ORIGINAL RESEARCH

Oral Midazolam-Ketamine versus Midazolam alone for Procedural Sedation of Children Undergoing Computed Tomography; a Randomized Clinical Trial

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Received: September 2014; Accepted: November 2014

Abstract

Introduction: Motion artifacts are a common problem in pediatric radiographic studies and are a common indication for pediatric procedural sedation. This study aimed to compare the combination of oral midazolam and ketamine (OMK) with oral midazolam alone (OM) as procedural sedatives among children undergoing computed tomography (CT) imaging. **Methods:** The study population was comprised of six-month to six-year old patients with medium-risk minor head trauma, who were scheduled to undergo brain CT imaging. Patients were randomly allocated to two groups: one group received 0.5 mg/kg midazolam (OM group; n = 33) orally and the other one received 0.2 mg/kg midazolam and 5 mg/kg ketamine orally (OMK group; n=33). The vital signs were monitored and recorded at regular intervals. The primary outcome measure was the success rate of each drug in achieving adequate sedation. Secondary outcome measures were the time to achieve adequate sedation, time to discharge from radiology department, and the incidence of adverse events. **Results:** Adequate sedation was achieved in five patients (15.2%) in OM group and 15 patients (45.5%) in OMK group, which showed a statistically significant difference between the groups (p = 0.015). No significant difference was noted between OM and OMK groups with respect to the time of achieving adequate sedation (33.80 ± 7.56 and 32.87 ± 10.18 minutes, respectively; p = 0.854) and the time of discharging from radiology department (89.60 ± 30.22 and 105.27 ± 21.98 minutes, respectively; p=0.223). The complications were minor and similar among patients of both groups. **Conclusion:** This study demonstrated that in comparison with OM, OMK was more effective in producing a satisfactory level of sedation in children undergoing CT examinations without additional complications; however, none of these two regimens fulfilled clinical needs for procedural sedation.

Key words: Midazolam; ketamine; conscious sedation; tomography, x-ray computed

Cite this article as: Majidinejad S, Taherian K, Khazaei K, Samaie V. Oral midazolam-ketamine versus midazolam alone for procedural sedation of children undergoing computed tomography; a randomized clinical trial. Emergency. 2015;3(2):64-9.

Introduction:

The results of imaging studies are negatively affected by patients' movements; hence, patient's cooperation is required during imaging. Children's movements and lack of cooperation are common indications for pediatric procedural sedation during imaging studies such as computed tomography (CT) scans (1). Different rates of success have been achieved by various sedation regimens such as diphenhydramine, propofol, ketamine, midazolam (2), chloral hydrate (3), pentobarbital (4), and dexmedetomidine (5); therefore, the efforts to find an ideal regimen are continued. The selected sedative should have a rapid onset of action, few adverse effects, short and sufficient duration of action, self-maintenance of a patent airway, minimal effects on respiration or hemodynamics, and rapid recovery (6). Over the last few years, researchers have shown a special interest in finding effective, nonparenteral, sedative agents that do not have injection problems (3). Ketamine is a noncompetitive antagonist of the N-methyl-D-aspartate receptor (NMDAR), which is used for premedication, sedation, and induction as well as maintenance of general anesthesia. Quick onset, short duration of action, and maintenance of laryngeal reflexes have made it a popular sedative choice for pediatric patients in the emergency department (7). Although ketamine is known as a parenteral agent, some researchers have successfully used it as an oral sedative drug (8, 9). Midazolam is

a potent benzodiazepine with rapid onset and offset effects as well as anxiolytic and amnestic properties, which can be administered through different routes (i.e. oral, intravenous, intramuscular, rectal, sublingual, and intranasal). Oral midazolam (OM) is a safe and effective choice for sedation in children (10). In previous studies, the authors have used a combination of oral midazolam and ketamine (OMK) as premedication and sedative regimens; besides, some studies reported that combination therapy has higher efficacy without any additional adverse effects in comparison to the methods using each drug alone (11, 12). To the best of our knowledge, limited number of studies have reported the use of OM during imaging, which had reported lower effectiveness rate in comparison with chloral hydrate (13, 14); however, OMK has not been used for this purpose, yet. Therefore, this study was conducted to compare the effects of OMK with OM as procedural sedatives in pediatric patients undergoing CT imaging.

