Comparison of the Effect of Thiopental Sodium with Midazolam-ketamine on Post-tonsillectomy Agitation in Children

Maryam Toliyat[1], Maliheh Zangoee[2], Shahnaz Ahrari[3], and Reza Zangoee[4]

[1] *Department of Paramedicine, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran*

[2] *School of Medicine, Birjand University of Medical Sciences, Birjand, Iran*

[3] *Department of Paramedicine, School of Nursing and Midwifery, Gonabad University of Medical Sciences, Gonabad, Iran*

[4] *Islamic Azad University, Birjand Branch, Birjand, Iran*

Received: 11 Jul. 2014; Accepted: 25 Dec. 2014

Abstract- The aim of this study was to determine the effect of thiopental sodium with that of midazolam-ketamine on relieving agitation after tonsillectomy in children. In a clinical trial, 50 children aged 5-10 years, candidates for tonsillectomy, were randomly divided into two 25-member groups. In the first group, thiopental sodium 5mg/kg/IV, and in the second group combination of midazolam 0.01 mg/kg/IV and ketamine 1 mg/kg/IV were used to induce anesthesia. The level of sedation was assessed after surgery with the Ramsay scale. There were no significant differences between the two groups in terms of heart rate, arterial oxygen pressure (PO_2), and duration of anesthesia. The Ramsay sedation score was significantly higher in the thiopental sodium group than in the midazolam-ketamine group (P=0.01). Thiopental sodium can be more effective than the combination of midazolam-ketamine for controlling agitation after tonsillectomy in children.

Acta Med Iran 2015;53(10):637-642.

Keywords: Ketamine; Midazolam; Thiopental sodium; Sedation; Agitation

Introduction

Tonsillectomy is one of the most common surgeries in children (1). Agitation is a common complication after surgery in children, particularly, those who receive Sevoflurane for anesthesia (2-4). Initial epidemiological studies report the incidence rate of tonsillectomy in different ages at 5.3%, but later studies estimated it at 18%-80% in children (5). Generally, agitation is defined as a series of physical symptoms or emotional distress with some or all of the following sings: crying, restlessness, grabbing, verbal presentations, kicking, purposeful or unintentional behavior, which might have logical connections with each other (5). This complication can be severe and chronic, expose the patient to physical harm, pain or bleeding, and prolong the recovery time (6). The widespread use of sevoflurane and desflurane in developing countries has increased agitation after surgery in children (7). Another problem of agitation after surgery is nursing problems in delivering care for the agitated child (8).

Although the etiology of this complication is not known, different factors have been mentioned in this regard: pre-school age, nervousness, previous surgery, the adaptability of the patient, pain in eye and ENT surgeries, using inhalation agents, particularly, sevoflurane and isoflurane for anesthesia, and the duration of anesthesia (5,9,10). Among these, pain and nervousness are known as the most common causes (11). Although agitation will be resolved on its own, it leads to the dissatisfaction of the parents, nurses, and caregivers (12). Premedication is needed in children to alleviate anger, induce anesthesia, and prevent aspiration, preventing bradycardia and psychological effects after surgery.

Different medicines are used to sedate children, such as a benzodiazepine, midazolam and ketamine (13,14). The properties of a good medicine lie in its rapid onset, short-term effect, and it's significantly fewer complications (15). Midazolam is a benzodiazepine with anxiolytic and sedative properties, which is commonly used in both children and adults in different diagnostic and therapeutic procedures due to its short-term effects and rapid onset.

Corresponding Author: Sh. Ahrari
Department of Paramedicine, School of Nursing and Midwifery, Gonabad University of Medical Sciences, Gonabad, Iran
Tel: +98 51 57225027, Fax: +98 51 57223815, E-mail address: sh.ahrar@gmail.com

This medicine prevents the formation of an undesirable memory of the painful procedure by creating anterograde amnesia However, It needs to be used with an analgesic in painful procedures due to its lack of an analgesic property (16,17). Although midazolam causes respiratory depression, it is used as a sedative before surgery (18).

