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Intramuscular compared to intravenous midazolam for paediatric sedation: A study on cardiopulmonary safety and effectiveness

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ABSTRACT

Background: Sedation in children remains a controversial issue in emergency departments (ED). Midazolam, as a benzodiazepine is widely used for procedural sedation among paediatrics. We compared the effectiveness and safety of two forms of midazolam prescription; intramuscular (IM) and intravenous (IV). **Patients and Methods:** A cohort study was conducted on two matched groups of 30 children referred to our ED between 2010 and 2011. The first group received IM midazolam (0.3 mg/kg) and the second group received IV midazolam (0.15 mg/kg) for sedation. For evaluating effectiveness, sedation, irritation and cooperation score were followed every 15 min for 60 min and for safety assessment, vital signs and O_2 saturation were observed. **Results:** Mean age was 6.18 ± 2.88 years and 31 patients (51.7%) were male. All patients were sedated completely after using first dose. There was an overall complication rate of 68.3%. 35 (58.3%) patients presented euphoria as the most common complication, but there was no statistical difference between the two groups ($P = 0.396$). Cases who received IV midazolam became sedated faster than those received IM midazolam ($P > 0.001$). The vital signs including heart rate, respiratory rate, systolic blood pressure and O_2 saturation changed significantly between and within groups during the sedation ($P < 0.05$). **Conclusion:** Both forms of midazolam, IM and IV, are effective and safe for paediatric sedation in ED. Although the sedative with IV form might appear sooner, IM form of midazolam can be effectively used in patient with limited IV access. Patients are better to observe closely for psychological side-effects.

Key words: Midazolam, safety, sedation

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INTRODUCTION

There are many painful procedures such as suturing, intubation, and limb reduction in emergency departments (ED). Up to 80% of children have anxiety before surgical and medical interventions.[1,2] Their anxiety should be decreased because the stress due to low cooperation can decrease the quality of medical procedures. Although sedation helps patients to bear painful and unpleasant procedures, they can have several side-effects such as an imbalance in haemodynamic status.[2] These drugs in children are associated with more complications than adults, especially in ED.[3]

Now-a-days, non-intravenous (IV) medications such as intramuscular (IM) or intranasal medications are more considered in children because of more tolerance.[4,5] Due to the considerable rate of failure of catheterisation, children agitation, and time of procedure, it seems that IM injection is more useful procedure than IV for sedation in ED. An ideal sedative drug is a drug with rapid and simple way of use, short-term effect, and absence of side-effects. In comparison with other benzodiazepines, effect of midazolam is more rapidly shown. Furthermore, midazolam is more commonly used due to its lower cardiovascular and pulmonary complications.[6,7] It has no serious impact on hemodynamic status at a low dose (0.5 mg/kg), but good and excellent sedation has been observed only in 60-80% of patients.[2,8]

Some studies have been conducted on effectiveness and cardiopulmonary safety of IV midazolam for pre-procedural sedation in comparison with other medications and they confirmed midazolam efficacy.[4,9-13] There are serious concerns about its side-effects, especially haemodynamic and cardiopulmonary imbalance; this issue has been more significant in injective type, especially in children.[7,14,15] We compared the effectiveness and cardiopulmonary safety of two forms of midazolam, IM and IV, while rarely compared in the previous literatures.

PATIENTS AND METHODS

The study was conducted as cohort study on children in the age range between 2 and 12 years old admitted in an ED of Baqiyatallah University Hospital for diagnostic or medical procedures during 2010-2011. Exclusion criteria included children with mental or physical underdevelopment, the extremely weak and ill children suffering from declined consciousness level, or recent administration of midazolam or other sedative medications for any reason, and/or presence of specific diseases such as seizures. This study was approved by Medical Ethics Committee of Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran. After taking an informed consent from signed by parents, 60 children were randomly allocated into two groups with 30 members. Used a single dose of midazolam in both groups were provided by a valid company. Initially, demographic characteristics were noted as also the vital signs consisting of blood pressure (BP), heart rate (HR), and respiratory rate (RR) as illustrating items for cardiopulmonary status were measured before administering IV or IM midazolam. Subsequently, the IM and IV groups were respectively injected with 0.30 mg/kg "IM midazolam" and 0.15 mg/kg "IV midazolam."[2,8] Vital signs, sedation status and oxygenation (using pulse-oximetry) were monitored using a validated sedation scale questionnaire[16] as following: The data were recorded every 5 min in the initial 15 min, and afterwards, every 15 min for 1 h by a physician who was blinded for the prescribed medications [Table 1].[16] Dizziness, euphoria and other probable complications were evaluated and reported by an emergency medicine specialist (MR Gh) based on the DSM-IV criteria.