Methods:

Study design and setting

This randomized, double-blinded, clinical trial was conducted from November 2012 to November 2013 in two teaching hospitals (Ayatollah Kashani Hospital and Alzahara Hospital) affiliated to Isfahan University of Medical Sciences, Isfahan, Iran. The study protocol was approved by Ethics Committee of the Isfahan University of Medical Sciences. All parents or guardians were informed of the study's protocol, risks, and benefits and were asked to sign an informed written consent.

Participants

We included six-month to six-year old children with medium-risk minor head trauma who were scheduled to undergo brain CT scan (15). Medium-risk minor head trauma was defined as initial Glasgow coma scale score of 15 with any history of brief loss of consciousness, posttraumatic amnesia, vomiting, headache, or intoxication. All of these patients were classified as status I or II according to American Society of Anesthesiologists (ASA) physical status classification. Children with neurological disorders, anomalies of the cardiovascular system, known allergy to midazolam, gastritis, any serious systemic diseases, those on long-term treatment with hepatic enzyme-inducing drugs or those receiving erythromycin concurrently (due to drug interaction), and patients who had received medication within the preceding 48 hours were excluded.

Procedure

Patients were randomly allocated to two groups; OM Group received 0.5 mg/kg midazolam (produced by; Tehran Shimi, Tehran, Iran) orally and OMK Group received 0.2 mg/kg midazolam and 5 mg/kg ketamine (produced by; Rotexmedica, Trittau, Germany) orally. Randomization was conducted using a computer-generated sequence and block randomization protocol. Demographic and basic characteristics such as age, height, gender, weight, body mass index (BMI), and history of any medical condition were recorded before administration of study drugs. Then a nurse, who was blinded to the study, mixed both of the medications with 5 mL of sugar syrup to make it palatable. The parents gave the prepared syrup to the children under the researchers' supervision. Pulse rate and oxygen saturation (SaO_2) were continuously monitored by a portable pulse oximeter. Blood pressure, heart rate, respiratory rate, and SaO_2 were recorded at baseline (just before drug administration) and every 30 minutes until the patient was discharged from the radiology department. The level of sedation of patients after drug administration was assessed using Ramsay sedation scale (RSS) (16). RSS of four was considered as adequate sedation depth to tolerate diagnostic imaging studies. Patients who did not show satisfactory response to the sedative drugs within 40 minutes and those who were awakened or moved during the imaging were excluded from further analysis. The interval between administration of sedative drugs and achieving RSS of four was considered as the time to achieve adequate sedation. Once the patients achieved adequate sedation, they were transferred to a scanner room and the imaging was performed according to the protocol. After the scan, the patients were transferred to another room in the radiology department to monitor and observe their conditions. The time to discharge from radiology department was defined as the interval between the start of sedative administration and return to the baseline alertness and spontaneous breathing.

Statistical analyses

All statistical analyses were performed using the SPSS 19.0 (SPSS Inc., Chicago, IL, USA). The categorical data were analyzed using Fisher's exact test. Parametric data were analyzed using the student's t-test. Descriptive statistics were expressed as mean ± standard deviation or number (percentage). Statistical significance was set at $p < 0.05$. Two-way ANOVA was used to compare changes of vital signs during 180 minutes after drug administration between two groups.

Results:

66 participants were enrolled. Figure 1 shows the CONSORT flow diagram of study. The mean age of participants was 2.8 ± 1.6 years (range: 6 months to 6 years) and 54.5% of the participants were male. Table 1 shows the basic characteristics of patients. There was no significant difference between the two groups in age, height, weight, and male to female ratio (Table 1). Table 2 compares outcomes between two groups. Adequate sedation (RSS of 4) was achieved in five patients (15.2%) in the OM group and 15 patients (45.5%) in the OMK group, which showed a statistically significant difference ($p = 0.015$). No significant difference was found between the

