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Original Contributions

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REPEAT INTRAVENOUS KETAMINE DOSING IN CHILDREN UNDERGOING EMERGENCY DEPARTMENT PROCEDURAL SEDATION

Katherine R. Forrester, MD,* Scott M. Thomas, MD,* Nita K. Gupta, MD,† Manasa Karumuri, MD,† and James M. Gerard, MD*

*Division of Pediatric Emergency Medicine and †Department of Pediatrics, Saint Louis University School of Medicine, Saint Louis, Missouri
Corresponding Address: Katherine R. Forrester, MD, SSM Health Cardinal Glennon Children's Hospital, 1465 South Grand Blvd, Saint Louis, MO 63104

☐ **Abstract—Background: Patients undergoing procedural sedation with intravenous ketamine often receive repeat doses to maintain dissociation; however, data between doses are lacking. Objectives: The purpose of this study was to characterize the frequency, time interval, and dosages of ketamine received by children undergoing procedural sedation and to explore the effects of age and body mass index on these parameters. Methods: This was a retrospective study of patients 1 to 18 years of age undergoing procedural sedation with intravenous ketamine in a pediatric emergency department between October 2016 and June 2017. Total repeat ketamine dosages were standardized to a 1-h sedation. Results: Four hundred nineteen patients were included in the analysis. The median sedation time was 33.0 minutes (interquartile range [IQR] 25.0–45.0). Three hundred sixty-three patients (86.6%) received at least 1 repeat ketamine dose. The median time between doses was 7.0 minutes (IQR 5.0–12.0). Children <6 years of age, compared with older children, received higher hourly doses of ketamine in mg/kg/h (2.8 [IQR 1.8–3.9] vs. 1.8 [IQR 1.2–2.6], $p_c < 0.01$). Children <3 years of age, compared with older children, received the highest hourly dose of ketamine in mg/kg/h (3.7 [IQR 2.3–5.0] vs. 1.9 [IQR 1.4–2.8], $p_c < 0.01$). Ketamine repeat and hourly dosing does not appear to be significantly different in children of differing body mass index classes. Conclusions: Patients undergoing ketamine sedation often receive repeat doses to maintain dissociation. Patients <3 years of age received the highest total repeat ketamine dosages.** © **2018 Elsevier Inc. All rights reserved.**

☐ **Keywords—ketamine; pediatrics; procedural sedation**

INTRODUCTION

Ketamine is a dissociative anesthetic agent that is frequently used for procedural sedation during painful procedures, particularly in the pediatric emergency department (ED). It is a unique agent in that it does not exhibit a dose-response continuum as seen with other sedatives. On the other hand, the dissociation seen with ketamine emerges at doses of approximately 1.0–1.5 mg/kg intravenously (IV) or 3–4 mg/kg intramuscularly (IM). Once a patient becomes dissociated under ketamine, the addition of more ketamine will not increase sedation, which is the case with other agents. Therefore, the only need is for titration of dosing to maintain the dissociated state (1).

Interruptions in the dissociated state are periods of time when a patient may feel pain or be aware of his or her surroundings. To prevent interruptions in dissociation, performing a ketamine sedation requires that the sedating provider closely monitors the patient to determine when the patient is emerging from the dissociated state. Ideally, to avoid pain or awareness, repeat ketamine doses should be administered before patients become undissociated. Numerous studies have reported on ketamine

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dosing (1–4). These studies, however, have focused on initial ketamine dosing but not on the repeat dosing requirements to maintain dissociation.

The purpose of this study was to characterize the frequency and time interval for ketamine dosing in children. In addition, this study aimed to explore the effects of age and body mass index (BMI) on repeat dosing. These data would be useful to emergency physicians in anticipating the timing for repeat doses during ketamine procedural sedations.

METHODS

Patient Selection

This was a retrospective study of patients between 1 and 18 years of age who were undergoing procedural sedation with IV ketamine between October 1, 2016 and June 30, 2017. The study was approved by the institutional review board of the university affiliated with the study location. We conducted this study at an urban, academic, freestanding, tertiary care referral center and level I pediatric trauma center. Patients who received IM ketamine were excluded. Patients who received propofol concomitantly were excluded. In addition, patients receiving IV ketamine were excluded if the initial dose administered was <1.0 mg/kg for patients weighing <50.0 kg or <50.0 mg for patients weighing ≥50.0 kg.