Data were analysed using SPSS software 16th edition (SPSS Inc., Chicago, IL, US). The differences between variables were checked by means of Chi-square test and *t*-test. Friedman, ANOVA, and repeated measurement tests were used for analysing the variables in specified and repeated intervals.

RESULTS

A total of 60 children with the mean age of 6.18 years and standard deviation (SD) of 2.88 years were studied. The mean ± SD weight was 21.47 ± 7.23 kg and 31 children were male (51.7%). Patients' demographic variables are presented in Table 2. Concerning the gender distribution, 14 individuals of IM group and 17 individuals of IV group were male, which showed no significant difference between the two groups ($P = 0.438$). The most common indication in the both groups was suturing (16.7% and 18.3% for IM and IV groups, respectively) following with imaging (both groups: 16.7%). No, statistically significant difference was observed in indications of sedation between the two groups ($P = 0.644$) [Table 2].

With respect to post-sedation complications, two individuals (6.7%) in the IM group suffered from dizziness and 20 of them (67%) experienced euphoria, while eight persons (27%) exhibited no complications at all. In the IV group, four cases (13%) felt dizziness, 15 cases (50%) experienced euphoria, and 11 individuals (36%) had no considerable complications. These differences in complications between two groups were not statistically significant ($P = 0.396$).

In the IM group, the arterial oxygen saturation varied from 97.5 in the baseline to 96.33 in the 60th min ($P < 0.001$). In the IV group, this value changed from 94.83 to 95.90 ($P = 0.031$) [Figure 1]. Also, trends of change in arterial O_2 saturation were statistically significant between two groups ($P < 0.000$). In the IM group, RR decreased from 22.23 ± 6.54 at the beginning of study to 18.80 ± 4.81 at the end of study, and in the IV group from 27.43 ± 6.51 to 25.36 ± 5.72 [Figure 2]. The changes within both groups were significant, and in addition, these variations were significant in comparison between the two groups

Table 1: Sedation scoring system[16]

Item	Condition	Scale
Sedation scale	Awake and active	1
	Awake and quit	2
	Sleepy and response to vocal stimuli	3
	Sleepy and gently response to vocal stimuli	4
	Sleepy without response to stimuli to wake up	5
Irritability scale	Aggressive	1
	Crying	2
	Calm	3
	Completely calm	4
Cooperation scale	Resistant (need to hold)	1
	Mild resistant (need to care)	2
	Good cooperation	3

Table 2: Baseline characteristics and indications for sedation

Items	IM group (%)	IV group (%)	*P* value
Age (year; mean±SD)	5.50±2.70	6.87±2.94	0.066
Weight (kg; mean±SD)	22.48±5.51	24.65±7.21	0.152
Male prevalence (%)	14 (46.6)	17 (56.6)	0.438
Suturing (%)	10 (16.7)	11 (18.3)	0.644
Imaging (%)	10 (16.7)	10 (16.7)	
Joint reduction (%)	5 (8.3)	7 (11.7)	
Other indications (%)	5 (8.3)	2 (3.3)	

SD: Standard deviation; IM: Intramuscular; IV: Intravenous; kg: Kilograms

($P < 0.001$ in three issues). Furthermore, HR in the IM group changed from 112.4 ± 14.82 at baseline to 103.9 ± 14.57 at the end of study ($P < 0.001$); this variation was from 137.3 ± 35.21 to 117.5 ± 13.18 in IV group ($P < 0.001$), and additionally, the difference between variations was significant between IM and IV groups ($P < 0.001$) [Figure 3].

