Emergency. 2018; 6(1): e53

OPEN ACCESS

ORIGINAL RESEARCH

Intravenous versus Subcutaneous Midazolam Using Jet-injector in Pediatric Sedation; a Randomized Clinical Trial

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Received: May 2018; Accepted: August 2018; Published online: 31 August 2018

Abstract: **Introduction:** The quality of interventions in children is largely dependent on their control. Hence, this study compared the sedative effects of subcutaneous (SC) and intravenous (IV) Midazolam in pediatric sedation induction. **Methods:** This randomized clinical trial was conducted on children aged 1-6 years presenting to emergency departments of Shahid Sadoughi and Shahid Rahnemoon Hospitals, Yazd, Iran. Participants were randomly assigned to IV or SC midazolam using a jet injector and success rate, degree of sedation, and satisfaction of parents and physician were compared between groups. **Results:** 60 cases with the mean age of 3.15±1.43 (1-6) years were randomly assigned to the SC (30 cases) or IV (30 cases) groups (56.7% female). SC and IV groups were similar regarding the mean age (p = 0.165) and sex (p = 0.121). Depth of sedation (p=0.900), control of child (p=0.711), in-charge physician's satisfaction (p=0.467), successful sedation and need for rescue dose (p=0.519) were not different between groups. IV midazolam group had a significantly shorter recovery time (about 10 minutes; p=0.040) and SC midazolam group had a significantly higher level of parent satisfaction (p=0.001). **Conclusion:** The findings indicate no significant difference in depth of sedation, control of child, in-charge physician's satisfaction, successful sedation (reaching stage 1 of sedation or higher), and need for rescue dose of SC and IV midazolam. Parents' satisfaction was significantly greater with SC administration and IV injection had shorter recovery time.

Keywords: Midazolam; sedation; jet injector; Injections, Subcutaneous; Personal satisfaction; children.

Cite this article as: Hajimaghsoudi M, Bagherabadi M, Zarepur E, Ahmadi Hanzaei V. Intravenous versus Subcutaneous Midazolam Using Jet-injector in Pediatric Sedation; a Randomized Clinical Trial. Emergency. 2018; 6(1): e53.

1. Introduction

Many patients present to the emergency department (ED). Children are vulnerable to many diseases and constitute a considerable number of traumatic patients presenting to ED. The correct implementation of diagnostic procedures requires control and tranquility of children as lack of children's cooperation due to anxiety and discomfort leads to lengthening of diagnostic procedures and reduces their quality. So, the use of sedatives is mandatory in younger children to increase the quality of the provided interventions and shorten the duration of these procedures. The use of diagnostic procedures and minor surgical operations outside the operating room has increased over the last decade. Yet, the administration of sedatives to children is associated with risks like hypoventilation, apnea, airway obstruction, laryngospasm, and impaired cardiopulmonary functioning. Hence, the selection of appropriate drugs for diagnostic and therapeutic interventions is as important as the diplomacy and tactfulness of the in-charge physician in reacting to drug complications (1-5). Midazolam is a short-acting benzodiazepine with sedative, narcotic, anxiolytic, anticonvulsive, and relaxing effects (1, 6, 7). Its acute complications include respiratory suppression and apnea which occur rarely in cases of rapid injection of high doses of the drug. Ad-

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ditionally, Midazolam is a rapid-acting sedative with minimal effect on blood oxygenation level and cerebral blood flow, which renders it a suitable drug for cerebral imaging studies like MRI (6). Midazolam can be administered via intravenous (IV), subcutaneous (SC), muscular, intranasal, buccal, and rectal routes. One modality of Midazolam administration is the subcutaneous injection in which the drug effect is initiated in 7 minutes reaching a peak during 23-49 minutes. The onset of IV Midazolam effect is 3-5 min, which is finally eliminated by the liver (7, 8). Given that the subcutaneous injection with a jet injector is almost painless, and also based on what has been said so far and considering the lack of sufficient related studies in this field, especially on the use of jet injector in ED (9-11), we embarked on comparing the SC midazolam using jet injector with IV midazolam in performing sedation for doing non-invasive diagnostic procedures in children aged 1-6 years.