Assessed Variables

We assessed patient medical records for demographic variables, including age, height, weight, initial and repeat ketamine dosages, time between dosages, coadministered medications, and total sedation time. According to our ED standard practice, patient heights are recorded in the medical record for patients undergoing procedural sedation. In cases where a height was not recorded at the time of the ED visit, we used patient growth charts to determine if a height had been recorded within 30 days of the ED visit. Subjects for whom no height was recorded at the time of the ED visit or within 30 days of the ED visit were excluded from the study.

We defined total sedation time as the period between the first dose of ketamine and the recorded procedural stop time. To account for differences in sedation times, we standardized repeat ketamine dosages to a 1-h sedation (in milligrams per kilogram per hour [mg/kg/h]). This was achieved using the following formula: (60/actual sedation time) × actual repeat ketamine dosages = standardized hourly repeat dosage.

To explore differences in ketamine requirements by age, we categorized patients into the following age groups: <3 years, 3–6 years, 6–9 years, 9–12 years, 12–15 years, and >15 years. To explore differences in body habitus, we categorized patients into 3 BMI classes: underweight, normal weight, and overweight/obese. These BMI classifications were determined using the Centers for Disease Control and Prevention and World Health Organization growth charts. We categorized patients between the ages of 1 and 2 years as either low weight-for-length (weight-for-length <2nd percentile), normal weight, or high weight-for-length (weight-for-length >98th percentile). We categorized patients who were ≥2 years of age as either underweight (BMI <5th percentile), normal weight (BMI of at least 5th percentile and <85th percentile), or overweight/obese (BMI ≥85th percentile) (5–7).

Statistical Analyses

Proportional data are presented as numbers and percentages. Total ketamine dosages and sedation times were nonnormally distributed; therefore, we used nonparametric tests to analyze these data. We used Kruskal–Wallis tests with post hoc Bonferroni-corrected Mann–Whitney *U* tests to compare subjects by age and BMI class. These data are reported as medians and interquartile ranges (IQRs). We considered an α of <0.05 as statistically significant. We performed analyses using SPSS software (v 24.0; IBM Corp., Armonk, NY).

RESULTS

A total of 419 patients were included in the analyses. Patient characteristics are shown in Table 1. Of the 419 patients, 363 patients (86.6%) received ≥1 repeat ketamine dose. For those who received repeat doses, the median initial dose was 1.3 mg/kg (IQR 1.0–1.7) compared with those who did not receive repeat doses (1.5 mg/kg [IQR 1.1–2.0], $p < 0.01$, Mann–Whitney *U*). For the entire cohort, the median sedation time was 33.0 min (IQR 25.0–45.0). The median number of repeat doses was 2 (IQR 1–3). The median time between doses was 7.0 min (IQR 5.0–12.0). For patients who received repeat ketamine doses, the standardized repeat ketamine dosage was 2.2 mg/kg/h (IQR 1.5–3.3).

Differences in repeat ketamine dosages by age are shown in Table 2. Children <6 years of age, compared with older children, received higher hourly doses of ketamine in mg/kg/h (2.8 [IQR 1.8–3.9] vs. 1.8 [IQR 1.2–2.6], $p_c < 0.01$). Children <3 years of age, compared with older children, received the highest hourly dose of ketamine in mg/kg/h (3.7 [IQR 2.3–5.0] vs. 1.9 [IQR 1.4–2.8], $p_c < 0.01$).