Ketamine is a derivative of phencyclidine and a sedative and analgesic, which can be used alone or with other medicines for analgesia during diagnostic and therapeutic procedures in children. This medicine can be prescribed orally, intravenously, intramuscularly or intrathecally for inducing anesthesia and relieving agitation in different diagnostic and therapeutic activities (19,20). The kind of medicine used for anesthesia depends on anesthesiologist's choice after considering the patient's condition and the length of the surgery.

Despite the widespread use of ketamine in adults as a suitable sedative and analgesic, its use in children is questioned due to its hallucinating and agitating complications (21). Thiopental sodium is barbiturate used for inducing anesthesia. The major complications of this medicine include spasm and respiratory depression (22). Its cardiovascular effects are the decreased mean arterial pressure and reduced cardiac output. A study by Darabi *et al*., showed that both combinations of propofol-alfentanil and midazolam-ketamine are safely and effectively used for sedation and analgesia in children during bone marrow aspiration (23).

A study by Khalili *et al*., showed that midazolam can reduce agitation and its mean duration after surgery significantly better than does ketamine (24). Kaviani *et al*., conducted a study to examine the sedative effect of the combination of oral midazolam and ketamine combined with inhalational nitrous oxide in controlling the movement of children during dentistry operations. Their study did not show a significant statistical difference between the two groups. Consciousness during the operation was higher in the midazolam group than in the ketamine group; also, the recovery period was shorter in the former (25).

A review of previous studies on the effectiveness of midazolam-ketamine combination, compared with thiopental sodium for inducing anesthesia confirms that no study has been performed about their effect on controlling agitation. However, due to the advantages and disadvantages of ketamine, midazolam, and thiopental sodium for pediatric anesthesia, the researchers compared midazolam-ketamine with thiopental sodium used intravenously in controlling agitation after tonsillectomy in children.

Materials and Methods

This clinical trial was conducted on children aged 5-15 years after briefing their parents and obtaining their written consent. The inclusion criteria for the study were children aged 5-15 years with grades 1 and 2 of the health criteria of the American Society of Anesthesiologists, who were applicants for tonsillectomy.

Patients with a history of consuming barbiturates, a history of acute respiratory failure or severe renal failure and mental retardation, or a history of anesthetic complications such as bleeding or complications during surgery, including the impossibility or difficulty of intubation, were excluded. The qualified patients were assigned to two groups using block randomization method to receive anesthetic. After selecting and preparing the patients for anesthesia, thiopental sodium 5 mg/kg/IV was used for the thiopental sodium group, and the combination of midazolam 0.01 mg/kg/IV and ketamine 1 mg/kg/IV was used in the other group to induce anesthesia (26).

The heart rate, respiratory rate, and oxygen saturation were controlled by the anesthesiologist during anesthesia. Apnea, arterial oxygen saturation fall, bradycardia or tachycardia, and agitation were recorded on a questionnaire. The same hydration therapy was used in both groups. After surgery, the anesthetics were discontinued, and the residual effects of the muscle relaxants were reversed with neostigmine and atropine, and the patient's endotracheal tube was preserved until his or her full consciousness.

The duration of anesthesia (from the injection of anesthetic until discontinuation), the extubation time (from discontinuing anesthetics until extubation), and the recovery period (from the beginning of recovery until the patient's discharge) were recorded on the questionnaire. In case of pain during recovery, patients were injected with meperidine 1mg/kg/IV. The patients were studied by a co-researcher who was not aware of the kind of anesthesia induction during recovery after anesthesia in terms of symptoms, the degree and duration of agitation, the extubation time, and the hospitalization length.

The agitation degree was examined with the Ramsay scale; then, the data were analyzed with the SPSS software version 16 and a statistical test with the confidence level of 95%. After collecting and encoding the data, they were entered into the computer, analyzed

with the SPSS software with the following statistical methods.

To describe the characteristics of the research units, descriptive statistics including frequency distribution, mean and standard deviation were used. The statistical t-test and chi-square were used for analysis. The confidence coefficient and the test power were estimated at 0.95 and 0.80, respectively.

Results

The results of the study showed that of 50 studied patients, 30 (60%) were male. In the thiopental sodium group, the majority was male, and in the midazolam-ketamine the majority was female. The chi-square test revealed a significant difference between the two groups. Twenty-one patients in each group (84%) did not mention the history of diseases.

