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Efficacy of oral ketamine compared to midazolam for sedation of children undergoing laceration repair

A double-blind, randomized, controlled trial

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Abstract

Objective: To assess the efficacy of oral ketamine versus oral midazolam for sedation during laceration repair at a pediatric emergency department.

Methods: Children between 1 and 10 years requiring laceration repair were randomly assigned to 2 groups, treated either with oral midazolam (0.7 mg/kg) or with oral ketamine (5 mg/kg).

Main outcomes measured were level of pain during local anesthesia, as assessed by the parent on a 10-cm visual analog scale (VAS) and the number of children who required intravenous sedation. Secondary outcomes included VAS by physician, pain assessment by child, maximal sedation depth assessed by the University of Michigan Sedation Scale, time until University of Michigan Sedation Scale 2 or more, general satisfaction of a parent and treating physician, length of procedure, total sedation time, and the incidence of any adverse events.

Results: Sixty-eight children were recruited of which 33 were girls. Average age was 5.08 ± 2.14 years. Thirty-seven children were treated with ketamine and 31 with midazolam. Parent-assessed VAS in ketamine treated patients was 5.07 ± 0.75 compared with 3.68 ± 0.7 in midazolam treated patients [mean difference = 1.39 95% confidence interval (CI) –0.47 to 3.26]. Twelve (32%) of the children treated with ketamine required the addition of IV sedation compared to only 2 children (6%) of the children treated with midazolam [odds ratio (adjusted for age and gender) 6.1, 95% CI: 1.2 to 30.5]. The rest of the measured variables were similar between the groups, with no statistical significance.

Discussion: No difference in the level of pain was found between ketamine and midazolam treated patients. Compared with oral midazolam (0.7 mg/kg), oral ketamine (5 mg/kg) was associated with higher rates of sedation failure, and thus is not recommended as a single agent for oral sedation in children requiring laceration repair.

Abbreviations: CI = confidence interval, ED = emergency department, ITT = intention to Treat, IV = intravenous, MD = mean difference, SD = standard deviation, UMSS = University of Michigan Sedation Scale, VAS = visual analog scale.

Keywords: emergency medicine, ketamine, midazolam, pediatrics, sedation

1. Introduction

Children referred to the pediatric emergency department (ED) for suturing a laceration often require sedation in order to lower anxiety and pain levels and to induce amnesia. Control of pain alone can be achieved by local anesthesia. Nevertheless, the injection itself is painful, leaving the child restless, uncooperative, and thus the stress involved in the procedure intensifies.

One of the commonly used protocols for sedation during laceration repair is oral midazolam.[1–3] It has been proven that the drug was efficacious compared to placebo.[3] However, its stress-reducing rates reached 60% to 80%,[3–5] leaving a large percentage of children awake and distressed, possibly leading to additional IV sedation.

When a procedure is performed in a crowded ED, we aim to perform the procedure as quickly as possible with minimal complications. A therapeutic failure in oral sedation and the transition to IV sedation prolongs the total length of stay, adds

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another painful procedure and is difficult for both the child and parent as well as requiring more resources. For all of these reasons, we prefer to use an oral medication that will minimize the transition to IV sedation.

Ketamine has been proven to be effective in inducing analgesia and amnesia when administered by the intravenous, intramuscular, and intranasal routes. Its efficacy upon oral administration was examined in various procedures, such as dental procedures,[6] wound dressing in burns,[7] invasive treatments in oncological patients,[8] dental treatments, and laceration repair in children.[9] Younge and Kendall[10] compared high doses of oral ketamine and oral midazolam for sedation of children prior to laceration repair and showed that higher tolerability to local anesthesia injection was observed under oral ketamine treatment. Less adverse reactions were reported in children treated with ketamine compared to those treated with midazolam. The combination of both oral ketamine and midazolam was examined in different settings.[11–14] In a previous study, we compared midazolam and the combination of midazolam and ketamine, administered orally, for sedation during laceration repair.[15] No statistically significant differences in pain response were found between the 2 groups. However, achieving adequate sedation was more common in children treated with the combination of ketamine and midazolam rather than oral midazolam alone.