With regard to BMI class, the initial dose of ketamine (mg/kg) was lower in overweight and obese patients (n = 133) when compared with normal weight (n = 262) and underweight (n = 24) patients (1.1 [IQR 0.9–1.5]

vs. 1.4 [IQR 1.1–1.8] and 1.7 [IQR 1.4–2.0], respectively, $p < 0.01$)]. However, the total dose of ketamine (mg/kg) was highest in normal weight patients (2.6 [IQR 2.0–3.3]) when compared with underweight patients (2.3 [IQR 2.0–3.5]) and overweight and obese patients (2.3 [IQR 1.6–3.0], $p = 0.02$). Differences in repeat ketamine dosages by BMI class are shown in Table 3. Overweight and obese children received a higher number of repeat ketamine doses ($p_c = 0.04$) though no differences between BMI class were seen with respect to time between doses or the standardized repeat dosage.

Differences in repeat ketamine dosages with regard to the coadministration of narcotics or benzodiazepines were also analyzed. Among all patients, those who received a narcotic received significantly less ketamine (in mg/kg/h) when compared with those who did not receive a narcotic (1.8 mg/kg/h [IQR 1.1–2.8] vs. 2.1 mg/kg/hr [IQR 1.2–3.3], respectively, $p = 0.04$). Similarly, among patients who received repeat ketamine doses, those who also received a narcotic had a significantly lower standardized repeat ketamine dosage when compared with those who did not (1.9 mg/kg/hr [IQR 1.4–3.0] vs. 2.4 mg/kg/hr [IQR 1.5–3.6], respectively, $p < 0.01$). On the other hand, these differences were not seen in those who concomitantly received benzodiazepines.

DISCUSSION

The frequency and time interval for ketamine dosing in children have not been well described in previous studies. The present study found that most children (86.6%) received ≥1 additional dose of ketamine for procedural sedations occurring in an ED setting. Across all age groups, the median time between ketamine doses was only 7.0 min—a surprisingly short time interval. We found that children <3 years of age received repeat ketamine doses even more frequently with a median time of 6.0 min between doses. When adjusting for length of sedation, children <3 years of age received the highest total repeat dosage.

Because of physiological changes that occur as children progress through infancy to childhood and adolescence, drug distribution and metabolism change (8). Ketamine is primarily metabolized in the liver by CYP3A4 into the active metabolite norketamine (9). In children >1 year of age, CYP3A4 enzyme activity levels exceed adult levels (10). Published literature has shown evidence that children require higher weight-corrected doses of drugs metabolized by CYP3PA4 to achieve a similar therapeutic effect (10). Younger children may require more frequent dosing of these drugs given the higher level of this enzymatic activity. The results from this study are congruous with these previous findings as children <3 years of age received both more frequent dosing of ketamine and a higher standardized repeat dose during their sedations.

In addition, the pharmacokinetics of certain drugs is known to change in obese patients. It is unclear from published literature whether excess adipose tissue affects the absorption and metabolism of ketamine. The lipophilic property of ketamine could potentially cause a difference in metabolism in overweight patients. Excess body fat changes tissue composition and cardiac output, and this potentially contributes to the metabolic and renal

Table 1. Patient Characteristics (n = 419)

	Age (years)					
	0–3 (n = 85)	3–6 (n = 100)	6–9 (n = 94)	9–12 (n = 54)	12–15 (n = 56)	15–18 (n = 30)
Female, n (%)	49 (42.4)	41 (41.0)	44 (46.8)	23 (42.6)	18 (32.1)	9 (30.0)
Body mass index, median (IQR)	16.6 (15.1–18.4)	15.8 (14.7–16.9)	16.7 (15.2–19.4)	19.1 (16.8–23.4)	20.3 (17.9–25.7)	22.2 (19.6–27.7)
Race, n (%)						
African American	43 (50.6)	18 (18.0)	25 (26.6)	10 (18.5)	15 (26.8)	9 (30.0)
Caucasian	33 (38.8)	74 (74.0)	62 (66.0)	40 (74.1)	35 (62.5)	19 (63.3)
Asian	0 (0.0)	0 (0.0)	3 (3.2)	1 (1.9)	1 (1.8)	1 (3.3)
Hispanic	6 (7.1)	4 (4.0)	2 (2.1)	1 (1.9)	3 (5.4)	0 (0.0)
Other	3 (3.5)	4 (4.0)	2 (2.1)	2 (3.7)	2 (3.6)	1 (3.3)
Procedure, n (%)						
Fracture reduction	15 (17.6)	60 (60.0)	72 (76.6)	43 (79.6)	47 (83.9)	21 (70.0)
Laceration repair	25 (29.4)	33 (33.0)	18 (19.1)	6 (11.1)	2 (3.6)	1 (3.3)
Abscess incision and drainage	30 (35.3)	5 (5.0)	2 (2.1)	2 (3.7)	5 (8.9)	7 (23.3)
Other	15 (17.6)	2 (2.0)	2 (2.1)	3 (5.6)	2 (3.6)	1 (3.3)
Coadministered medications, n (%)						
Narcotic	16 (18.8)	38 (38.0)	51 (54.3)	26 (48.1)	37 (66.1)	24 (80.0)
Benzodiazepine	7 (8.2)	7 (7.0)	7 (7.4)	5 (9.3)	12 (21.4)	10 (33.3)
Ondansetron	12 (14.1)	32 (32.0)	32 (34.0)	26 (48.1)	35 (62.5)	15 (50.0)

