ORIGINAL ARTICLE

Comparison of Intranasal Ketamine and Midazolam in Peripheral IV Access in Children Presenting to the Emergency Department, a Randomized Clinical Trial

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ABSTRACT

Background: Peripheral Intravenous (IV) line, despite being the cornerstone of treatment in emergency care, remains the most common anxiety and pain-inducing experience for children.
Aim: To compare the clinical efficacy of intranasal (IN) administration of midazolam and ketamine in managing pain and distress associated with peripheral IV access in children presenting to emergency departments (ED).
Method: This study is an open-label, controlled clinical trial. Seventy children between the ages of 2 and 8, presenting to the EDs of Iran University of Medical Sciences, were divided into groups of 35. 0.2mg/kg of midazolam or 5mg/kg ketamine was administered intranasally, with the use of a syringe, twenty minutes before the procedure. The sedation & analgesia score was obtained using the Observational Score of behavioral Distress-Revised (OSBD-R). The procedure success was defined as an OSBD-R less than five and no need for physical restraint. The P-value of less than 0.05 was considered significant.
Results: 82.9% in the ketamine group and 85.7% in the midazolam group had successful procedures. 17.1% in the ketamine group and 14.3% in the midazolam group had unsuccessful procedures. There was no significant difference regarding the success of the procedure between the two groups (P-Value= 0.743). The mean OSBD-R score was 3.51 in the ketamine group and 3.56 in the midazolam group. There was no significant difference between the two groups in the OSBD-R score (P-Value= 0.852). There was no difference between the vital signs in the two groups. No adverse effects requiring intervention were noted.
Conclusion: There is no difference in the clinical efficacy of IN ketamine and midazolam in sedation & analgesia before obtaining peripheral IV access in children. IN ketamine provides adequate sedation before obtaining peripheral IV access in the ED, and it could be considered an ideal medication for this purpose.
Keywords: Peripheral IV access in children, Ketamine, Midazolam, Intranasal, IN Emergency Department, ED

INTRODUCTION

Peripheral IV access in children, as an integral part of care in the emergency department, is one of the most common causes of induced pain and distress in this age group[1-6].Although different guidelines callfor management of needle-stick pain, compliance with recommendations is often inadequate in practice[7-10].Therefore reducing the stress and pain associated with this procedure remains a challenge[11-13] Regardless of the existence of some non-pharmacological and topical methods to facilitate obtaining IV access, they are not always effective enough[5,7,11,14,15], which may lead to the requirement of pharmacological sedation[6].

In a crowded ED, the goal is to perform the necessary procedures as quickly as possible and with minimal complications. A therapeutic failure in sedation prolongs the total length of stay, adds another possible painful procedure, requires more resources, and is difficult for both the child and parents to endure[16,17].

Given the need to optimize the sedative technique, different routes of drug delivery have been investigated; the intranasal route of sedative-analgesic agent sappears to be a very logical and practical option for procedural sedation;it omits the needle's fear and pain; is theoretically available and feasible, is faster and has more predictable effects[16,18-22].

Intranasal administration may cause the drug levels to rise above the therapeutic threshold for sedation while avoiding the high peaks achieved by IV administration [21].

The best single medication for procedural sedation and analgesia in peripheral IV access in children is still to be found[11, 12, 23]. Emergency providers have long sought an agent that is universally efficacious as well as safe. An ideal agent for a short-term procedure should be noninvasive, have a rapid onset and offset, minimal adverse effects, nopost-procedural pain or residual symptoms and, preferably, should be cost-effective[5, 24-27] Different agents (alone or in combination) at varied doses via multiple routes, have been used in the search for this ideal medication[28].Currently, midazolam is the gold standard medication for sedation in various settings, including the emergency department[7, 29]. In recent years many have questioned its superiority to other medications available for this purpose[29, 30].

When used intranasally, itdoes not fulfills all of the goals suggested by the American Academy of pediatrics for sedating children during procedures [25, 29, 31-33].

Midazolam provides no analgesia; thus, local anesthetic or oral/intranasal analgesics are required for painful procedures. Although midazolam as a single agenthas minimal respiratory effects in healthy children, patients should be monitored for respiratory depression[21].Since IN use of midazolam cause nasal

irritation and discomfort, intravenous administration is the preferred route[29, 34].

Many studies suggest that ketamine can be considered the potential sedative of choice as it offers quick, reliable sedation with minimal side effects and has a rapid onset and offset time[32].