2. Methods

2.1. Study design and setting

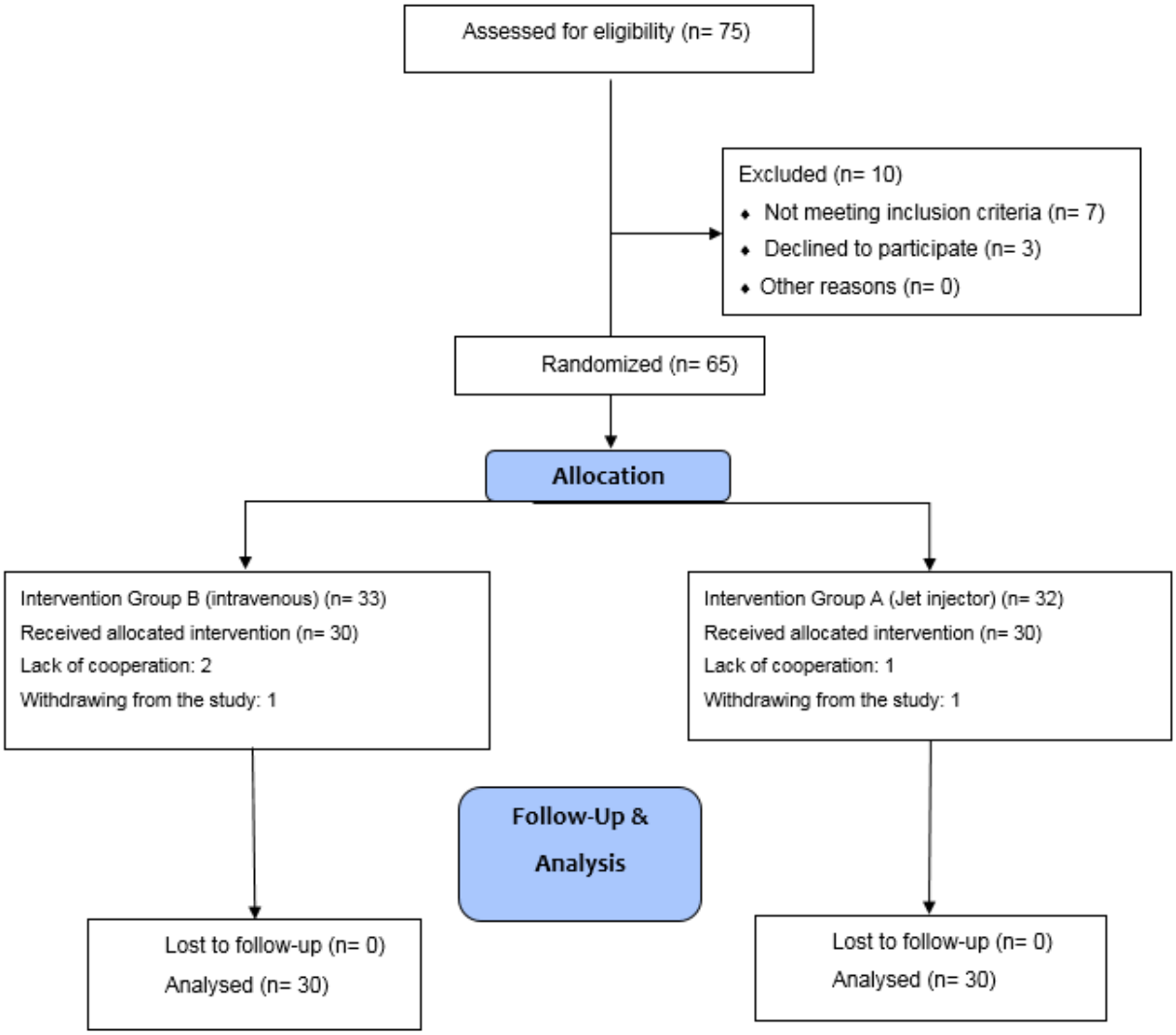
This parallel randomized clinical trial was carried out on traumatized children aged 1-6 years presenting to EDs of Shahid Sadoughi Hospital and Shahid Rahnemoon Hospitals in Yazd, central Iran, from April to June 2015, who needed control and sedation for undergoing a diagnostic procedure. The research goals and procedures were explained clearly to the parents and the possible complications of drug administration (hypoxia, respiratory depression, apnea, coma, hypotension, agitation, confusion, and cough) were elucidated in a crystal-clear fashion. Informed written consent was obtained from the children's parents. The research proposal was approved by Committee of Ethics in Research at Shahid Sadoughi University of Medical Sciences, Yazd, Iran, with code of ethics no.: IR.SSU.Medicine.REC.1393.30 and registered in Iranian Registry of Clinical Trials with no.: IRCT no.: IRCT201510018640N2.