The mean age of the studied patients was 6.7 ± 2.64, being 6.4 ± 2.64 in the thiopental sodium and 7.1 ± 2.7 in the midazolam-ketamine group. The t-test did not show a significant difference between the two groups. The mean duration of anesthesia in the midazolam group was 37.6 ± 6.5 in the midazolam-ketamine group, which showed a statistically significant difference with the thiopental sodium group. The mean heart rate was not significantly different between the two groups. The groups were not significantly different in terms of the duration of agitation and the incidence of agitation, either.

The duration of anesthesia was significantly different between the two groups, being notably higher in the midazolam-ketamine group than in the thiopental sodium group. The sedation degree was also significantly different between the two groups, being significantly higher in the thiopental sodium group. The results of the statistical tests are presented in the tables below.

Table 1. The comparison of the frequency of sex and history of diseases in in thiopental sodium and midazolam-ketamine groups

Variable		Thiopental sodium group	Midazolam-ketamine group	*P*-Value
Sex	**Male**	19 (76%)	11 (44%)	0.04*
	Female	6 (24%)	14 (56%)	
History of Disease	**Positive**	4 (16%)	4 (16%)	0.56
	Negative	21 (84%)	21 (84%)	
Age (year)		6.4 (±2.6)	7.1 (±2.7)	0.34
Duration of anesthesia (minute)		32.4 (±8.1)	37.6 (±6.5)	0.01*
Heart Rate		112.2 (±16.7)	116.7 (±20.8)	0.40

Table 2.The comparison of mean arterial blood oxygen saturation, recovery duration, and sedation degree in the thiopental sodium and midazolam-ketamine groups

Variable	Thiopental sodium group	Midazolam-ketamine group	*P*-Value
The Recovery Duration	27.9 (14.2)	32.0(9.7)	0.236
Mean arterial blood oxygen saturation	97.4(1.5)	97.1(1.1)	0.462
The Sedation Degree	3.2(±0.9)	3.9 (1.0)	0.01*

Table 3. The comparison of the frequency of pain and need for analgesics, and agitation in the thiopental sodium and midazolam-ketamine groups

Variable		Thiopental sodium group	Midazolam-ketamine group	*P*-Value
Pain	**Positive**	10 (40%)	9 (36%)	0.77
	Negative	15 (60%)	16 (64%)	
Need for Analgesics	**Positive**	1 (4%)	4 (16%)	0.15
	Negative	24 (96%)	21 (84%)	
Agitation	**Positive**	11 (44%)	9 (36%)	0.56
	Negative	14 (56%)	16 (64%)	
Agitation Duration		3.5 (5.3%)	3.5 (5.8%)	1.000

Discussion

Agitation right after surgery is a common problem during recovery, particularly, in children (3). This complication can be severe and prolonged, exposing the patient to physical harm, pain or bleeding, and prolong the recovery period (6). In addition, nowadays, using different pharmacological methods for analgesia, agitation, and sedation of children has been ever-increasing. This study compared thiopental sodium and midazolam-ketamine in causing sedation after tonsillectomy in children. The results of the present study showed that the mean sedative degree of the midazolam-ketamine group was lower than that of the thiopental sodium group after tonsillectomy. This difference was statistically significant, meaning that thiopental sodium better controlled sedation after surgery than the midazolam-ketamine combination.

Different studies have been conducted on various medicines for sedating and anxiety after different surgeries in children. Darabi *et al*., compared the two drug combinations of propofol-alfentanil and midazolam-ketamine in sedation and analgesia during bone marrow aspiration in children in 2006 in Tehran. In this study, consistent present research, the modified Ramsay score was used and all the patients of the two treatment groups had acceptable sedation scores during bone marrow aspiration. The onset time of sedation and the duration of recovery were significantly lower in the propofol-alfentanil group, compared with the midazolam-ketamine group.

After inducing sedation, systolic blood pressure and heart rate increased in the ketamine-midazolam group, decreased and in the propofol-alfentanil group compared with the baseline values; the increase of the systolic blood pressure and heart rate in the ketamine-midazolam group might be attributed to anxiety. A disadvantage of the ketamine-midazolam combination is the long recovery period, which is compatible with this study. The observed recovery period in the current study was also longer in the ketamine-midazolam group than in the thiopental sodium group (23).