There is an increasing need for implementation of procedural sedation training and the use of ketamine in the everyday practice outside the operating room in pediatric EDs [35]. For children with difficult venous access, intramuscular ketamine can be used as an alternative to intranasal midazolam, which despite the popular belief, is unpleasant for all involved and is less effective [35].Ketamine is absorbed nasally within 2 minutes and has a 45% bioavailability. Its onset of action is about 5 minutes. Its highest blood level appears after 30 minutes and provides a suitable blood level for analgesia and sedation [31, 33].

Although the efficacy of intranasal ketamine for analgesia has been demonstrated, because of the limited bioavailability and increased nasal run-off at higher doses, it is unclear if dissociative levels of sedation can be achieved consistently, in particular when using standard concentration parenteral ketamine[21, 31, 33].

There are many studies on the comparison of the efficacy of IN ketamine and midazolam. These studies have reported mixed results and are usually for procedures other than IV access and not in the emergency department setting[20, 36-38].

We hypothesized that intranasal ketamine with a dose of 5mg/kg is clinically effective as intranasal midazolam for accessing an IV line in children. Therefore, we conducted a study to investigate the clinical efficacy of sedation and analgesic effects of IN ketamine and midazolam in obtaining peripheral IV access in children presenting to ED.

METHODS

Study design: This was a randomized, parallel, open-labeled clinical trial. It was registered on the Iranian Registry of Clinical Trialson August 10, 2020 (IRCT20200728048242N1). It was conducted from July 2019 to May 2020 in EDs of Iran University of Medical Sciences. The ethics committee of Iran University of Medical Sciences approved the protocol of the study on July 16, 2019 (IR.IUMS.FMD.REC.1398.143).Informed written parental consent was obtained for all the participants.

Study population: Patients over one to 10 years old presenting to the ED, Who did not meet any of the exclusion criteria, were enrolled in the study conveniently. All the participants were a candidate for ED or hospital wards admission and needed an IV line. The main researcher enrolled all the cases in emergency departments of three hospitals of Iran University of Medical Sciences in Tehran. Exclusion criteria included level one triage, parental dissatisfaction, history of drug allergies, history of epilepsy, cystic fibrosis, cerebral palsy, severe underlying diseases, and maxillofacial abnormalities.

According to N = $\{z_{1-\alpha/2} * \sqrt{\bar{p} * \bar{q} * \left(1+\frac{1}{k}\right)} + z_{1-\beta} * \sqrt{p_1 * q_1 + \left(\frac{p_2 - q_2}{k}\right)}\}^2 \Delta^2$ $N_2 = k * N_1$, and Khatavkar et al. study (N_1=13.30, N_2=43.30, α=0.05, β=0.2), at least 34 patients per group were needed for detecting a difference between the groups with a power of 80%[38, 39].

Randomization and blinding: The participants were randomly assigned to two groups.Simple randomization was carried out by using RRApp software[40]. For this purpose, in the order of participation in the research, the participants received midazolam or ketamine based on the group they were assigned by RRApp software. Allocation concealment and blinding were not carried out.

Intervention: Each group was given one of the medications, midazolam (0.2 mg/kg) or ketamine (5 mg/kg), twenty minutes before the procedure. Ketamine and midazolam are available in concentrations of 50 mm/cc and 5 mg/cc. The route of administering the medications was intranasally, with a regular 2ml syringe. To administer the medications, children held their heads back in their parents' arms or sitting and under parental control. To reduce nasal runoff, half of the calculated dose of the medication was slowly poured in each nostril. After holding the head back for a few seconds, the administering process ended. Re-administration was not performed.

Outcome: The main outcome was evaluating the sedation and analgesia after IN administration of midazolam and ketamine during the IV line procedure. This evaluation was performed one time. The secondary outcomes included the success rate of obtaining an IV line, heart rate changes, oxygen saturation levels, and possible side effects.