In this study, we aimed to examine the possibility that oral ketamine as a single agent will provide better sedation, compared to oral midazolam.

1.1. Study hypothesis

Oral ketamine will provide better sedation than oral midazolam for children during laceration repair.

2. Methods

2.1. Study design and setting

This was a prospective, double-blind randomized trial conducted at the ED of a University affiliated general hospital. The study was undertaken in accordance with Good Clinical Practice and the Declaration of Helsinki, and had the approval of the institutional ethics committee. It was registered in the www.clinicaltrials.gov site (NCT01925898).

2.2. Patient selection

Children between 1 and 10 years of age who visited the pediatric ED between January 1, 2014 to June 30, 2014, and required sedation for laceration suturing, were recruited to the study. Children who suffered from extensive trauma, children with neurologic impairment and children with hypersensitivity to midazolam or ketamine were excluded from the study. Children were also excluded if they had other known contraindications for the study drugs, for example, hypertension, hyperthyroidism, glaucoma, or known psychiatric disease; American society of anesthesiology score of more than 2 or if informed consent could not be obtained from a legal guardian.

Legal guardians of the eligible children were approached for consent. After obtaining a singed informed consent, demographic data and wound characteristics were documented by a pediatrician.

2.3. Randomization and masking

Using a computer-generated sequence, children were randomly assigned in blocks of 6 to 1 of 2 groups treated with ketamine 5 mg/kg (maximal dose 70 mg) or midazolam 0.7 mg/kg (maximal dose 20 mg). The allocation sequence was kept by the pharmacy staff and the investigators were blinded to randomization until statistical analysis of the study was completed.

2.4. Medication preparation

The trial medicine vials were prepared at the hospital's pharmacy and contained either ketamine 10 mg/mL (ketamine 50 mg/mL manufactured by Rotexmedica from Tritau, Germany diluted in Ora Sweet solution manufactured by Paddock, Minneapolis, MN) or midazolam 1.4 mg/mL (midazolam 5 mg/mL manufactured by Rafa, Jerusalem, Israel and diluted in Ora Sweet solution manufactured by Paddock). All medications were numbered by the pharmacy with a serial number and had to be used within 1 month.

2.5. Administration of sedation

As the child was prepared for the procedure, a dressing with LET (lidocaine, epinephrine, and tetracaine) was placed on the wound 30 minutes prior to the procedure. A presedation standard assessment form was filled by a physician. The study medication was administered by the nursing team of the ED.

2.6. The procedure

Following the administration of sedative drugs the children were attached to cardiac, blood pressure and pulse oximeter monitor, and vital signs were documented. An investigator assessed the child's pain before the procedure started, on a 10-cm visual analog scale (VAS) where 10 cm reflects worst pain. Depth of sedation was measured using the University of Michigan Sedation Scale (UMSS)[16] every 5 to 10 minutes.

Suturing was performed by the attending physician or on call surgeon (plastic/orthopedic, depending on the laceration site). The laceration repair procedure began once the sedation reached UMSS $\geq$ 2. In children who reached only UMSS 1, an attempt to proceed with the repair was performed. If the suturing physician was under the impression that the procedure cannot be performed (e.g., if the child was crying or uncooperative during the disinfection of the wound), or in cases in which the child was unable to reach the required level of sedation, IV sedation was administered and the procedure details were documented in the study file.