Khalili *et al*., examined the effect of midazolam and ketamine on anesthesia-induced agitation in the lower abdominal and lower extremity surgeries in children. The results of this study showed that midazolam, compared with ketamine, can reduce the frequency of agitation and the mean of its duration after surgery significantly better (24). It seems that ketamine, alone, is not effective in causing sedation after surgery and needs to be combined with another medicine. Furthermore, Yaraqi *et al*., has reported the sedative effect of propofol higher than that of midazolam; it seems that combination of these two medicines is more effective in sedation.

Kaviani *et al*., studied the effect of oral midazolam and oral ketamine in combination with nitrous oxide for sedation in children during dental treatment. The extent of crying, consciousness, movement, and general behavior of the children during injection and operation were evaluated with the Houpt scale. The results indicated that this sedative combination is effective in more than 90% of the patients, without any statistically significant difference between the two groups.

In the midazolam group, consciousness during operation and the recovery period were, respectively, higher and shorter than in the ketamine group. The results of this study were compatible with other studies. The difference between this and other studies, including the present study, lies in the sedation scale used; the Ramsey scale was used in other studies.

As a result, oral midazolam and ketamine combined with nitrous oxide have a positive effect in inducing sedation and controlling children's movements during dental operations. Due to the simplicity of the use of these medicines and their few complications, these methods can be employed for controlling children's movements during dental operations (25). A study by Run Keeve (2011) compared Remifentanil with nitrous oxide in controlling agitation and pain after tonsillectomy and adenoidectomy (27). This study did not mention a significant difference between the two groups, either.

According to the results of the current research, the thiopental sodium group, compared with the midazolam-ketamine group, enjoyed more sedation and had less pain; therefore, thiopental sodium seems to be a better medicine for inducing anesthesia among tonsillectomy patients.

A limitation of the present study is its small sample size. Future studies, therefore, are recommended to be conducted with larger samples. Another limitation might be that neither of the patients was visited the night before surgery, thus, not receiving a sedative premedication; accordingly, stress caused by operation room and anesthesia was definitely effective in causing agitation and anxiety after surgery.

Acknowledgment

All people who assisted us in carrying out this research are appreciated.