Sedation and analgesia were evaluated by the Observational Scale of Behavioral Distress-Revised. The OSBD-R includes eight behaviors and is typically evaluated during the whole procedure and in four general stages; waiting period before the procedure, the preparation phase, the procedure itself (starting from the needle entering the skin to withdrawal), and after the procedure. The score ranges from zero to 23.5 (each behavior is multiplied by a pre-assigned value based on the intensity of distress - cry and information seeking are weighted at 1.5; emotional support at 2; verbal resistance and verbal pain at 2.5; and scream, restraint and flail at 4).Higher OSBD-R scores indicate greater distress[41]. In our study, these steps were performed after the twentieth minute of drug administration in the form of scoring every 15 seconds; two minutes for the procedure itself and one minute for the other steps. Observed behaviors were recorded twenty times in terms of occurrence

The successful procedure was defined as an OSBD-R below five and no need for physical restraint, regardless of the score. The success of obtaining an IV line was not defined as a successful procedure. Almost all of the cases had an IV line placed at the end of the procedures. If accessing the IV line was postponed, the case was not followed. Heart rate and blood oxygen saturation were measured twice at 10-minute intervals. During the waiting period, children and parents were in the ED and under the researcher's direct supervision. Possible side effects were assessed during this time. At the end of the twenty

minutes, the nurses obtained the IV access. Parents were present during the procedure. The researcher did OSBD-R Scoring during the IV access procedure, which typically lasted about 5 minutes in total. After the procedure was over, the children were monitored in the ED for at least thirty minutes. A portable pulse oximeter documented heart rate and blood oxygen saturation. Side effects and procedure success was recorded by observation and checklist.

Statistical analysis: Quantitative and qualitative data obtained were analyzed respectively by t-test and chi-square test. Shapiro-Wilk test (probability value> 0.05) and observation of histogram, box design, and normal Q-Q design (quadratic-quadratic diagram) were used to evaluate the normality of dispersion in OSBD-R scores in both groups. Repeated measures ANOVA with assumptions of Box's M test,Mauchly's test, andLevene's Test of Equality of Error Variances were used to analyze the subgroups' scores of OSBD-R, heart rate and oxygen saturation. All the analysis was done by SPSS software (IBM® SPSS® Statistic, Version 26.0). A P-value of less than 0.05 was considered significant.

RESULTS

In this study, seventy children aged two to eight years were randomized into two groups (35 each). The flowchart of the study is presented in figure 1. The minimum age was two years old, and the maximum age was eight-years-old. The mean age was 5.17 years old, with a standard deviation of 1.72. There was no significant difference between the two groups regarding the age of the patients (P-Value = 0.784). There were 19 boys, 16 girls in the ketamine group, 16 boys, and 19 girls in the midazolam group. There was no significant difference in gender between the two groups (P-Value = 0.473).

The results showed an almost normal distribution of the OSBD-R score between the ketamine and midazolam groups. The amount of clogging and the degree of the peak in the ketamine group were 0.607 (SE = 0.398) and 0.381 (SE = 0.778), respectively, andin the midazolam group were 0.320 (SE = 0.398) and 0.199 (SE = 0.778). Therefore, t-test was used for further statistical analysis. Overall, the highest score of OSBD-R was 6.88, and the lowest score was 1.38. The mean score was 3.49, with a standard deviation of 1.14. The total mean score of OSBD-R in the ketamine group was 3.51, and in the midazolam group was 3.46. There was no statistically significant difference in the mean score of OSBD-R between the two groups (P-Value = 0.852).

Based on the definition of a successful procedure in our study, 29 cases had a successful procedure in the ketamine group. In the midazolam group, this number was 30. Six cases in the ketamine group had unsuccessful procedures. In the midazolam group, five unsuccessful procedures were observed. The success rate in the midazolam group was one case higher than in the ketamine group. There was no statistically significant difference in the success rate of the procedure between the IN ketamine and midazolam group (P-Value = 0.743).

With the validation of Box's test for heart rate and oxygen saturation (P-value > 0.05), Multivariate tests of Hotelling's trace indicated that time had a non-significant effect on heart rate. There was a non-significant heart rate change at 10^{th} and 20^{th} minutes (F (1, 68) =2.042, P-Value = 0.158). There was no significant difference in the effect of time on heart rate between the two groups (F (1, 68) = 2.691, P-value =0.106).

Oxygen saturation was different and within normal limits, with no significant effect of time at 10^{th} and 20^{th} minutes (F (1, 68) = 1.157, P-value = 0.286). The oxygen saturation was similar at different time points between ketamine and midazolam (F (1,68)=1.913,P-value = 0.171).

No serious complication requiring intervention, including hypoxia or excessive sedation, was observed in ketamine and midazolam groups. There were no side effects such as an emergence reaction in the ketamine group or a paroxysmal reaction in the midazolam group. The most common side effects were nausea and vomiting, observed in 18 children. One case of hiccups was observed in the ketamine group, which lasted about a minute and resolved spontaneously. Nasal irritation and throat irritation were also common.