2.2. Participants

Traumatized children aged 1-6 years presenting to EDs of the mentioned hospitals and in need of sedation for doing non-invasive diagnostic procedures were enrolled. Un-stable vital signs, reduced level of consciousness, a positive history of taking anticonvulsive drugs, allergy to midazolam, lack of consent for participating in the study, and children with moderate to severe pain (pains with scores greater than 4 out of 10 form the researcher's perspective) were among the exclusion criteria.

2.3. Procedure and data gathering

After history taking and complete medical examination, children diagnosed by the medical emergency specialist to be in need of sedation for performing diagnostic intervention who met the inclusion criteria were randomly and blindly (without awareness of the researcher and the assessor) assigned to SC or IV midazolam groups using convenience sampling method. In doing so, random numbers were selected by a computer and placed in opaque envelopes, which were numbered sequentially. The number in the envelope was placed in the SC with jet injector group if it was an even number and in the IV group if it was an odd number. Injection was done in the brachial area for jet injector patients while IV injection was performed in the cubital zone after phlebotomy in the IV group. Phlebotomy was performed by nurses with a 5-year work experience. If phlebotomy failed in the cubital area of one hand, the other hand was then used for injection. Midazolam with the initial dose of 0.2 mg/kg was administered subcutaneously using jet injector (INJEX^{TM} 30, Carpol 0.3 cc, Needle Free, Made in Germany) in the case group and given to the IV group with the dose of 0.1 mg/kg by a peripheral vein catheter. The assessor was also blind to the site of injection in both groups not to be aware of the type of injection. The children underwent cardiac monitoring and pulse oximetry before the onset of sedation and their level of consciousness was measured by the assessor once per min before and after sedation (Stage 0: conscious; stage 1: silence; stage 2: drowsy; stage 3: napping; stage 4: deep sleep). When the child reached stage 1 of sedation, the intended procedure was commenced. Successful sedation (achieving stage 1 of sedation), degree of sedation before and after injection (by the assessor once per min), and parents' and the physician's satisfaction with the whole process of sedation and diagnostic technique (completely dissatisfied, dissatisfied, indifferent, satisfied, and completely satisfied) were measured as primary variables. In addition, the time of regaining full consciousness (level A of AVPU), child control, and the need for reinjection of drug in the case of failure were assessed as secondary variables. Child control was defined as the degree of difficulty in positioning and controlling the child during performance of the procedure for which the physician was asked by the assessor using a 5-point Likert scale item (very difficult, difficult, moderate, easy, and very easy). In cases that the child did not enter stage 1, reinjection was performed 20 minute after the first injection in the case group and 3 minute after the first injection in the control group. If after one reinjection the required sedation was not achieved, the procedure was considered as failure and the resident medical emergency specialist decided on the continuation or discontinuation of the procedure. The child was monitored during and after completion of the procedure till full consciousness was reached and the time of full consciousness recovery was measured.



Flowchart 1: Enrollment and allocation of patients to the studied groups.

2.4. Statistical Analysis

The sample volume in each group was set at 42 on the basis of the study by Bennett et al. (12) considering type I error of 0.05 and type II error of%20, which was increased to 60 to enhance the validity of the study results. The data were analyzed by an experienced statistician blind to the groups using SPSS Ver. 17 (SPSS, Chicago, IL, USA). Descriptive statistics of mean ± standard deviation and frequency (percentage) were used to report the results. Also, Chi-square test was used to analyze nominal data, and independent sample t-test or their nonparametric equivalents were used to analyze the quantitative data. The level of significance was considered 0.05.

