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Comparison of Oral Midazolam and Promethazine with Oral Midazolam alone for Sedating Children during Computed Tomography

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Abstract

Introduction: Both midazolam and promethazine are recommended to be used as sedatives in many studies but each have some side effects that limits their use. Combination therapy as an alternative method, may decreases these limitations. Therefore, this study aimed to compare midazolam with midazolam-promethazine regarding induction, maintenance, and recovery characteristics following pediatric procedural sedation and analgesia. **Methods:** Children under 7 years old who needed sedation for being CT scanned were included in this double-blind randomized clinical trial. The patients were randomly divided into 2 groups: one only received midazolam (0.5 mg/kg), while the other group received a combination of midazolam (0.5 mg/kg) and promethazine (1.25 mg/kg). University of Michigan Sedation Scale (UMSS) was used to assess sedation induction. In addition to demographic data, the child's vital signs were evaluated before prescribing the drugs and after inducing sedation (reaching UMSS level 2). The primary outcomes in the present study were onset of action after administration and duration of the drugs' effect. **Results:** 107 patients were included in the study. Mean onset of action was 55.4±20.3 minutes for midazolam and 32.5±11.1 minutes for midazolam-promethazine combination ($p<0.001$). But duration of effect was not different between the 2 groups ($p=0.36$). 8 (7.5%) patients were unresponsive to the medication, all 8 of which were in the midazolam treated group ($p=0.006$). Also in 18 (16.8%) cases a rescue dose was prescribed, 14 (25.9%) were in the midazolam group and 4 (7.5%) were in the midazolam-promethazine group ($p=0.02$). Comparing systolic ($p=0.20$) and diastolic ($p=0.34$) blood pressure, heart rate ($p=0.16$), respiratory rate ($p=0.17$) and arterial oxygen saturation level ($p=0.91$) showed no significant difference between the 2 groups after intervention. **Conclusion:** Based on the findings of this study, it seems that using a combination of midazolam and promethazine not only speeds up the sedation induction, but also decreases unresponsiveness to the treatment and the need for a rescue dose.

Key words: Promethazine; midazolam; anti-anxiety agents; conscious sedation

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Introduction:

Procedural sedation and analgesia are constantly used procedures range from pain-free interventions such as imaging, to painful intervention like fracture reduction, wounds care, bone marrow aspiration, and placing a central venous catheter (1, 2). Sedating the patients, allows them to bear these unpleasant procedures while their cardiorespiratory function remains constant. These measures lead to increased quality of care, patients' satisfaction, reduced pain and anxiety, and earlier diagnosis and treatment (3-8). Pediatric imaging is one of the most indication of procedural sedation and analgesia. In the pediatric patient, performing CT scan is stressful and leads to increased mental stress, absence of cooperation with the staff, restlessness, and anxiety in the patient. These reactions not only interfere with the treatments but also lead to changes in physiologic parameters such as blood pressure, heart rate, res-

piratory rate, and etc. (9, 10). Selecting the precise medication is very important in these situations. Using a suitable sedative, results in a decrease in the rescue dose and increases the safety of the procedure (11). Most of these medications can be prescribed through various routes and selecting the best drug varies based on the procedure, level of pain, optimum depth of sedation, and the patient's condition (1, 12, 13). Although there are lots of drugs that induce conscious sedation, but their side effects have limited their clinical use (14, 15). Some studies have suggested using combination therapy as they show increased effectiveness, decreased loading dose, and therefore decreased side effects (8, 9, 16, 17).

Midazolam has been used as a sedative in children for a long time. This short-acting benzodiazepine acts as a sedative, amnesic and stress reliever. It is preferred to long-acting benzodiazepines such as diazepam (18, 19). But using oral midazolam alone, shows a high rate of failure in sedation (20, 21). Promethazine is another agent that is used for sedating children (22, 23). It is a common antiemetic that has been used as a safe and effective drug with a low rate of side effects and failure. Therefore using it combined with midazolam, may decreases midazolam's limitations, but to date no study has been done to compare the sedative effect of midazolam alone with midazolam-promethazine, in children undergoing CT scan. For these reasons, this study aimed to compare midazolam with midazolam-promethazine regarding induction, maintenance, and recovery characteristics following pediatric procedural sedation and analgesia.

