0.99) statuses between the two groups (p>0.05). Only the number of patients who were awake but in a calm state was higher in the CM group than the MK group (44% vs. 17.64%, p=0.01) (Table 3).

Comparison of the incidences of nausea and vomiting between the groups over time after the operation showed that the time effect (p=0.21) and interaction between time and groups (p=0.84) were not significant (p>0.05). Only the group effect was significant (p=0.02) (Figure 3).

In the cumulative analysis of PONV between the groups, it was found that the CM group had a lower PONV with an incidence of 47% compared to the MK group, 76.47% (p=0.02).

Figure 1. The Baker-FACES pain scale

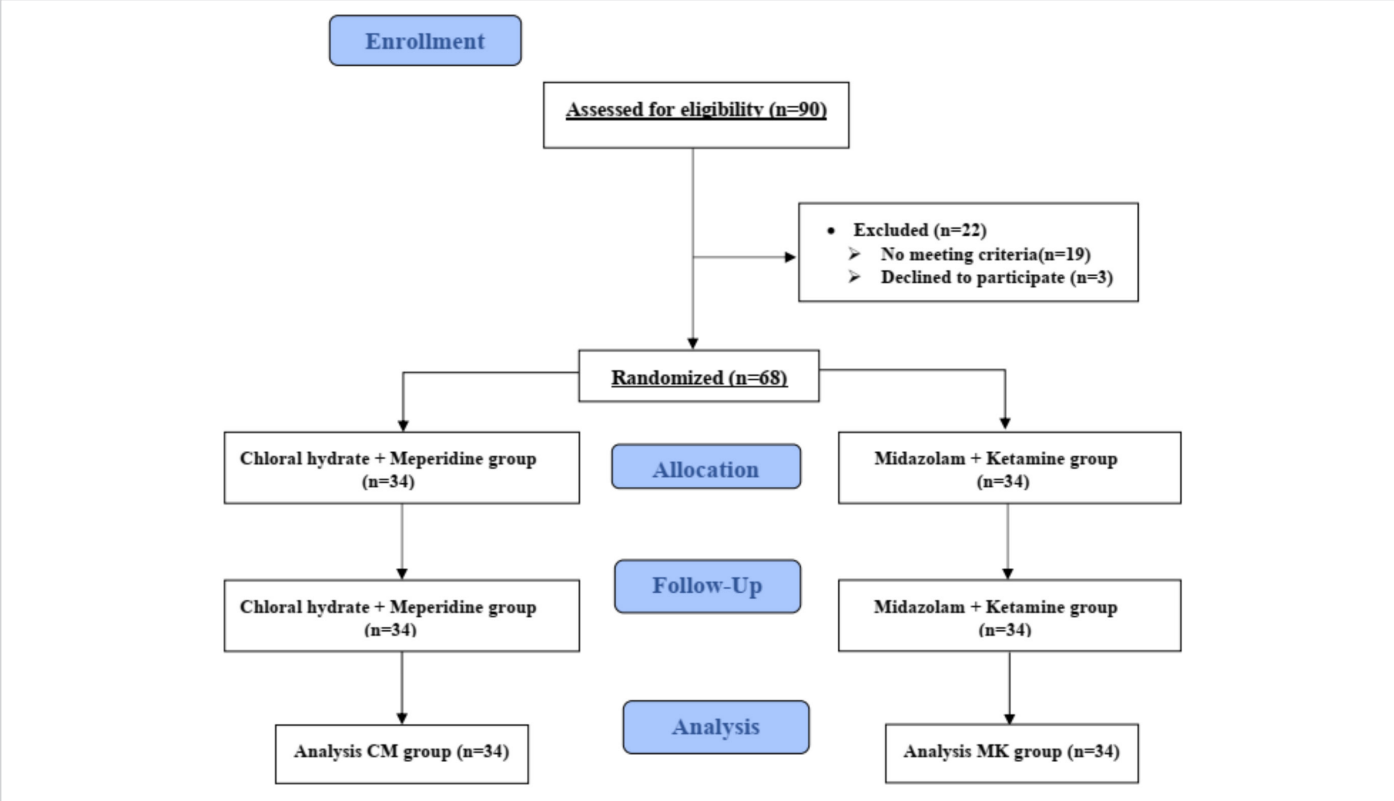


Figure 2. Flowchart and consort diagram of patients

Table 1. Demographic characteristics of pediatric patients in the studied groups

	CM group (n=34)	MK group (n=34)	p-value
Age (year)	5.21±1.23	4.82±1.14	0.18
Weight (Kg)	17.68±3.44	16.85±3.64	0.34
Sex; Male	22 (65)	21 (62)	0.55
Surgery duration (min)	35.89±10.2	38.19±8.9	0.32
Anesthesia duration (min)	45.73±13.25	49.55±12.11	0.21