Finally, the differences between trend of changes in two groups in terms of systolic BP, sedation, irritability and cooperation scale were statistically significant while the differences in diastolic BP between two groups was not significant ($P = 0.224$). Variations of systolic and diastolic BP, sedation score, stimulability and collaboration can be seen in Table 3.

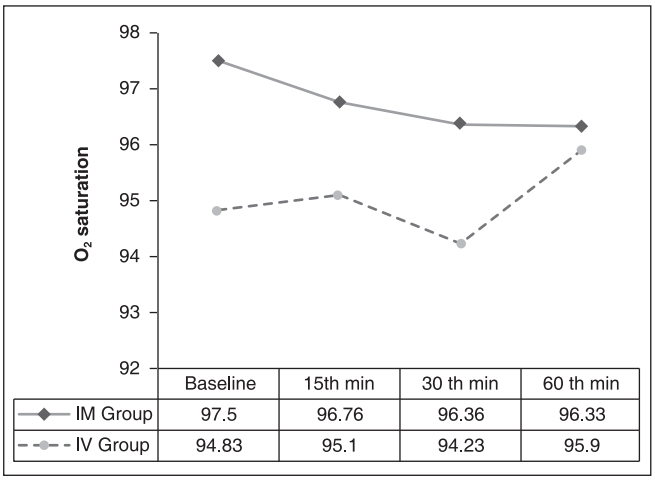
DISCUSSION

Overall, it seems that two groups had no remarkable difference in terms of side-effects, but significant contrasts were observed concerning clinical effectiveness and its impacts on vital signs, which were known as cardiopulmonary status. Although both forms of midazolam provided sufficient level of sedation for the procedure as assessed by the physician, the onset of sedation in IV injection was evidently faster than the IM procedure which was as expected.

Midazolam is a good sedative premedication, which can be prescribed in several ways.[17,18] There are some limitations in both the oral and the intranasal routes of administration. "The oral route can lead to unreliable concentrations in serum and clinical effect due to first pass hepatic metabolism. The intranasal route typically has a mucosal irritating effect, which can be painful and produce anxiety in the child."[2] Paradoxical responses (such as unexpected agitation and hyperexcitability, euphoria) are not uncommon while it was reported between 1% and 15% of children receiving midazolam. The children in the current research experienced high levels of sedation as equal as deep sedation using an equal dose of IM and IV for everyone.

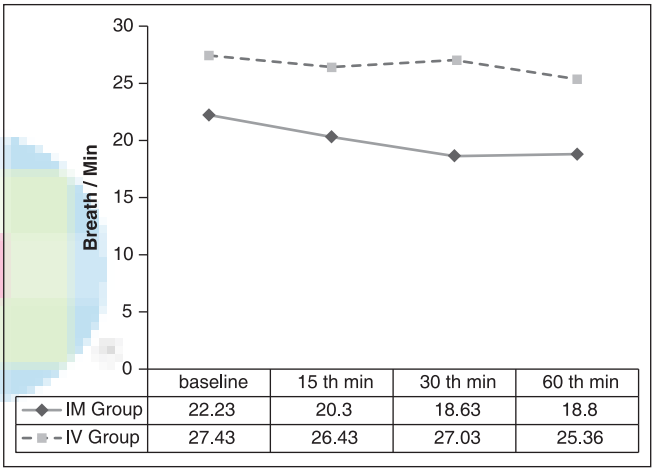
Interestingly, HR, BP, RR and irritability scale in the IV group were higher than the IM group at the baseline although O_2 saturation and sedation scale in the IV group was lower than the IM group at the baseline. These differences, which were not statistically significant, can be explained by the fact that IV line access was carried out before midazolam injection.