Methods:

Study design:

This double-blind randomized clinical trial was done in a medical center in Ahwaz, Iran in 2013. Protocol of the study was approved by the ethics committee of Jondishapour University of Medical Sciences, Ahwaz, Iran. The researchers abided by the principles of Helsinki Declaration in the evaluations and prescribing the medications. Signed consent forms were obtained from patients' parents.

Patients:

Healthy children under 7 years old who needed sedation for undergoing CT scan were included based on American Society of Anesthesiologists (ASA I and II) scale. Exclusion criteria included allergy to midazolam or promethazine, gastritis, any serious systemic disease, severe systemic reaction, severe cardiovascular disease, coronary artery disease, head trauma, eye trauma, central nervous system disease, contraindications to sedation, receiving sedative-hypnotic drugs in the last 48 hours. Sampling was consecutive. The sample size was determined as 51 patients in each group, considering standard deviation range of 3 to 23 minutes for midazolam's duration of effect (4, 5, 24), with α=0.05 and β=0.1 and maximum error of 1.5 minutes (d=1.5).

Intervention:

Patients were enrolled consecutively and randomly divided into 2 groups: one only received midazolam (a dose of 0.5 mg/kg weight), while the other group received midazolam (a dose of 0.5 mg/kg weight) plus promethazine (a dose of 1.25 mg/kg weight). Block randomization was executed using a computer software. The drugs were obtained from Rotexmedica Company (Germany). To ensure that the patients remained unaware of the treatment assignment, an hour before CT scan, oral promethazine was prescribed for the combination group while the other group drank a sugar syrup. 20 minutes before the CT scan, both groups received midazolam. All the drugs were mixed with fruit juice. In case of vomiting in the initial 15 minutes after receiving midazolam, this drug would be prescribed again with the same dose. The data were gathered by another researcher for ensuring blindness to therapy. The drugs were administrated when the level of arterial saturated oxygen was above 95% and in case of any drop in the oxygen saturation, oxygen therapy would be started. If the patient didn't respond to treatment, a rescue dose (50% of the initial midazolam dose) would be used.

Variables:

Level of sedation was assessed every 10 minutes since receiving midazolam based on University of Michigan Sedation Scale (UMSS). This scale has 5 levels which is shown in panel 1. In addition to demographic data (age, sex, weight), the child's vital signs (respiratory rate, heart rate and level of arterial saturated oxygen) were evaluated before prescribing the drugs and after induc-

Panel 1: University of Michigan Sedation Scale

Score	Definition
0	Awake/Alert.
1	Minimally Sedated: Tired/sleepy, appropriate response to verbal conversation and/or sounds.
2	Moderately Sedated: Somnolent/sleeping, easily aroused with light tactile stimulation.
3	Deeply Sedated: Deep sleep, arousable only with significant physical stimulation.
4	Unarousable

Table 1: Comparing demographic and clinical factors of the patients before intervention

Variable	Midazolam	Midazolam+ Promethazine	P
Age (Month)	36.0 (15.5)	36.8 (13.7)	0.79
Weight (kg)	14.7 (3.3)	14.2 (2.6)	0.46
SBP (mm Hg)	97.1 (8.1)	98.9 (5.5)	0.17
DBP (mm Hg)	59.1 (5.5)	60.6 (3.5)	0.09
Heart rate (per min)	115.1 (11.1)	112.9 (10.3)	0.29
Respiratory rate (per min)	19.9 (2.7)	18.8 (2.0)	0.01
Oxygen saturation (%)	98.6 (0.7)	98.7 (0.6)	0.6

ing sedation (reaching UMSS level 2). Finally, any side effect related to the prescribed drugs would be recorded.