References

1. Patel A, Davidson M, Tran MC, et al. Dexmedetomidine Infusion for Analgesia andPrevention of Emergence Agitation in Children with Obstructive Sleep Apnea Syndrome Undergoing Tonsillectomy and Adenoidectomy. Anesth Analg 2010;111(4):1004-10.
2. Tazeroualti N, De Groote S, De Hert A, et al. Van der Linden.Oral clonidine vs midazolam in the prevention of sevoflurane-induced agitation in children. A prospective,randomized, controlled trial. Br J Anaesth 2007;98(5):667-71 .
3. Kim J, Kim SY, Lee JH, et al. Low-Dose Dexmedetomidine Reduces Emergence Agitation after DesfluraneAnaesthesia in Children Undergoing Strabismus Surgery. Yonesi Med J 2014;55(2):508-16.
4. .Aouad MT, Nasr VG. Emergence agitation in children: an update. Curr Opin Anaesthesiol 2005;18(6):614-9.
5. Voepel-Lewis T, Malviya S, Tait AR. A prospective cohort study of emergence agitation in the pediatric postanesthesia care unit. Anesth Analg 2003;96(6):1625-30.
6. Dalens BJ, PinardAM, Letourneau DR, et al. Prevention of emergence agitation after sevoflurane anesthesia for pediatric cerebral magnetic resonance imaging by small doses of ketamine or nalbuphine administered just before discontinuing anesthesia. Anesth Analg 2006;102(4):1056-61.
7. Dahmani S, Stany I, Brasher C, et al. Pharmacological prevention of sevoflurane- and desflurane-related emergence agitation inchildren: a meta-analysis of published studies. Br J Anaesth 2010;104(2):216-23 .
8. Voepel-Lewis T, Burke C, Hadden SM, et al. Nurses' diagnoses and treatment decisions regarding care of the agitated child. J Perianesth Nurs 2005;20(4):239-48.
9. Fan KT, Lee TH, Yu KL, et al. Influences of tramadol on emergence characteristics from sevoflurane anesthesia in pediatric ambulatory surgery. Kaohsiung J Med Sci 2000;16(5):255-60.
10. Guler G, Akin A, Tosun Z, et al. Singledosedexmedetomidine reduces agitation and provides smooth extubation after pediatric adenotonsillectomy. Paediatr Anaesth 2005;15(9):762-6.
11. Holzki J, Kretz FJ. Changing aspects of sevoflurane in paediatricanaesthesia: 1975-99. Paediatr Anaesth 1999;9(4):283-6.
12. Galinkin JL, Fazi LM, Cuy RM, et al. Use of intranasal fentanyl in children undergoing UK myringotomy and tube placement during halothane and sevoflurane anesthesia. Anesthesiology 2000;93(6):1378-83.
13. Sathishkumar S, Malviya S, Dorje P. Management of emergence agitation. Anaesthesia 2007;62(5):530-1.
14. Kuratani N. Emergence agitation in pediatric anesthesia. Masui 2007;56(5):554-9.
15. Kanto JH. Midazolam: the first water-soluble benzodiazepine. Pharmacology, pharmacokinetics and efficacy in insomnia and anesthesia. Premedication. Pharmacotherapy 1985;5(3):138-55.
16. Sievers TD, Yee JD, Foley ME, et al. Midazolam for conscious sedation during pediatrie oncology procedures: safety and recovery parameters. Pediatrics 1991; 88(6):1172-9.
17. Shane SA, Fuchs SM, Khine H. Efficacy of rectal midazolam for the sedation of preschool children undergoing laceration repair. Ann Emerg Med 1994;24(6): 1065-73.
18. Shoroghi M, Arbabi S, Farahbakhsh F, et al. Perioperative effects of oral midazolam premedication in children undergoing skin laser treatment. A double-blinded randomized placebo-controlled trial. Acta Cir Bras 2011;26(4):303-9.
19. Marx CM, Stein J, Tyler MK, et al. Ketamine-midazolam versus meperidine-midazolam for painful procedures in pediatric oncology patients. J Clin Oncol 1997;15(1):94-102.
20. Parker RI, Mahan RA, Giugliano D, et al. Efficacy and safety of intravenous midazolam and ketamine as sedation for therapeutic and diagnostic procedures in children. Pediatrics 1997;99(3):427-31.
21. SerkanSener, CenkerEken, Carl H. Schultz, Mustafa Serinken, Murat Ozsarac. Ketamine With and Without Midazolam for EmergencyDepartment Sedation in Adults: A Randomized Controlled trial. Ann Emerg Med 2011;57(2):109-14.
22. Zahavi GS, Dannon P. Comparison of anesthetics in electroconvulsive therapy: an effective treatment with the use of propofol,tomidate, and thiopental. Neuropsychiatric Dise Treat 2014:10:383-9.
23. Darabi MA, Mireskandari SM, Sadeghi M. Propofol-Alfentanyl versus Midazolam-Ketamine for sedation and analgesia during bone marrow aspiration in children. TUMJ 2007;65(6):17-22.
24. Khalili GR, Sajedi P, Danesh H. Midazolam versus ketamine in the management of emergence agitation in children undergoing lower abdominal and limb surgeries. TUMJ 2012;69(11): 730-6.
25. Kaviani N, Eshghi E, Tabibian P. Comparative Evaluation of Sedative Effects of Oral Midazolam and Oral Ketamine in Combination with Inhalation Sedation for Pediatric Behavior Control during Dental Treatment. J Isfahan Dent School 2007;2(4):46-51.
26. Miller RD, editor. Miller's Anesthesia. 7th ed. Elsevier: Churchill Livingstone; 2010: p. 100-2

27. Choi HR, Cho JK, Lee S, et al. The effect of remifentanil versus N2O on postoperative pain and emergence agitation after pediatric tonsillectomy/ adenoidectomy. Korean J Anesthesiol 2011;61(2):148-53.