Values are presented as mean ± Standard deviation or numbers (percentages)

CM: Chloral hydrate and meperidine, MK: Midazolam and ketamine,

Table 2. Separation anxiety scores in the studied groups

	CM Group (n=34)	MK Group (n=34)	p-value
Sleep	11 (32.35)	8 (23.52)	0.42
Full awake-calm	19 (55.88)	20 (58.82)	0.80
Crying	4 (11.76)	6 (17.64)	0.49
Violent movement	0 (0.00)	0 (0.00)	> 0.99

The values are presented as numbers (percentages)

CM: Chloral hydrate and meperidine, MK: Midazolam and ketamine

Table 3. Postoperative agitation score of the children in both groups

	CM Group (n=34)	MK Group (n=34)	p-value
Asleep	16 (47)	24 (70.5)	0.08
Awake but calm	15 (44)	6 (17.64)	0.01*
Agitated	1 (2.94)	3 (8.82)	0.33
Severely agitated and difficult to comfort	0 (0%)	0 (0%)	>0.99

Values are presented as numbers (percentages)

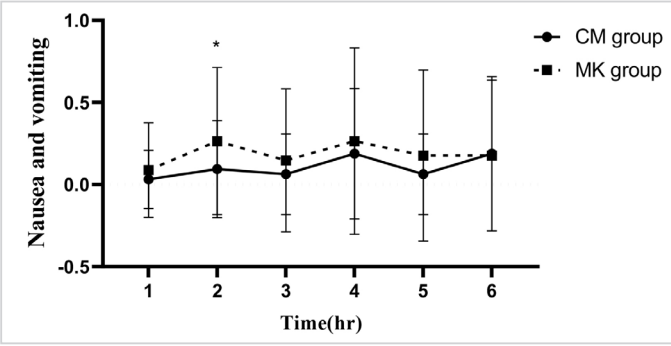
*Indicates significant p-value

CM: Chloral hydrate and meperidine, MK: Midazolam and ketamine

Figure 4 shows postoperative pain intensity in the studied group over time.

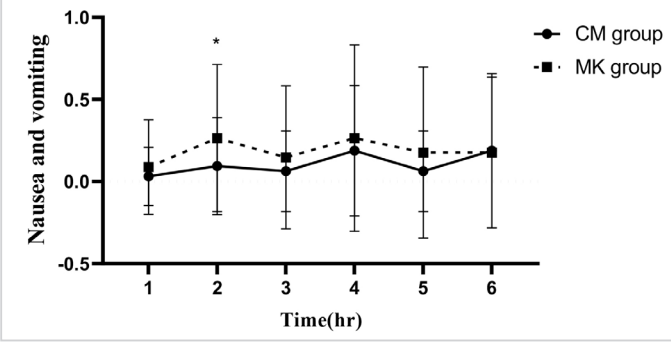
The repeated measurement analysis results for postoperative pain intensity indicate that the pain had decreased after the surgery over time in both groups ($p<0.001$), and the premedication did not affect the pain intensity of patients ($p=0.12$). Therefore, patients in both groups had the same pain intensity experience after the surgery.

It should be noted that during the study, no respiratory depression was observed in any of the patients. Also, the two groups were not different in taking morphine (4±2 vs. 3.88±2, $p=0.79$).



Time effect =0.21, interaction (time* group) =0.84, group effect =0.02
Bonferroni correction p-value =0.008
$p_{t=2}$ <0.001
*Indicates significant p-value
CM: Chloral hydrate and meperidine, MK: Midazolam and ketamine

Figure 3. Postoperative nausea and vomiting in the studied groups over time



Time effect<0.001, interaction (time* group)= 0.046, group effect=0.129
CM: Chloral hydrate and meperidine, MK: Midazolam and ketam

Figure 4. Postoperative pain intensity in the studied groups over time

Discussion

This randomized clinical trial furnishes substantiation indicating that an oral combination of CM elicited a greater sense of comfort and alertness in children upon emergence from anesthesia when compared to an oral combination of MK. Moreover, the CM combination demonstrated superior efficacy as a premedication.

Historically employed as a premedication in pediatric contexts, oral midazolam lacks the requisite analgesic efficacy crucial in the aftermath of a painful procedure. Numerous investigations have explored the impact of a combination of MK. Banerjee et al. (20) demonstrated that such a composite formulation proved more efficacious than either constituent administered in isolation. Funk et al. (21) observed analogous findings. Due to the inherent absence of analgesic properties in midazolam alone, these investigations incorporated ketamine alongside midazolam to induce analgesia. Furthermore, the concurrent administration of midazolam served to diminish the emergence phenomena associated with oral ketamine (21). Nevertheless, oral premedication necessitates a longer duration to induce sedation. Consequently, to expedite the onset, a higher dose of the drug is required. However, this escalated dosage results in prolonged postoperative sedation and hinders timely discharge from the recovery room (21). Oral ketamine undergoes a pronounced first-pass effect in the liver, leading to the formation of nor-ketamine. This metabolite of ketamine plays a role in the analgesic effects observed after the administration of oral ketamine (22, 23).

