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ORIGINAL RESEARCH

Comparing Two Different Doses of Intravenous Midazolam in Pediatric Sedation and Analgesia

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Abstract: **Introduction:** Midazolam has turned into a common drug for pediatric procedural sedation and analgesia. However, there is not much data regarding its proper dose and potential side effects in the Iranian children population. Therefore, the present study was done to compare 2 doses of IV midazolam in this regard. **Methods:** The present clinical trial was performed to compare 0.1 and 0.3 mg/kg doses of IV midazolam in induction of sedation for head trauma infant patients in need of brain computed tomography (CT) scan. Conscious infants under 2 years old, with stable hemodynamics were included. Onset and duration of action as well as probable side effects were compared between the two groups using SPSS version 22. **Results:** 110 infants with the mean age of 14.0 ± 5.9 months (range: 4–24) and mean weight of 9.7 ± 2 kg (range: 5–15) were randomly allocated to one of the 2 study groups (54.6% female). Success rate in 0.1 and 0.3 mg/kg groups were 38.2% (21 patients) and 60% (33 patients), respectively ($p = 0.018$). Overall, 56 (50.9%) patients did not reach proper sedation and were sedated receiving ketamine (22 patients) or another dose of midazolam (34 patients, mean additional dose needed was 2.1 ± 1.1 mg). **Conclusion:** The results of the present study demonstrated the higher success rate and longer duration of action for 0.3 mg/kg midazolam compared to 0.1 mg/kg. The groups were equal regarding onset of action, effect on vital signs and probable side effects.

Keywords: Midazolam; conscious sedation; dose-response relationship, drug; infant; emergency service, hospital

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1. Introduction

Sedation induction is one of the most important and sometimes most difficult stages of carrying out a diagnostic or therapeutic procedure in children (1). Children not cooperating for diagnostic evaluations such as computed tomography (CT) scan and magnetic resonance imaging are among the most common cases of using procedural sedation and analgesia (PSA) in emergency departments (ED). An ideal sedative drug should be rapid and short-acting, with minimum side effects on the patients respiratory condition and hemodynamic.

Various drugs such as chloral hydrate, phenobarbital, propofol, midazolam, and etomidate are among the available drugs for this purpose Yet, selection of the safest and most efficient drug and its proper dose for sedation are a matter of debate (1–4). Many of pediatric patients do not receive enough drug due to concerns about probable side effects of the drug (5). Midazolam has turned into a common drug for induction of sedation in EDs as a result of its short half-life, various methods of prescription and less pain at the time of injection. This relatively short-acting benzodiazepine has anti-stress, sedative, anti-seizure, and muscle relaxant effects.

Singh et al. showed that use of intravenous (IV) midazolam with a 0.2 mg/kg dose, can induce proper sedation with minimum side effects for pediatric imaging (6). However, there is not much data regarding its proper dose and potential side effects especially in the Iranian children population. Therefore, the present study was done to compare 2 doses of IV midazolam in sedation induction for doing brain imaging in infants.

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2. Methods

2.1. Study design

The present clinical trial was performed to compare 0.1 and 0.3 mg/kg doses of IV midazolam in induction of sedation for infants in need of brain CT scan following head trauma. The infants presented to the ED of Golestan and Imam Khomeini Hospitals, Ahvaz, Iran, during April 2014 to March 2015 were studied. After completely explaining the study protocol to the parents, informed consent form was filled for each participant to enter the study. All the researchers adhered to Helsinki declaration. If the parents were not content with the study process or did not want their infant to continue participating at any stage, the infant was excluded. The present study has been registered on the Iranian Registry of Clinical Trials (IRCT) under the number IRCT201592121289N2 and approved by the Ethics Committee of Ahvaz Jundishapour University of Medical Sciences.

2.2. Participants

Infants presented to the ED following head trauma in need of sedation induction for undergoing brain CT scan were enrolled. Conscious infants under 2 years old, with stable hemodynamics were included. Exclusion criteria consisted of high probability of difficult airway, history of uremia and allergy to benzodiazepine, presence of hemodynamic instability, congestive heart failure, liver diseases, decreased level of consciousness, uncontrolled vomiting, history of reflux, and simultaneous use of opioids.

2.3. Procedure

All patients were prepared with a proper peripheral IV line and continuous heart, blood pressure, pulse rate, and pulse oximetry monitoring. Participants underwent low-flow oxygen therapy via nasal cannula during the procedure. They were divided into equal groups of A and B, using 4-block randomization. Group A, received IV midazolam with 0.1 mg/kg dose, while the dose was 0.3 mg/kg for group B. The goal was reaching sedation level of 3 or 4 based on Ramsay scale (7). Not reaching the desired level of sedation was considered as sedation failure. In these cases IV ketamine with 1 mg/kg dose or another dose of midazolam was used. All injections were done via the peripheral vessel using a blue or yellow angiocatheter, and slowly during 10 seconds. Brain CT scan indication was decided by an emergency medicine specialist based on the standard protocols of advanced trauma life support (ATLS). Injections were done by trained nurses under supervision of a senior emergency medicine resident. Over the course of the procedure, all the required equipment for probable need for airway management were present at the patients bedside. Midazolam ampule containing 5 mg/cc was used. We should note that the physician prescribing the drugs and the patientsâĂŹ parents were blinded to the drug dose.