According to literature review, there are few similar studies dealing with analysis of effectiveness and



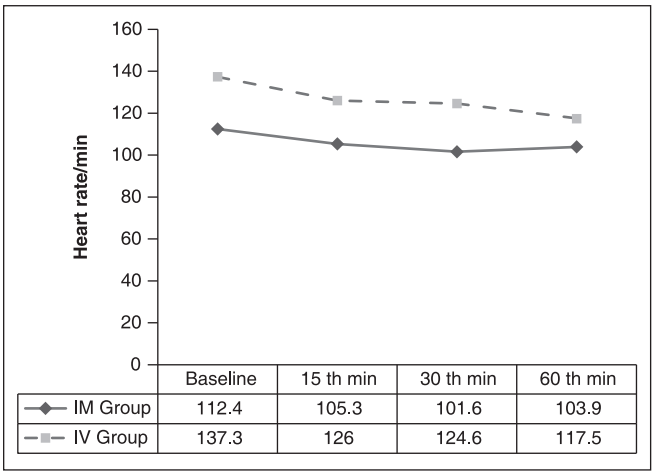
	Baseline	15th min	30 th min	60 th min
IM Group	97.5	96.76	96.36	96.33
IV Group	94.83	95.1	94.23	95.9

Figure 1: Trend of O_2 saturation during the study. Changes of heart rate within the intramuscular (IM) group ($P < 0.001$) and intravenous (IV) group ($P = 0.031$) are significant. The difference of changes between IM and IV groups was also significant ($P < 0.001$)



	baseline	15 th min	30 th min	60 th min
IM Group	22.23	20.3	18.63	18.8
IV Group	27.43	26.43	27.03	25.36

Figure 2: Trend of respiratory rate during the study. The changes within both groups and additionally, between the two groups were significant; $P < 0.001$ in three issues



	Baseline	15 th min	30 th min	60 th min
IM Group	112.4	105.3	101.6	103.9
IV Group	137.3	126	124.6	117.5

Figure 3: Trend of heart rate during the study. The changes within both groups and additionally, between the two groups were significant; $P < 0.001$ in three issues

Table 3: Vital signs and sedation scores changes during the study in terms of two groups

Item	Group	Baseline	15th min	30th min	60th min	*P* value within group	*P* value between group
Systolic BP	IM	125.2±15.10	110±9.81	104.6±8.22	111.5±7.20	<0.001	0.030
	IV	126.3±24.95	95.96±25.37	100.2±15.08	107.9±15.26	<0.001	
	P	0.832	0.007	0.163	0.245		
Diastolic BP	IM	77.90±9.25	70.23±9.05	65.86±7.86	71.40±7.57	<0.001	0.224
	IV	80±12.51	64.30±18.56	65.80±14.35	68.53±9.46	0.001	
	P	0.463	0.123	0.982	0.200		
Sedation scale	IM	1.66±0.99	2.30±0.98	3.33±1.15	2.50±1.16	<0.001	<0.001
	IV	1.36±0.55	3.26±0.73	3.46±0.68	3.50±1.10	<0.001	
	P	0.224	0.000	0.080	0.009		
Irritability scale	IM	2.06±0.69	2.73±0.63	3.30±0.87	3.03±0.66	<0.001	<0.001
	IV	2.20±0.92	3.30±0.46	3.53±0.50	3.60±0.56	<0.001	
	P	0.327	0.004	0.154	0.004		
Cooperation scale	IM	1.30±0.65	2±0.78	2.66±0.65	2.26±0.73	<0.001	<0.001
	IV	1.60±0.81	2.43±0.50	2.63±0.49	2.80±0.40	<0.001	
	P	0.240	0.005	0.158	0.006	<0.001	

IM: Intramuscular; IV: Intravenous; BP: Blood pressure

safety of IM and IV midazolam in children, and former researches have mainly compared this medication with other sedative drugs.[19] In a study about effects of IV midazolam on hemodynamic variations and cerebral blood flow rate in infants with very low birth weight who were mechanically ventilated, no change in HR was observed, but mean arterial pressure value decreased to 3 mmHg compared with the base level after 5 min. Also, an unremarkable haemodynamic change was observed at 20 min after the prescription. According to the results related to IV injection, findings of these two studies are different from each other. However, the studied groups have been selected from absolutely different spectra (in terms of age) and this can justify this discrepancy.[20]

In another research conducted in Japan by Nishiyama *et al*. on 20-25 years old patients, midazolam as a premedication was administrated and they concluded that "receiving IM midazolam 0.06 mg/kg 1 h before operation as a premedication following IV midazolam 0.02 mg/kg might be effective and safe."[21] This finding and this dosage is concomitant with our result although the studied population is different with our study.