Prior to laceration suturing, local anesthesia with Lidocaine 1% was performed. Both the investigator and a parent were asked to assess the child's pain, on VAS, at the moment the local anesthesia injection was administered. In addition, children above the age of 4 years were asked to evaluate the level of pain during the procedure using a face pain scale. This grading was conducted by the child after full recovery from the sedation. Parents and physician satisfaction from the procedure was assessed utilizing a VAS score. The length of the procedure, from disinfection to bandage administration after the procedure, and time for achieving UMSS of 0 were documented. Complications were documented on a standard form. Following the completion of laceration repair the patient was monitored in the ED. Patients were discharged from the ED after regaining full consciousness and when able to sit or stand independently, drink without vomiting, and presented normal vital signs.

2.7. Outcome measures

The main outcome measures were VAS by a parent and the number of children who failed oral sedation. The secondary outcomes measures were VAS by physician, pain assessment by

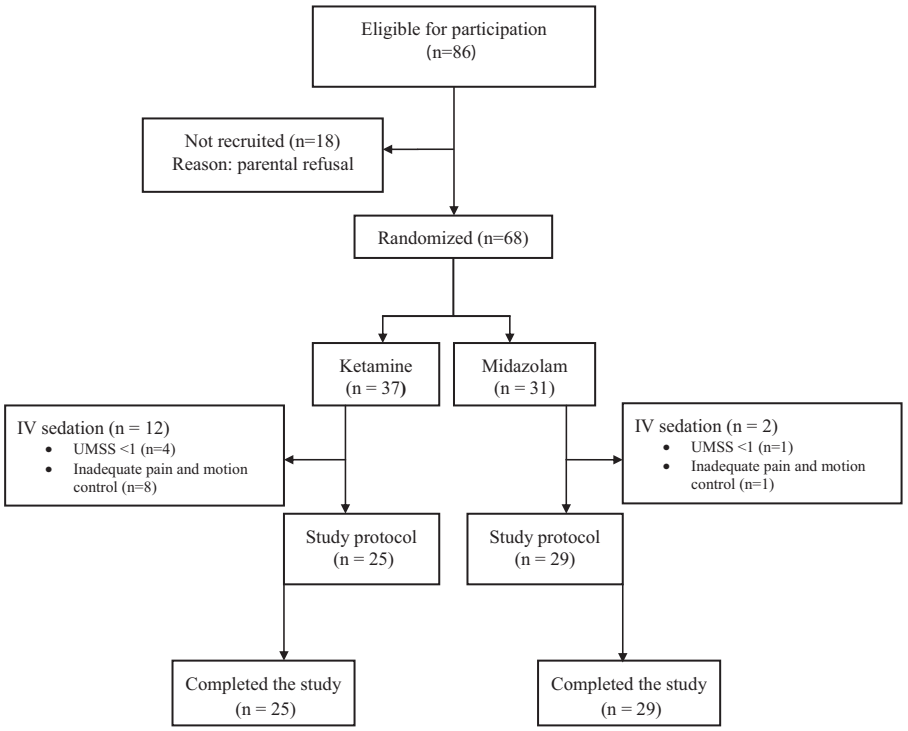

Figure 1. Consort flow diagram.

child, time until UMSS 2 or more, maximal UMSS by ED physician, general satisfaction of a parent and treating physician, length of procedure (measured from the injection of local anesthetics until completion of wound dressing), total sedation time and the incidence of any adverse events.

2.8. Data analysis

Descriptive statistics were used to describe the study population. The analysis of the data was done by intention to treat (ITT) and per protocol. For the analysis of the data in the ITT analysis, missing data were completed by multiple imputations. Statistical calculations were performed by *t*-test or Mann–Whitney for continuous variables, and by Fisher exact test for discrete variables. P values < 0.05 were considered statistically significant. Multiple logistic regression was used to calculate the odds ratio for oral sedation failure. Variables were entered into the model if they met a significance level of 0.1 in the univariate analysis. Statistical analysis was conducted using the SPSS (SPSS 21st edition; IBM Corp Armonk, NY) computer program.