3. Results

3.1. Baseline characteristics of participants

75 children were evaluated, 10 of which were excluded due to not meeting the inclusion criteria or declining to participate (flowchart 1). Finally, 60 cases with the mean age of 3.15±1.43 years were randomly assigned into the SC (30 cases) or IV (30 cases) groups (56.7% female). Owing to lack of cooperation, 1 child from the jet injector group and 2 children from the IV group were excluded from the study. Also, 1 child was omitted from each group due to the parents of the two children deciding to withdraw from the study (flowchart 1). SC and IV groups were similar regarding the mean age (2.8 ± 1.2 vs 3.4 ± 1.6, respectively; p = 0.165) and sex (56.7% vs 36.7% female, respectively; p = 0.121).

Table 1: Comparing the procedural sedation and analgesia (PSA) characteristics of subcutaneous and intravenous midazolam in 1- 6 year old children

PSA characteristics	Subcutaneous n=30	Intravenous n=30	P
Depth of sedation			
Fully conscious	5 (16.7)	3 (10.0)	
Silent	1 (3.5)	1 (3.3)	
Drowsy	0	0	0.900
Napping	1 (3.3)	1 (3.3)	
Deep sleep	23 (76.7)	25 (83.3)	
Child control			
Very difficult	1 (3.3)		
Difficult	4 (13.3)	5 (16.7)	
Moderate	2 (6.7)	2 (6.7)	0 (0)
Easy	22 (73.3)	23 (76.6)	
Very easy	1 (3.3)	0 (0)	
Physicians' satisfaction			
Completely dissatisfied	4 (13.3)	4 (13.3)	
Dissatisfied	3 (10)	1 (3.3)	
Indifferent	1 (3.3)	0 (0)	0.467
Satisfied	8 (26.7)	22 (73.3)	
Completely satisfied	14 (46.7)	3 (10.0)	
Parents' satisfaction			
Completely dissatisfied	3 (10.0)	4 (13.3)	
Dissatisfied	2 (6.7)	7 (23.3)	
Indifferent	3 (10.0)	12 (40.0)	0.001
Satisfied	18 (60.0)	6 (20.0)	
Completely satisfied	4 (13.3)	1 (3.3)	
Successful sedation*			
Yes	25 (83.3)	27 (90.0)	0.519
No	5 (16.7)	3 (10.0)	
Recovery time (minute)			
Mean ± standard deviation	35.8 ± 9.71	24.8 ± 7.60	0.040

Data are presented as number (%). *: Achieving sedation stage 1.

3.2. PSA characteristics of two groups

Table 1 compares the characteristics of PSA between SC and IV midazolam groups. Two groups were similar regarding the depth of sedation (p=0.900), control of child (p=0.711), in-charge physician's satisfaction (p=0.467), successful sedation and need for rescue dose (p=0.519). IV midazolam group had a significantly shorter recovery time (about 10 minutes; p=0.040) and SC midazolam group had significant higher level of parent satisfaction (p=0.001). None of the possible midazolam side effects (hypoxia, respiratory depression, apnea, coma, hypotension, agitation, confusion, and cough) were manifested in any child in this study. Moreover, no dermal reaction like arythema, swelling, or inflammation was observed at the site of injection.

4. Discussion

The findings indicate no significant difference in depth of sedation, control of child, in-charge physician's satisfaction, successful sedation (reaching stage 1 of sedation or higher), and need for rescue dose between SC and IV midazolam. Parents' satisfaction was significantly greater with SC administration and IV injection had shorter recovery time. The traumatized children ought to be controlled and immobilized during diagnostic procedures such as CT scanning, MRI, radiography, and ultrasonography. There are various medications with different complications for induction of sedation. The study by Pecking et al. (2002) conducted in France investigated the biological power of SC midazolam in volunteers and the results showed that the biological potency of SC injection of the drug was not significantly different from the IV injection so that when the IV route was not accessible, the SC route could be used safely, which is consistent with our findings (13). Moreover, the study by Greenberg et al. (1995) explored the effect of administration of different doses of midazolam with jet injector on 40 children and found that jet injector administration quickly induced the effect of Midazolam. This is again consistent with our findings (14). The highly appropriate effect of the drug in the jet injector group may be attributed to proper distribution of the drug in the tissue leading to greatly acceptable absorption and the rapid effect of the drug (12). Generally speaking, although in the