Outcomes:

The primary outcomes in the present study were onset of action after administration and duration of the drugs' effect. To evaluate the onset of action, the time interval between midazolam prescription and sedation induction (reaching UMSS level 2) was calculated. For evaluating the duration of effect, the time interval between sedation induction and complete awareness (reaching UMSS level 0) was recorded. Secondary outcomes included incidence of the drugs' side effects, heart rate, blood pressure, respiratory rate, arterial oxygen saturation level, needing a rescue dose and no response to the treatment (not reaching UMSS level 2).

Statistical analysis:

The data were entered in SPSS 21.0. Quantitative data were expressed as mean ± standard deviation and qualitative data were shown as frequency and percentage. To compare the 2 groups regarding demographic and clinical factors before intervention chi square test (for nominal qualitative variables) and Mann-Whitney U test (for quantitative and ordinal variables) were used. Also, the 2 groups were compared regarding onset and duration of effect, using Mann-Whitney U test. Since the children's vital signs before intervention was significantly different in the 2 groups, non-parametric analysis of covariance was used to compare these factors in the groups. In all the analyses $p<0.05$ was considered the significance level.

Results:

107 children were included in the study (54 patients in the midazolam group and 53 in the midazolam-promethazine group). Mean age was 36.0±15.5 months in the midazolam group and 36.8±13.7 months in the midazolam-promethazine group (p=0.79). 31 (57.4%) patients in the midazolam group and 28 (52.8%) in the midazolam-promethazine group were male (p=0.63). Table 1 shows the distribution of demographic and clinical factors before intervention. As can be seen, only respiratory rate was significantly different in the groups (p=0.01).

Mean onset of action for midazolam (55.4±20.3 minutes) was significantly more than midazolam-promethazine combination (32.5±11.1 minutes) (p<0.001). But duration of effect was not different between the 2 groups (p=0.36) (figure 1). 8 (7.5%) patients were unresponsive to the medication, all 8 of which were in the midazolam

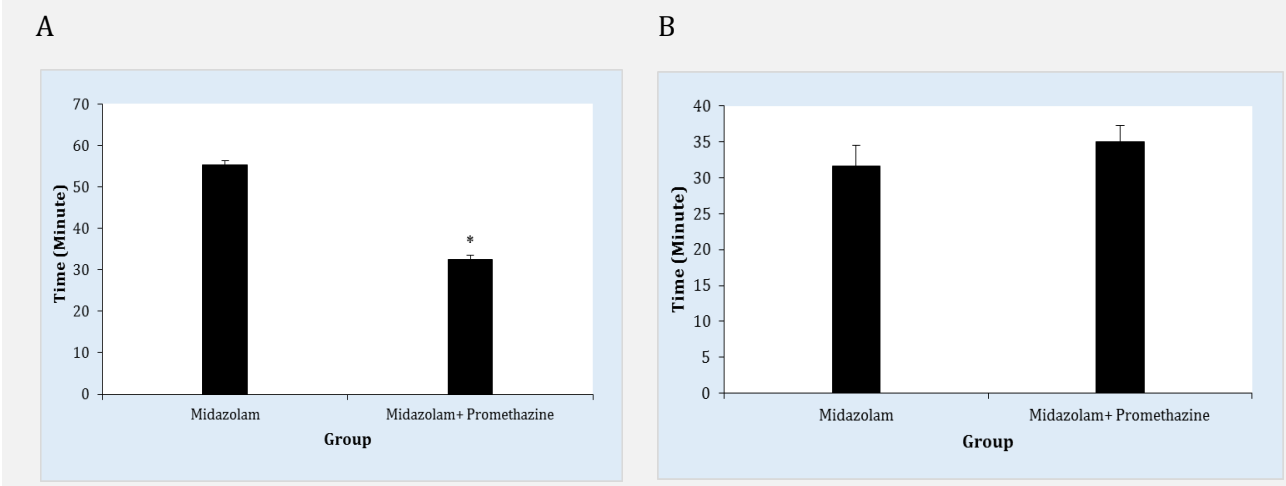

Figure 1: Onset of action (A) and duration of effect (B) of midazolam and midazolam-Promethazine in sedation of the children. *, shows significant difference at p<0.001.