In a study carried out by Bleiberg *et al*., complications of IM midazolam and ketamine were analysed in children with emergency conditions. They eventually stated that midazolam causes more intense fear and muscular reactions compared with ketamine. Although no significant difference was seen in the present study between two groups of IV and IM injections in terms of side effect, euphoria was the dominant psychological complication in both groups, which needed no treatment in either groups and was alleviated spontaneously. This finding is in alignment with current research results.[22]

In another investigation by Wenzel *et al*. in Germany, psychoneurologic side-effects of midazolam including euphoria occurred in 5.7% of adults sedated for transesophageal echocardiography; this complication was recovered after fentanyl prescription. Note that low dose of midazolam (0.25-0.5 mg) was considered as a cause of this phenomenon in that research. Nonetheless, their results are not comparable with those obtained in the current research because their studied population is adults only. Yet, they reported less occurrence of euphoria compared to the present study.[14] In a research by Alp *et al*. in Turkey, it was shown that rectal form of midazolam has a much lower effectiveness in paediatric sedation than IM form of thiopental and hybrid cocktail of sedative medications. The contrast between the findings of this study and our study might be attributed to the difference between prescription forms of midazolam.[15]

In a study conducted in India, Sing *et al*., demonstrated that IV midazolam with dosage of 0.2 mg/kg didn't suffice for sedating of 7.75% children, and hence, higher dosage is required. The reported side-effects also were not similar to those of the present study; decline of blood oxygen saturation was observed in 9.11%, hiccup in 1.38%, and agitation in 0.79%, which are absolutely different from results of the current research and the differences could be resulted of different brands of the medications used in two studies.[23] It was shown in another research by Cheuk *et al*. in Hong Kong that psychological complications such as hallucination in 8.7% of cases were observed with IV administration of midazolam for paediatric sedation along with ketamine, which is different with the current research results in terms of occurrence percentage.[24]

In one of the rare similar study by Kaufman *et al.*, they illustrated that midazolam as an intranasal or bolus IV sedative agent could be effective, but similar efficacy with continues form of IV administration was obtained in higher dose. Furthermore, they found that midazolam administration with continues pump was more useful than the other methods to decrease the body movement during the dental procedure. They did not evaluate IM form of midazolam and therefore it is impossible to compare it to our findings.[25] We administrated a fix dose per kg for every patient and then assessed the sedation depth. On the other hand, this study could be differently designed if it was a retrospective cohort. In the above design for future study, researchers can administrate a variable dose of midazolam to achieve a fixed level of sedation and according to patient's response to drug; complications and changes in vital signs and haemodynamic status will be observed.

There are some limitations in this study; we did not assess the blood cumulative dose of midazolam administered and it was one of our limitations of the study. Pulse-oximetry of extremity is a routine but not gold standard of blood oxygenation and it is better to use atrial blood gas sampling. On the other hand, It was therefore of most importance to measure the capnometry detecting even small changes in respiratory function to assess if the dose of drugs used for sedation is safe as well as effective. This is particularly true in children who are a category of patients most sensitive.[26,27] As one of the limitations, we did not used capnometry in this study and we suggest it for further researches.

Although it is not a randomised controlled trials (RCT), it is better to use RCT criteria such as probable randomisation. Also, our research had some strength; it is the first report that comparing this two form of midazolam in a cohort study in children. Moreover, we used a valid sedation scoring system that was not used in the previous studies.

CONCLUSION

Although none of two studied forms of midazolam including IM and IV injection caused risky complications and both provided a suitable degree of sedation, it is advised to use IV midazolam for faster sedation. It is better to more care and supervises regarding the occurrence of probable psychological disorders during and after sedation. Taking into account the problems including failure to find vein access in some cases, agitation of children in EDs, and time-consuming procedure and need to skilled personnel to provide vein access, IM injection seem to have more advantages than the IV method. Moreover, in ED, the safer sedatives such as local anaesthesia are more interested than the general anaesthesia particularly if the procedure is less invasive.[28]

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