jet injector method it logically takes longer for the drug to show its effect compared to the IV method, in the studies conducted so far the effect of drug is seen faster when using jet injector compared to the oral route since administration of the drug using jet injector can induce the intended plasma level of Midazolam with the same speed as the IM injection of the drug. Also, when there is oral route resistance in the child (15) or when there is the need for avoiding phlebotomy tension in the child, the use of jet injector is a suitable method. Of course, the time of full recovery in jet injector group was 35.8Âś9.71 minute, which was significantly higher compared to the IV group. This can be viewed as a weak point of the method. The study by Bennett et al. (1998) conducted in USA investigated the effect of SC Midazolam with needle and syringe compared to the SC injection of this drug using jet injector. The findings of the mentioned clinical trial conducted on 14 children suggested that the discomfort caused by subcutaneous Midazolam in the jet injector group was less compared to the needle and syringe group though the difference between the two was not significant. Finally, they concluded that the peak plasma level was achieved more rapidly with jet injector probably due to the distribution of the medicine in the tissue by the jet injector (12). Our findings also suggested that the parents were significantly more satisfied with jet injector method. In the study by Bennett et al., the rate of discomfort was smaller with jet injector, though the difference was not significant due to small sample volume (14 samples) or the study design (12). Overall, parents were more satisfied with the jet injector method while physicians were less satisfied with this route. It appears that the child sustains less pain and discomfort with the jet injector route causing more satisfaction among the parents; nonetheless, physicians are more satisfied with the IV method since the drug exerts its effect more rapidly leading to faster sedation. However, our results demonstrated that the physicians in the jet injector group assessed child controlling and positioning of 23 (%76.6) children as easy and very easy during the procedure. The same was true with the IV group indicating another positive factor in the jet injector method compared to the IV route. Considering the complications of Midazolam (hypoxia, respiratory depression, apnea, coma, hypotension, agitation, confusion, and cough), none of these undesirable side effects were manifested in any child in this study. Moreover, no dermal reaction like erythema, swelling, or inflammation was observed in the site of injection, a finding which is consistent with the results obtained by Bennett who reported no specific complication in 14 adult patients who underwent SC Midazolam injection with jet injector compared to subcutaneous needle and syringe IV injection (12). Also, the results of the study by Domino et al. (1998) showed that the SC injection of Midazolam with jet injector was associated with appropriate effect (16). It seems that SC injection using jet injector as a well-known old method could be considered as an alternative root for induction of sedation in pediatric non-invasive diagnostic procedure. Considering the need that is felt for a painless, safe, and rapid-acting method, jet injector as a needleless injection system can serve as an effective tool with little complications to be used for inducing sedation, especially in stressful situations like ED that demands more tranquility. It is suggested that future studies investigate other aspects of these two methods such as comparison of the resulted infection or dermal complications in a longer time interval after injection. Different jet injectors may be applied for various age groups or greater carpols may be used with jet injectors. Additionally, jet injector may be explored for induction of anesthesia or sedation in painful or invasive procedures. A combination of the main drug with local anesthetics along with their merits and demerits is also suggested.

5. Limitation

The children could not be made blind to the study due to the nature of the use of jet injector. There was no placebo due to ethical considerations to avoid pain in the children.

6. Conclusion

The findings indicate no significant difference in depth of sedation, control of child, in-charge physician satisfaction, success rate of sedation (reaching stage 1 of sedation or higher), and need for rescue dose between SC and IV midazolam. Parents' satisfaction was significantly greater with SC administration and IV injection had shorter recovery time.

7. Appendix

7.1. Acknowledgements

The authors give their special thanks to all the staff in EDs of Shahid Sadoughi and Shahid Rahnemoon Hospitals in Yazd and also all the children and their parents. The manuscript was extracted from a Medical Emergency Residency Thesis by Vahid Ahmadi Hanzaei.