Table 2: Comparing clinical factors of the patients after intervention

Variable	Midazolam	Midazolam+ Promethazine	P*
SBP (mm Hg)	93.2 (7.5)	94.8 (4.7)	0.20
DBP (mm Hg)	60.4 (6.7)	63.0 (5.4)	0.34#
Heart rate (per min)	111.5 (10.5)	108.6 (10.8)	0.16
Respiratory rate (per min)	18.9 (2.4)	17.6 (1.7)	0.17#
Oxygen saturation (%)	98.9 (0.8)	98.9 (0.7)	0.91

*, based on Mann-Whitney U test; #, based on non-parametric analysis of covariance adjusted for pretreatment values.

treated group (p=0.006). Also in 18 (16.8%) cases a rescue dose was prescribed, 14 (25.9%) were in the midazolam group and 4 (7.5%) were in the midazolam-promethazine group (p=0.02). Only 2 cases of nausea and vomiting was seen both of which were in the midazolam group (p=0.99).

Comparing systolic (p=0.20) and diastolic (p=0.34) blood pressure, heart rate (p=0.16), respiratory rate (p=0.17) and arterial oxygen saturation level (p=0.91) showed no significant difference between the 2 groups after intervention (table 2).

Discussion:

The findings of this study showed that mean onset of action for midazolam is significantly longer compared to midazolam-promethazine combination, while their duration of effect is no different. In addition, the frequency of not responding to treatment and needing a rescue dose is higher in the midazolam treated group. Yet, both treatments have similar effects on nausea and vomiting, blood pressure, heart rate, respiratory rate and arterial oxygen saturation level. Therefore, it seems that using a combination of midazolam and promethazine not only speeds up the sedation induction, but also decreases unresponsiveness to the treatment and the need for a rescue dose.

In line with this study, Cengiz et al. showed that the onset of action in a combination of midazolam and diphenhydramine is shorter than midazolam alone, while their duration of effect in no different (25). Also, Jain et al. expressed the same results regarding onset of action comparing midazolam-ketamine combination with midazolam (26). In addition, Parkinson et al. (27) and Crean (28) demonstrated in their respective studies that promethazine combined with chloral hydrate has a better sedative effect on children compared to midazolam alone. Houpt et al. showed that using chloral hydrate (dose: 25 mg/kg) combined with promethazine, is no different to using a 50 mg/kg chloral hydrate regarding sedation level and hemodynamic factors (29).

In the present study, 2 cases of nausea were seen in the midazolam group despite this drug having an antiemetic properties, which might be due to its bitter taste. In the combination group no nausea and vomiting was seen. Since promethazine had been received earlier in this group, the anti-histaminic and anti-cholinergic effects of promethazine might have controlled the nausea (22).

The combination treatment using midazolam plus promethazine in children under 7 years old lead to a significant decrease in midazolam's failure and improved its effectiveness as expected. Midazolam is a short-acting benzodiazepine that exerts its effect by affecting GABA receptors and resulting in chloride ion influx to the neuron (25), while promethazine acts on histamine and cholinergic receptors of medullary reticular formation to show its sedative effects (23). Based on the findings of this study we can conclude that promethazine amplifies the effects of midazolam by affecting medulla and pons and leads to a decrease in its failure rate.

Little sample size and short follow-up time are of the limitations of this study. Therefore it is recommended to increase sample size and follow-up time in future studies.

Conclusion:

The findings of this study showed that mean onset of action for midazolam is significantly longer compared to midazolam-promethazine combination, while their duration of effect is no different. In addition, the frequency of not responding to treatment and needing a rescue dose is higher in the midazolam treated group. Yet, both treatments have similar effects on nausea and vomiting, blood pressure, heart rate, respiratory rate and arterial oxygen saturation level. Therefore, it seems that using a combination of midazolam and promethazine not only speeds up the sedation induction, but also decreases unresponsiveness to the treatment and the need for a rescue dose.

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Conflict of interest:

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