Ancillary analysis: Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated, $\chi 2$ (2) = 17.40, $p < 0.001$, therefore a Greenhouse-Geisser correction was used. There was a significant effect of time on OSBD-R subgroups' scores (F (99.24, 1.62) = 153.77, P-value < 0.001), which indicates a different OSBD-R subgroup scores at different stages. There was no significant difference in the effect of time on OSBD-R subgroups' scores between the two groups (F (0.264, 1.62) = 0.408, p-value > 0.001). Ketamine and midazolam had a similar subgroups' score at different stages of the procedure.

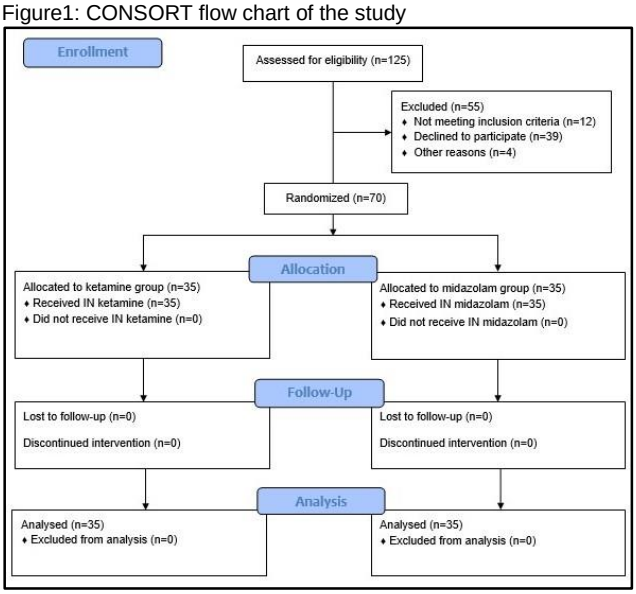
Levene's Test of Equality of Error Variances was validated for different stages of OSBD-R score (P value > 0.005). Tests of Between-Subjects Effects, based on the average score, indicated different subgroups' scores at different stages (F (1, 245.6) = 588.01, P value < 0.001). The two medications did not differ significantly regarding the subgroups' scores (F (1, 0.006) = 0.014, P value= 0.905).

Table 1: Different results between the ketamine and midazolam groups

Variables		Ketamine (n = 35)	Midazolam (n = 35)	P-Value [95% CI]
		Mean ± Standard Deviation / Percentage		
Age (year)		5.22±1.8	5.11±1.67	0.784
Sex (%)	Boy	27.1%	22.9%	0.473
	Girl	22.9%	27.1%	
OSBD-R		3.51±1.33	3.46±0.94	0.852
Successful IV (%)		82.9%	85.7%	0.743
Unsuccessful IV (%)		17.1%	14.3%	

HR Mean(beats/min)	108.62±12.39	107±10.37	0.779
O2 Sat Mean (%)	94.65±0.93	94.68±0.95	0.900

Figure1: CONSORT flow chart of the study



DISCUSSION

The IN medications were administered with a regular syringe in this study. This method is not superior to using an atomizer. Due to the lack of atomizers in our medical centers and a very high cost, we were forced to use this method. Atomizers are rarely used in Iranian health centers. Using a syringe does not atomize the drug. As a result, not all the medication can be expected to be efficiently delivered to the nasal mucosa. The probability of absorption through swallowing rather than through the nasal mucosa is higher in this method. As a result, the final effect of the medication is different. In our study, the mean heart rate after receiving the medications was similar and without statistically significant differences between the ketamine and midazolam groupat 10th and 20th minutes after administration (P = 0.106). The mean percentage of blood oxygen saturation in the two groups were in the normal and similar range (P = 0.171). This finding was similar to the studies of Christensen, Elliott, and Gyanesh[41,42]. It can be concluded that IN ketamine and midazolam do not significantly affect the heart rate and blood oxygen saturation in children[41,42].

We showed that there is no difference in the clinical efficacy of ketamine compared to midazolam. 5mg/kg of intranasal ketamine provided similar sedation to intranasal midazolam. The success rate of sedation for IV access was similar between the two.