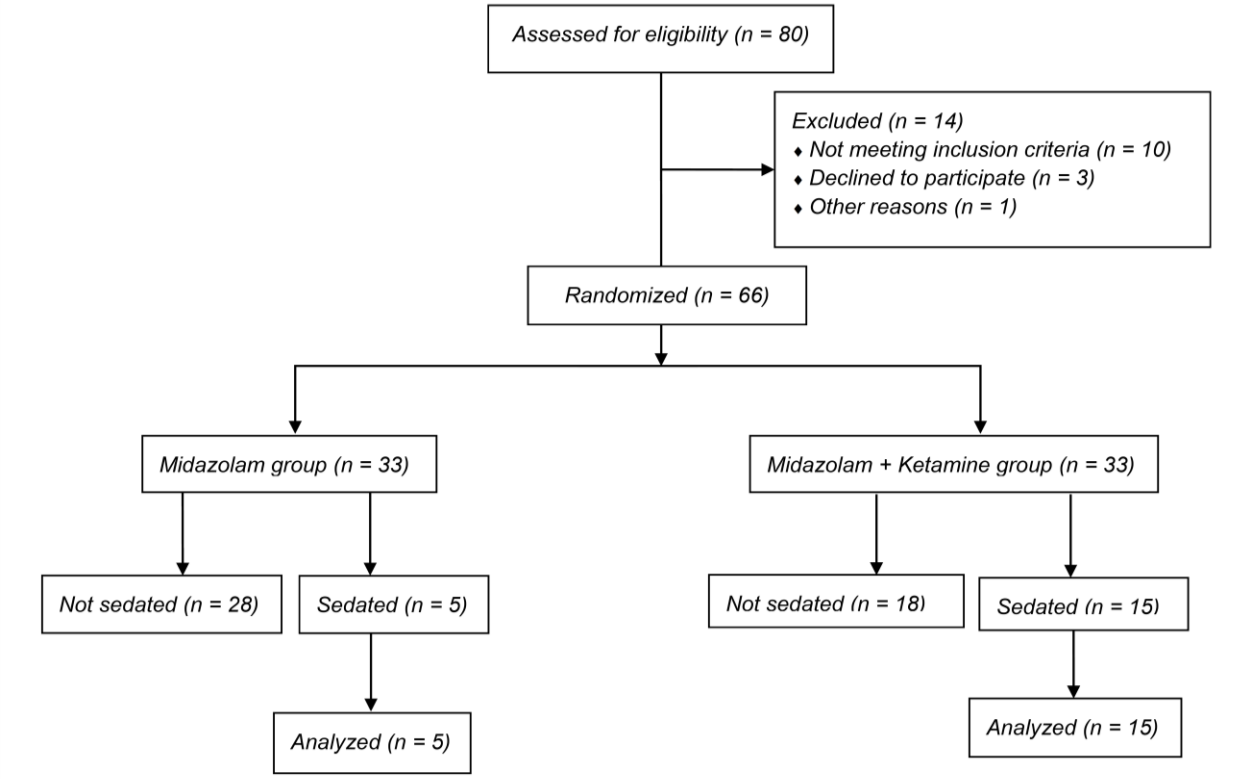

Figure 1: CONSORT flow diagram of study

Table 1: Demographic characteristics of the participants [a]

Characteristics	Midazolam	Midazolam-Ketamine	P Value
Height (centimeter)	101 ± 19	103 ± 20	0.147
Weight (kilogram)	15.7 ± 4.8	17.5 ± 14.6	0.234
Age (year)	3.0 ± 1.6	2.6 ± 1.6	0.369
Male to Female ratio	17:16	19:14	0.805

[a], Data are presented as mean ± standard deviation.

Table 2: The outcomes of patients in Midazolam and Midazolam-Ketamine groups

Outcome	OM Group	OMK Group	P Value
Adequately Sedated[1]	5 (15.2%)	15 (45.5%)	0.015
Time[2] to Become Adequately Sedated	33.80 ± 7.56	32.87 ± 10.18	0.854
Time[2] to Discharge From RD	89.60 ± 30.22	105.27 ± 21.98	0.223

OM: Oral midazolam; OMK: Combination of oral midazolam-ketamine; RD: Radiology department. [1], Number (%); [2], Mean ± standard deviation (minute)

groups in time of achieving adequate sedation (p = 0.854) and the time of discharging from radiology department (p = 0.223). Adverse effects observed in two patients (one with nausea and another with vomiting) in the OM group and three patients (two with nausea and one patient with vomiting) in the OMK group. Complications were minor and transient and did not differ between study groups (p > 0.05). No serious adverse events were seen in the study participant. Systolic blood pressure, SaO_2 level, pulse rate, and respiratory rate