Table 1: Baseline characteristics of studied patients

Variable	Groups		P value
	0.1 mg/kg	0.3 mg/kg	
Sex			
Boy	26 (47.3)	24 (43.6)	< 0.424
Girl	29 (52.7)	31 (56.4)	
Age (Month)	15.7 ± 5.4	12.4 ± 6.0	0.003
Weight (Kg)	9.8 ± 1.9	9.5 ± 2.0	0.465

The number of patients in each group = 55; measures presented as number (%) or mean ± standard deviation.

2.4. Data gathering

A checklist consisting of demographic data and pharmacodynamics (onset and duration of action and side effects) was filled for all the patients in both groups. Drop of oxygen saturation to < 95, decreased blood pressure, inconsolable crying, restlessness and anxiety, hiccup, opisthotonus, seizure, nausea and vomiting, and respiratory depression and apnea were among the studied side effects.

2.5. Statistical analysis

Data were analyzed using SPSS statistical software version 22. Quantitative data were reported as frequency and percentage, and qualitative ones as mean ± standard deviation. Chi-square and Independent sample t-test were used for comparing data between two groups. $P < 0.05$ was considered as significance level.

3. Results

110 infants with the mean age of 14.0 ± 5.9 months (range: 4–24) and mean weight of 9.7 ± 2 kg (range: 5–15) were randomly allocated to one of the 2 study groups (54.6% female). Table 1 shows the baseline characteristics of the patients. Success rate in 0.1 and 0.3 mg/kg groups were 38.2% (21 patients) and 60% (33 patients), respectively ($p = 0.018$). Overall, 56 (50.9%) patients did not reach proper sedation and were sedated receiving ketamine (22 patients) or another dose of midazolam (34 patients, mean additional dose needed was 2.1 ± 1.1 mg). Table 2 compares the therapeutic characteristics and side effects of the 2 doses of midazolam.

4. Discussion

The results of the present study demonstrated the higher success rate and longer duration of action for 0.3 mg/kg midazolam compared to 0.1 mg/kg. The groups were equal regarding onset of action, effect on vital signs and probable side effects.

Table 2: Baseline characteristics of studied patients

Variable	Groups		P value
	0.1 mg/kg	0.3 mg/kg	
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Girl	29 (52.7)	31 (56.4)	
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The number of patients in each group = 55; measures presented as number (%) or mean ± standard deviation.

Facing children in ED has always been special. Presentation of a pediatric trauma patient, accompanied by restless parents, to an overcrowded ED has been a nightmare for emergency medicine physicians, especially if a diagnostic and therapeutic procedure is required. The need for keeping the child motionless during procedures, has made using PSA inevitable for this age group. Being familiar with various kinds of available drugs and their dosage is a necessary skill for all emergency physicians. Therefore, the present study was designed and carried out to compare the effectiveness and side effects of two different IV midazolam doses.

In the study by Singh et al., midazolam's onset of action was shorter than this study (6). This difference may be due to the differences in age distribution of the participants in the 2 studies and the chief complaints on admission. In both studies, a relatively significant number of the patients needed additional doses to reach proper sedation and a single dose of the drug had a significant failure rate. In addition, in a study by Sutherland et al., use of 0.2 mg/kg alone was not enough to induce proper sedation for undergoing CT scan in most children; it was efficient for only 19% of them (2). Regarding onset of action, the results of the present study were in line with those of Jevdjic et al. in their 2011 study, especially in the 0.1 mg/kg dose (8). Additionally, regarding probable side effects and effects on vital signs a thorough correlation was seen between the results of this study and Rahman study (9). Treatment success rate in this study was less than 50% for both doses. This means that about half the patients need higher doses of midazolam or other drugs such as ketamine to reach the proper level of sedation. The results of a review study in 2007 showed that despite the similar effects of midazolam and ketamine, ketamine was the drug of choice for both parents and physicians to sedate children (10). Therefore, it seems that although midazolam is safe and emergency physicians are familiar with its probable side effects, its success rate, at least with the doses mentioned in the present study, is not high. Therefore, we should either revise the dose of this drug, or use other drugs with higher success probability. The importance of this matter is that most of the time, when children are not sedated with the initial injection, it makes the parents more anxious and therefore makes the atmosphere more chaotic. It is suggested to carry out other trials with various doses and bigger sample size, to find the proper dose of drug. Parents not being content about their children participating in the study was among the limitations of the present study, which made case collection somehow difficult.

5. Conclusion

The results of the present study demonstrated the higher success rate and longer duration of action for 0.3 mg/kg midazolam compared to 0.1 mg/kg. The groups were equal regarding onset of action, effect on vital signs and probable side effects.

6. Appendix

6.1. Acknowledgements

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6.2. Author contribution

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

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6.4. Conflict of interest

None.

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