7.2. Authors' contribution

All authors contributed to this project and article almost equally. All authors read and approved the final manuscript.

7.3. Funding/Support

None.

7.4. Conflict of interest

All authors declare that they have no conflicts of interest.

References

1. Hijazi OM, Ahmed AE, Anazi JA, Al-Hashemi HE, Al-Jeraisy MI. Chloral hydrate versus midazolam as sedative agents for diagnostic procedures in children. Saudi Med J. 2014;35(2):123-31.
2. Cote C, Wilson S. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. Pediatrics. 2006;118(6):2587-602.
3. Imanian M, Ghasemzadeh MJ, Zarepur E, Zarepur A, Farahani RS, Farahani RS. The Relationship between Pneumonia with Parental Smoking in Children under 10 Year Old: A Case- Control Study. Int J Pediatr-Masshad. 2018;6(6):7791-6.
4. Sasannejad P, Rezaei F, Bidaki R, Zarepur E. Rare Presentation of Moyamoya Disease with Sub acute Presentation in Iran. Iran J Child Neurol. 2018;12(1):89-93.
5. Jafari M, Biuki AA, Hajimaghsoudi M, Bagherabadi M, Zarepur E. Intravenous Haloperidol versus Midazolam in Management of Conversion Disorder; a Randomized Clinical Trial. Emergency.6(1):43.
6. Khurmi N, Patel P, Kraus M, Trentman T. Pharmacologic Considerations for Pediatric Sedation and Anesthesia Outside the Operating Room: A Review for Anesthesia and Non-Anesthesia Providers. Paediatr Drugs. 2017;19(5):435-46.
7. Martinez JL, Sutters KA, Waite S, Davis J, Medina E, Montano N, et al. A comparison of oral diazepam versus midazolam, administered with intravenous meperidine, as premedication to sedation for pediatric endoscopy. J Pediatr Gastroenterol Nutr. 2002;35(1):51-8.
8. Fallah R, Fadavi N, Behdad S, Fallah Tafti M. Efficacy of chloral hydrate-hydroxyzine and chloral hydrate-midazolam in pediatric magnetic resonance imaging sedation. Iran J Child Neurol. 2014;8(2):11-7.
9. Playfor S, Jenkins I, Boyles C, Choonara I, Davies G, Haywood T, et al. Consensus guidelines on sedation and analgesia in critically ill children. Intensive Care Med. 2006;32(8):1125-36.
10. Hajimaghsoudi M, Vahidi E, Momeni M, Arabinejhad A, Saeedi M. Comparison of local anesthetic effect of lidocaine by jet injection vs needle infiltration in lumbar puncture. Am J Emerg Med. 2016;34(7):1225-9.
11. Luhmann JD, Kennedy RM, Porter FL, Miller JP, Jaffe DM. A randomized clinical trial of continuous-flow nitrous oxide and midazolam for sedation of young children during laceration repair. Ann Emerg Med. 2001;37(1):20-7.
12. Bennett J, Nichols F, Rosenblum M, Condry J. Subcutaneous administration of midazolam: a comparison of the Bioject jet injector with the conventional syringe and needle. J Oral Maxillofac Surg. 1998;56(11):1249-54.
13. Pecking M, Montestruc F, Marquet P, Wodey E, Homery MC, Dostert P. Absolute bioavailability of midazolam after subcutaneous administration to healthy volunteers. Br J Clin Pharmacol. 2002;54(4):357-62.
14. Greenberg RS, Maxwell LG, Zahurak M, Yaster M. Preanesthetic medication of children with midazolam using the Biojector jet injector. Anesthesiology. 1995;83(2):264-9.
15. Fine B, Castillo R, McDonald T, Paisansathan C, Zsigmond E, Hoffman WE. Jet injector compared with oral midazolam for preoperative sedation in children. Paediatr Anaesth. 2004;14(9):739-43.
16. Domino EF, Zsigmoid EK, Kovacs V, Olajos B, Fekete G. A new route, jet injection for anesthetic induction in children. IV. Midazolam plasma levels. Int J Clin Pharmacol Ther. 1998;36(8):458-62.