2.9. Sample size

In previous trials, parents grading the level of pain during laceration repair with VAS had a standard deviation (SD) of 20[17] and 28 mm.[15] Assuming the SD will be 25 mm, there was a need for 26 patients in every group in order to recognize a 20 mm difference in VAS score with 80% power and alpha of 0.05. In order to compensate for the possibility of a larger SD, the decision was made to recruit 30 patients for every group. In order to consider abnormal distribution, 68 children were recruited.

3. Results

During the study period, 86 children were found to be eligible for the study. In 18 cases, the parent did not sign the informed consent; thus, 68 children were included in the study and were randomly assigned to 2 groups: 31 children were treated with midazolam and 37 children were treated with ketamine (Fig. 1). Children in the ketamine group were older than children in the midazolam group [5.6 ± 2.1 vs 4.5 ± 2.1 years, mean difference (MD) 1.1 95% confidence interval (CI): 0.5 to 2.1]. There were

Table 1

Demographic data.

Demographic characteristics	Midazolam (n = 31)	Ketamine (n = 37)	Statistical significance	Mean difference	95% CI
Age, y	4.50 ± 2.12	5.57 ± 2.07	0.04*	1.06	0.05 to 2.08
Weight, kg	18.51 ± 6.64	19.91 ± 6.36	0.36*	1.39	−1.66 to 4.46
Female gender	12 (38%)	21 (56%)	0.15†	18%	−6% to 43%
Face laceration	24 (77%)	27 (72%)	0.78†	−4%	−25% to 17%
Length of laceration, cm	2.31 ± 1.57	2.04 ± 1.38	0.46*	−0.26	−0.98 to 0.45
Length of procedure, min	11.3 ± 4.32	13.43 ± 6.31	0.18*	−2.08	−5.19 to 1.04

* *t* test.

† Fisher's exact test.

Table 2

Intention to treat analysis.

Variables	Midazolam (n = 31)	Ketamine (n = 37)	Statistical significance	Mean difference	95% CI
VAS before procedure	0.39 ± 1.71	0.33 ± 0.73	0.85*	−0.05	−0.70 to 0.58
Time to UMSS ≥ 2, min	25.79 ± 10.52	23.61 ± 9.23	0.44*	−2.17	−7.79 to 3.44
Maximal UMSS	1.7 ± 0.65	1.6 ± 0.84	0.6*	−0.10	−0.47 to 0.27
Transition to IV sedation	2 (6%)	12 (32%)	0.014†	26%	8% to 44%
VAS by investigator	3.88 ± 0.91	4.43 ± 0.75	0.61*	0.55	−1.68 to 2.79
VAS by parent	3.68 ± 0.7	5.07 ± 0.75	0.14*	1.39	−0.47 to 3.26
General satisfaction investigator	7.29 ± 0.75	6.31 ± 0.76	0.34*	−0.97	−3.03 to 1.08
General satisfaction parent	8.04 ± 0.48	6.69 ± 0.64	0.96‡	−1.35	−2.95 to 0.24
General satisfaction suturing physician	7.29 ± 0.81	6.4 ± 0.72	0.42*	−0.88	−3.12 to 1.35
VAS by child	2.29 ± 2.16	3.27 ± 1.71	0.53*	0.98	−2.14 to 4.10
Time from drug to dismissing, min	105.08 ± 29.09	98.78 ± 30.63	0.49*	−6.30	−24.86 to 12.26

* *t* test.
† Fisher's exact test.
‡ Mann Whitney test.

no significant differences between the 2 groups in other demographic parameters (Table 1). The majority of the children had a laceration of the face, mostly involving the forehead and chin. Laceration repair of limbs involved mostly the fingers. No significant difference in the length of the laceration was found. The children in both groups did not seem to suffer from pain prior to the procedure (Table 2). The average time from administration of the medication until reaching UMSS > 2 and the length of the procedure were similar between the groups.