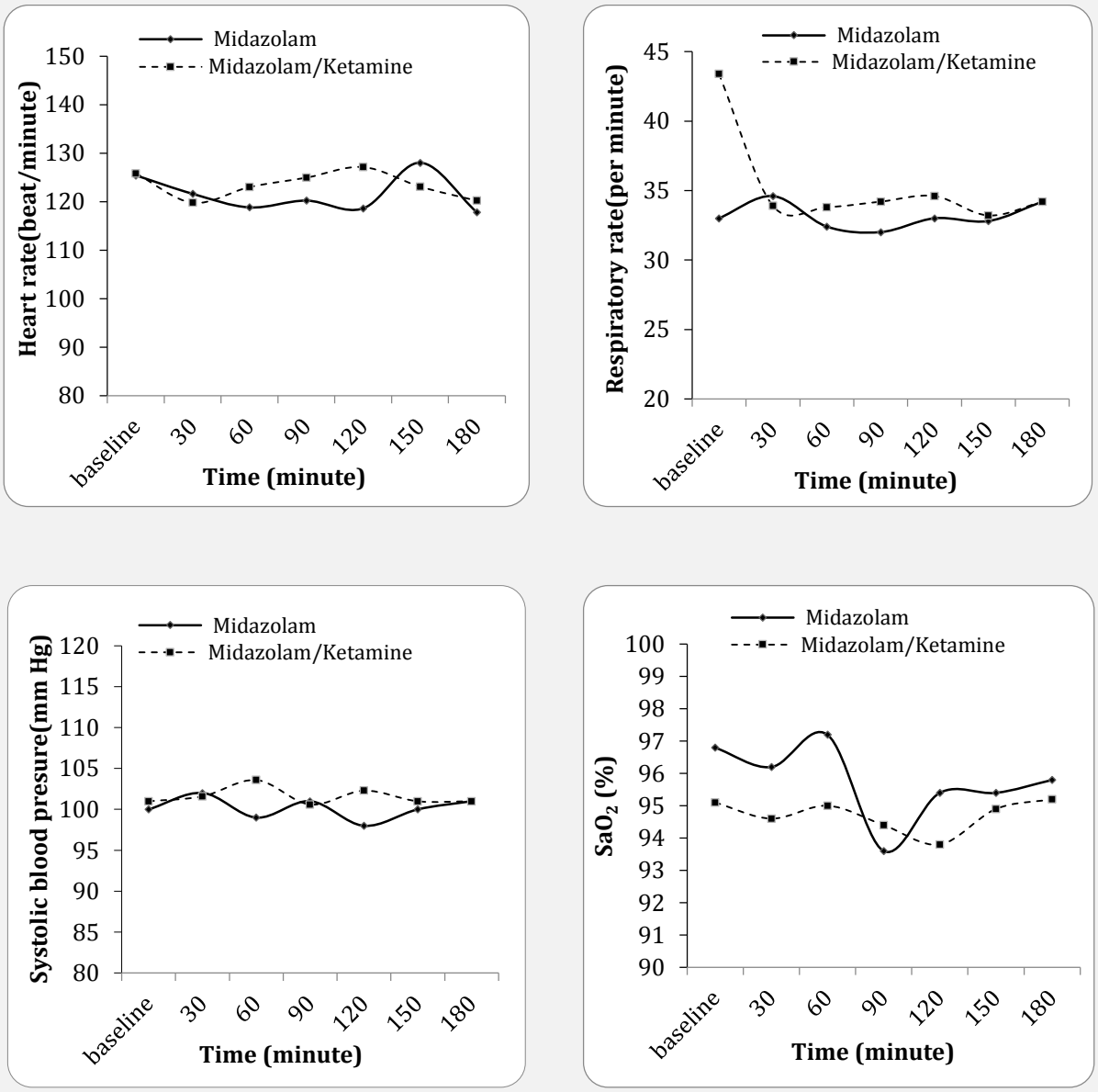

Figure: Inter-group differences of vital signs at baseline and at various time points after administration of midazolam and combination of midazolam-ketamine (df: 18, $p > 0.05$ for all comparisons).

showed no significant inter-group differences at baseline and at various time points after administration of the drugs (for all analysis: df = 18, $p > 0.05$, Figure 2).

Discussion:

Our investigation showed that in comparison to OM, OMK successfully induced sedation in 45% of the patients. OM failed to sedate the patient in 85% of the cases and led to administration of additional medication and longer time to obtain the scan.