In our investigation, we observed concordant findings with Funk et al.'s (21) study, notwithstanding the analgesic impact of ketamine in conjunction with midazolam. This combination induced increased drowsiness among patients in the recovery room, resulting in a delay in discharge-a phenomenon not observed with the CM mixture.

While oral chloral hydrate has been employed for sedation in pediatric patients, akin to midazolam, it lacks analgesic properties (24,25). As a consequence, chloral hydrate emerges as the preferred sedative for pediatric patients undergoing diagnostic procedures that do not necessitate analgesic intervention (24).

Nathan and Vargas (13) ascertained that augmenting midazolam with meperidine enhanced both the effectiveness and the duration of midazolam in pediatric patients. Furthermore, their investigation revealed that premedicated patients exhibited diminished postoperative pain and displayed reduced distress upon separation from their parents. In our investigation, we supplemented chloral hydrate with meperidine to elicit a combined analgesic and sedative effect. Our findings indicate that the amalgamation of meperidine and chloral hydrate induced drowsiness in children upon separation from their parents, facilitating a smooth induction of anesthesia. After the surgical procedure, the patients exhibited prompt wakefulness and comfort, enabling expedited discharge from the recovery room.

PONV following tonsillectomy represent a significant concern due to its potential to elevate the risk of postoperative bleeding, pulmonary aspiration, and the necessity for hospitalization (26). Nonetheless, in our investigation, the incidence of PONV was lower with the combination of CM when compared to the combination of MK. Although the statistical analysis did not show a significant difference in pain intensity between the groups, the results reveal that children in the MK group experienced more pain from two hours post-surgery until the end of the study (six hours after surgery) compared to the CM group. We believe that even though the difference between the pain levels is small and not statistically significant, it could be clinically important and might lead to a higher incidence of PONV in the CM group, given the high sensitivity of children. This observation

highlights an additional advantage of the CM combination over the midazolam-ketamine combination.

Study Limitations

This study possesses certain limitations. Firstly, a more extended observation period, ideally encompassing at least 24 hours, is warranted to thoroughly assess the sustained analgesic efficacy of these mixtures. Secondly, future investigations would benefit from an augmented sample size to discern potential further distinctions between the two mixtures. Thirdly, the examination of drug-related side effects, such as an elevation in muscle tone and salivation in the ketamine-midazolam group, and potential interference with surgical techniques should be taken into consideration.

Conclusion

In summary, this investigation demonstrated comparable effects between an oral mixture of MK and a mixture of CM concerning anxiety levels upon separation from parents and anesthesia induction. Each group was administered a combination of sedative drugs for pre-operative sedation and analgesic drugs for postoperative pain. This was done to assess the level of sedation before anesthesia and to observe any postoperative restlessness and pain relief.

Nevertheless, following the emergence from anesthesia, the oral combination of CM could exhibit a superior outcome by promoting wakefulness and greater comfort in patients, in contrast to the oral mixture of MK, which induced increased drowsiness during the emergence phase, consequently leading to delayed discharge from the recovery room. Moreover, the oral combination of CM could have better efficacy in managing agitation in the early postoperative period compared to the combination of MK.

Ethics

Ethics Committee Approval: The study was duly registered in the Iranian Registry of Clinical Trials (IRCT2015111611662N8) (https://www.irct.ir/trial/11836) and received approval from the Shiraz University of Medical Sciences Ethics Committee (IR.sums.med.rec.1394.351).

Informed Consent: The study did not require patient consent as it was based entirely on the university clinic's database of questions obtained from publicly available online medical textbooks.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.N., S.E., E.S., M.A.S Concept: N.N., S.E., M.B., M.G., E.S., Design: N.N., S.E., M.B., M.G., E.S., Data Collection and/or Processing: N.N., M.B., M.G., Analysis and/or Interpretation: M.B., E.S., Literature Search: S.E., Writing: N.N., E.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Main Points

- There was no significant difference in separation anxiety scores between the chloral hydrate and meperidine (CM) or midazolam and ketamine (MK) groups.
- An oral mixture of CM was found better than a MK in postoperative agitation in pediatric patients undergoing tonsillectomy.
- The CM group had less postoperative nausea and vomiting than the MK group.
- The patients in both groups experienced the same levels of pain intensity after the surgery.

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