The level of sedation during the procedure in children treated with ketamine was not significantly different from those treated with midazolam, with an average UMSS of 1.6 ± 0.84 vs 1.7 ± 0.65, respectively (MD –0.1, 95% CI: –0.47 to 0.27). Failure to achieve adequate sedation was more common among children treated with ketamine. Twelve (32%) children treated with oral ketamine required additional IV sedation compared with only 2 (6%) of the children treated with midazolam. The odds ratio (adjusted for age and gender) was 6.1 (95% CI: 1.2 to 30.5). The length of the procedure from disinfection of the wound until the dressing was not significantly different between the 2 study groups (13.43 ± 6.31 minutes) and the midazolam group (11.3 ± 4.32; MD, –2.08, 95% CI: –5.19 to1.04).

In the 54 children who completed the study protocol with oral sedation, the VAS reported by both the parent and the investigator was similar between the 2 groups (Tables 2 and 3). Among older children who could perform self pain assessment, there was no difference between the groups (n = 27, Table 3). There was no difference between the groups in length of stay at the ED (time from sedation until discharge; Tables 2 and 3). Few adverse effects were observed during the study. Of the children treated with ketamine, 1 child suffered from vomiting and another from nausea and vertigo, which extended their stay in the ED. Among those treated with midazolam, 1 child suffered from vomiting and hiccups. Agitation was noticed in 3 children (2 treated with ketamine and one treated with midazolam). No significant adverse effects were noted in either group.

4. Discussion

In this prospective double-blind study, there was a higher rate of procedure failure and need for IV sedation among children treated with oral ketamine compared to those treated with oral midazolam. No difference was found in the level of pain, depth of sedation (measured by UMSS), and total length of stay.

The need to add IV sedation in the ketamine treated group observed in the current study contradicts the data presented by Younge and Kendall,[10] who found that oral ketamine is more effective than midazolam for sedation in laceration repair in children. However, it should be noted that Younge and Kendall, used higher doses of ketamine (10 mg/kg) than the dose used in our study (5 mg/kg). In addition, Younge measured the child's tolerance to the procedure using an anxiety scale ranked by the parents and not a VAS that monitors pain. More so, there was no assessment of the need for adding IV sedation. A 10 mg/kg dose was also used in a small placebo controlled trial by Qureshi et al.[9] Although there were no major respiratory or cardiovascular adverse events, 26% of patients who received ketamine in that study experienced minor, transient adverse effects, such as vomiting and abnormal movements. The 5 mg/kg oral dose of ketamine in the current study was chosen based on reported bioavailability ranging from 17% to 45%,[18] thus, a 5 mg/kg

Table 3

Per protocol analysis.

variables	Midazolam (n = 29)	Ketamine (n = 25)	Statistical significance	Mean difference	CI 95%
VAS by investigator	4.12 ± 3.07 (n = 29)	4.31 + 3.34 (n = 25)	0.82*	0.18	−1.53 to 1.91
VAS by parent	3.78 ± 2.95 (n = 29)	4.75 ± 3.29 (n = 25)	0.26*	0.96	−0.74 to 2.67
General satisfaction investigator	7.14 ± 3.14 (n = 27)	6.19 ± 3.66 (n = 24)	0.32*	−0.95	−1.53 to 0.96
General satisfaction parent	8.05 ± 2.32 (n = 27)	7.00 ± 3.74 (n = 24)	0.22†	−1.35	−2.95 to 0.24
General satisfaction—suturing physician	7.00 ± 2.99 (n = 27)	6.64 ± 3.55 (n = 24)	0.69*	−0.88	−3.12 to 1.35
VAS by child	2.29 ± 3.03 (n = 12)	2.26 ± 3.84 (n = 15)	0.98*	−0.02	−2.14 to 4.10

* *t* test.
† Mann–Whitney test.

should be roughly equivalent to the typical IV dose of 1 to 2 mg/kg.