Our study results are different from the study of Bahetwar et al., in which the success rate was assessed by the observational method and personal perception of the researcher, by a 6-point Likert scale, while performing peripheral IV access[36]. The overall success rate in the IN ketamine group was 89%, intramuscular ketamine/midazolam, 84%, and IN midazolam was 69%, which is different from the studies of Surendar, Khatavkar, Peerbhay, Narendra and our study. The doses used in Bahetwar study were 0.3 mg/kg for midazolam, 6 mg/kg for ketamine, and 0.2 mg/kg for midazolam, which is different from the doses used in our study [36, 38, 43, 44].

In dental procedures, Sado-Filho et al. rated the overall success rate of IN ketamine/midazolam at 50%, oral ketamine at 46.4%, and oral midazolam at 32.1%. Despite the same general conclusion, the method of administration and evaluation criteria are different from our study[20].

In the study of Surendar et al., the success rate of IN midazolam and ketamine was similar and effective in sedation and analgesia (61.9% vs. 66.7%, respectively). The sedation level in the ketamine group was higher than that of midazolam, but there were no statistically significant differences. The dosage used and the results of this study are similar to our study[43].

According to Khatavkar et al. IN midazolam/ketamine (0.15 mg/kg / 0.1 mg/kg) is better than IN midazolam alone (0.2 mg/kg)[38]. Midazolam/ketamine had a better onset and level of sedation, peripheral IV access success rate, acceptance of mask before anesthesia, and analgesic effect after surgery[38]. However, there was no statistically significant difference between the two drug regimens, which may be due to the small sample size. A complete comparison of Khatavkar's study with ours is not feasible due to the concomitant use of ketamine and midazolam in the former.13.3% in the midazolam group and 43.3% in the ketamine group had effortless venipuncture. This result is different for midazolam in our study. This dissimilarity is expected, considering different definitions of sedation[38].

Like Khatavkar, Akçay et al. also recommended the concomitant use of ketamine and midazolam as pre-anesthetics, with more sedative effects compared to using them separately. 35% of the midazolam group and 75% of the ketamine group had desirable venipuncture. Regarding sedation during venipuncture, Akcay's result is different from ours[45].

The dosage and method of administration in our study is similar to Narendra's and Akcay's. The differences in the three studies may be attributed to the difference in the time of evaluation of the maximum sedation rate, as well as the use of different evaluation scales. Assessing the results of these studies regarding the efficacy and safety, it can be concluded thatIN ketamine can be used in peripheral IV access in children[37,45].

Guthrie et al. evaluated the use of IN ketamine for sedation and analgesia in the ED as very successful, safe, and useful. Doses of 3 mg/kg to 5 mg/kg intranasal ketamine were most satisfactory. The results of our study are in line with this finding[46].

Gyanesh et al. showed the superiority of IN sedation (Ketamine and Dexmetomidine) over IN saline[42]. Children in which IN sedation was used showed only slight or no resistance to obtaining the peripheral IV access before magnetic resonance imaging. This study was performed in a more controlled environment than the ED. Regarding peripheral venipuncture, 82.7% of anesthesiologists were satisfied with the ketamine group (P = 0.253). Despite the different IN medications used in the Gyanesh study compared to ours (Dexmetomidine VS Midazolam), the

effectiveness of this sedation method is clearly shown in both studies[42].

In the study of Nemeth et al.,IN ketamine and midazolam were evaluated as efficient and safe in the ED[47]. This result is similar to our study. In this study, sedation and analgesia were performed for only six children before obtaining peripheral IV access. The type of drug used before peripheral IV access has not been reported. IN ketamine and midazolam alone were used in four and one cases, respectively. As noted by Nemeth, it is nearly impossible to compare and draw conclusions about IN ketamine and midazolam due to the variety of drug regimens used, the different indications, and the small population studied[47].

Our study has several limitations. It was an open-labeled study with its drawbacks. Our sample size was relatively small. There were no control groups. The procedures and children were not videotaped for obtaining more accurate OSBD-R scores. The objective evaluation of the pain was not performed. All these limitations should be in mind when interpreting the overall result.

CONCLUSION

There is no difference in the efficacy of IN ketamine and midazolam in sedation & analgesia before obtaining peripheral IV access in children. Both medications cause acceptable levels of sedation. There is no difference in the overall success rate between the two drugs. In addition, there is no difference between the two drugs regarding their effects on heart rate and oxygen saturation.

Based on the result of our study, ketamine seems to be the ideal IN medication for sedation and analgesia before accessing IV line. The dose of 5mg/kg of ketamine seems to have a desirable effect for this purpose. Conducting large-scale studies in order to optimize the gold standard medication for intranasal sedation and analgesia in children in ED will be valuable.

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