Ketamine is used for premedication, sedation, and induction as well as maintenance of general anesthesia with minimal effect on respiration and tendency to preserve autonomic reflexes (7). Oral ketamine (OK) has been used for pediatric sedation in previous studies. It has been reported that 10 mg/kg of ketamine provides effective sedation and analgesia in young children undergoing wound repair processes (9). Moreover, 6 mg/kg of OK was reported to be effective in sedation for outpatient pediatric dental surgeries (10). OM is the most commonly used premedication in the United States (18), which has been used as a safe and effective sedative in pediatrics, mainly in pediatric dentistry (10, 17); however, intravenous midazolam has been found to induce more sedation (18). Intravenous or nasal midazolam has gained widespread popularity as a sedative for children undergoing radiographic studies such as CT scan (19-

21). The OMK and OM alone are safe, effective, and practical approach to manage children for minor dental procedures (22, 23). The efficacy of OM and ketamine, alone or in combination has been studied in pediatric dentistry sedation and premedication (24-26). Younge et al. reported better sedative effects during suturing lacerations with OK (10 mg/kg) in comparison to OM (0.7 mg/kg) (27). Although our study was consistent with the previous studies regarding the higher efficacy of OMK in comparison to OM, most of the previous studies reported success rates of 60% to 90% for OM (11, 17, 28) and 46% to 95% for OMK (11, 22). Barkan et al. showed that the combination of oral midazolam (0.5 mg/kg) and ketamine (5 mg/kg) led to deeper sedation in comparison with OM (0.5 mg/kg) alone in children requiring laceration repair. In addition, 27% of patients in the OM group and 6% in the OMK group needed further intravenous sedation (11). Moriera et al. (12) compared the efficacy of OM (1 mg/kg) and the OMK (midazolam, 0.5 mg/kg; and ketamine, 3 mg/kg) for guiding the behavior of children undergoing dental treatment and reported higher efficacy of OMK. On the other hand, there are several studies reporting lower success rate, which are similar to our findings. Moro-Sutherland et al. (6) compared the sedative effects of intravenous midazolam with pentobarbital during brain CT imaging in children aged six months to six years. They administered pentobarbital to 29 patients (53%) and midazolam (mean dose, 0.2 ± 0.03 mg/kg) to 26 patients (47%). In the midazolam group, only five patients (19%) were successfully scanned with midazolam alone and the remaining 21 patients (81%) required additional medication and took a longer time to scan. Another investigation reported a failure rate of 60% in administrating intranasal midazolam (0.2 mg/kg) for sedation of children undergoing CT scan (3). Molter et al. (29) used 0.4 mg/kg of OM 20 minutes before the induction of general anesthesia and reported a mild or no sedative effect in 76% to 84% of patients. In this study, the onset time of adequate sedation was 33 minutes in OM group and 32 minutes in OMK group. Younge et al. (27) reported an onset time of 20 minutes for OK and 43 minutes for OM. Other studies reported that the time to reach optimal sedation level would be 15 minutes for OM (10, 17). Studies, which used OM (0.5-1 mg/kg) as premedication reported that the best time for optimal preoperative sedation would be 30 to 45 minutes before scan (30). This time for ketamine is 25 to 45 minutes (9, 31). Barkan observed that the needed time to achieve adequate sedation was 17 minutes for OM and 14 minutes for OMK. The patients' blood pressure, respiratory rate, pulse rate, and SaO_2 levels did not show any significant changes during the sedation. Although ketamine and midazolam affect the respiratory and hemodynamics responses (11), our results were in line with the findings of previous studies that reported minimal effects of low-dose OM and OK on these parameters (17, 31). Although further studies are needed to confirm or refute our results and attention to the pharmacological aspects is necessary, lower efficacy of OM in this study could be explained as follows:

First, we used these drugs for CT imaging that needs a deeper level of sedation in comparison with some other studies that used those drugs in other settings as premedication. Second, in the previous studies, intravenous forms of these drugs were used, which might bring about unexpected results; the same drugs in different studies should be compared with caution. Third, the ethnic differences in response to these sedative agents might affect the results. Variability of drug response is an important consideration in clinical medicine. A major cause of variations in drug responses is hepatic cytochrome P450 oxidase (CYP450)-mediated drug metabolism (29). Distribution volumes and metabolism determine the pharmacokinetics of midazolam. Midazolam is almost exclusively metabolized by CYP450 3A (CYP3A) isoenzymes (32). There are several limitations to this study. First, we could not purchase the oral form of drugs. Although previous studies have shown that these parenteral forms can be used orally, the oral form of drugs might bring about results that are more precise. Second, the number of participants who were included in the final analysis (as sedated patients) was small.

Conclusion:

This study demonstrated that in comparison with OM, OMK was more effective in producing a satisfactory level of sedation in children undergoing CT examinations without additional complications; however, none of these two regimens fulfilled clinical needs for procedural sedation.

Acknowledgments:

The authors appreciate the insightful cooperation of staff of the Emergency Department.

Conflict of interest:

None

Funding support:

None

Authors' contributions:

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors.

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