Oral midazolam in a dose of 0.7 mg/kg is within the typical 0.5 to 1 mg/kg for this drug[1–5,10,15] and similar to the dose used in the study by Younge and Kendall.[10]

Our study showed no significant difference between the groups in the length of time from administration of the medication until reaching UMSS ≥ 2. Similar findings were found by Funk et al.[19] Our study demonstrated a significant difference between the percentages of children who required IV sedation (32% in the ketamine group compared with 6% in the midazolam group) which was not anticipated in the study hypothesis.

In the current study, the 10-cm VAS scale was used for pain assessment during local anesthetic injection. This scale is commonly used to assess pain in adults. Using VAS by an observer in order to assess pain in children is commonly used[20,21] yet controversial. Several studies suggest that VAS assessment in children, especially when performed by an observer is an unreliable measure,[22] and does not correlate with the child's self-reported level of pain.[23] However, Taddio et al,[24] found VAS pain assessment by an observer in infants undergoing immunization to have good interrater reliability, suggesting that VAS can serve as an outcome measure for acute procedural pain in infants. Pain assessment in children is based on age-appropriate scales. Due to the variability of ages in the current study, it was impossible to use one uniform scale. In children aged 4 years and older, we assessed pain perception using a face scale —a validated pain scale.[25] A reliable assessment during the procedure was impossible since the children were sedated. Therefore, the assessment was performed after the child recovered from the sedation. Clearly, some of the children did not remember the procedure itself and the pain they experienced during it, but the result may be regarded as the summary of their experience. There was no significant difference between the groups.

During the local anesthesia injection, there was no significant difference in pain assessment between the 2 groups, neither by parent nor by investigator. There was no significant difference in the level of sedation and the length of the procedure. These results are surprising due to the significant difference in transition to IV sedation. It should be noted that the level of pain measured during local anesthesia was only recorded in patients who completed the protocol with oral sedation, and not in those treated IV. If the child was too agitated and the suturing attempt failed, the child was transitioned to IV sedation. It is possible that the lack of difference in pain levels between the groups results from more children treated with ketamine not completing the study.

There was no difference between the groups in time to recovery from sedation. Average recovery time was similar to other previous studies in which recovery time was 70 to 128 minutes in midazolam sedation and 70 to 120 minutes in ketamine sedation.[10]

Our study had no clinically significant adverse events unlike other studies,[10,13,14] some of which used larger doses of ketamine.

In this study, we evaluated the satisfaction of the parents, investigator, treating physician, and to a certain extent the child from the whole procedure. This was done in order to avoid referring only to the anesthetic injection stage, which is the most stress related stage for the parent and the child. There was no difference in satisfaction between the 2 groups. The measurement of overall satisfaction was done using VAS—not a validated tool for such assessments and should be interpreted with caution.

4.1. Study limitations

It is important to note that the experience of the child was not examined over time in our study. Funk et al[19] preformed an interview 1 day and again 1 week following the procedure. They did not find any difference in the prolonged effect of the experience between the 2 groups.

We cannot ignore the large number of children who did not complete the treatment protocol and needed IV sedation. Although both the per-protocol analysis and the intention-to-treat analysis did not show significant differences in the variables examined, a larger study may achieve more significant results.

Another limitation is the size differences between the 2 groups. We used block randomization in an attempt to avoid such differences. Although randomization was adhered to, some expired vials of prepared medications had to be discarded resulting in uncompleted blocks.

This study demonstrated that oral ketamine (5 mg/kg) versus oral midazolam (0.7 mg/kg), did not lead to either a decrease in pain or deeper sedation during laceration repair. Rather, it showed an increased percentage of children who required IV sedation. On the other hand, oral ketamine did not prolong the recovery time from sedation or cause any significant adverse effects.

In order to further examine the optimal agent for oral sedation, more studies should be conducted in larger groups, in which stratification of patients based on the laceration location and various drugs doses can be tested. At this stage, we recommend midazolam as a single medication for sedation for laceration repair in the ED.

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