Table 2. Differences in Ketamine Dosages by Age* (n = 363)

	Age (years)						
	<3 (n = 78)	3–6 (n = 87)	6–9 (n = 79)	9–12 (n = 44)	12–15 (n = 50)	>15 (n = 25)	*p* Value*†
Initial ketamine dose in mg/kg, median (IQR)	1.6 (1.3–1.9)	1.5 (1.2–1.9)	1.4 (1.1–1.7)	1.1 (1.0–1.4)	1.0 (0.8–1.1)	0.8 (0.7–0.9)	<0.01
Repeat ketamine dose in mg/kg, median (IQR)	0.8 (0.5–1.1)	0.8 (0.6–1.0)	0.6 (0.5–0.8)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.4 (0.3–0.4)	<0.01
Time between doses in minutes, median (IQR)	6.0 (4.0–8.0)	7.0 (5.0–11.0)	9.0 (6.0–14.0)	9.5 (6.0–12.0)	8.0 (5.0–11.0)	8.0 (5.0–12.8)	<0.01
Hourly ketamine in mg/kg/h, median (IQR)	3.7 (2.3–5.0)	2.3 (1.6–3.3)	1.9 (1.4–2.8)	1.5 (0.9–2.3)	1.7 (1.3–2.5)	1.6 (1.1–3.0)	<0.01

IQR = interquartile range.
* Among patients who received repeat doses.
† Kruskal–Wallis test.

clearance of drugs. In addition, it may lead to a higher risk of toxicity or reduced therapeutic effects (11–14).

In recent years, several studies looking at ketamine sedations in overweight or obese children have been reported. Kinder et al. evaluated BMI and its relation to emesis, a well-described adverse effect of ketamine (15). Their findings suggested that pediatric patients with higher BMIs are at a greater risk of emesis during ketamine sedation (15). An additional study by Street and Gerard evaluated a fixed-dose ketamine protocol and compared normal weight with overweight and obese patients (4). This study found that a fixed-dose of ketamine for adolescents achieved desirable sedation regardless of patients' BMI status. However, this study was limited to adolescent patients and did not include those <12 years of age (4).

To date there have been no studies investigating ketamine dosing requirements in overweight or obese children across the entire pediatric age range. In the present study, we sought to determine if ketamine dosing differs in children who are overweight or obese. We found that, although overweight and obese children received a lower initial dose and a higher number of repeat ketamine doses, the time between doses and the standardized repeat dosage were not significantly different when compared to normal weight patients. In addition, the lower initial dose in mg/kg is likely related to most practitioners giving a maximum of 50.0 mg IV as the initial dose for patients weighing ≥50.0 kg. The repeat dosage findings are consistent with findings reported by Street and Gerard who also found that BMI status did not appear to affect ketamine dosing (4).

Finally, our study also found that patients who concomitantly received a narcotic received significantly less ketamine in mg/kg/h. As narcotic use appears to decrease the amount of ketamine given during a procedural sedation, this finding highlights the importance of good pain control before performing a procedural sedation.

Limitations

Our study has significant limitations. Because of the retrospective nature of the study, the quality of the sedations was not assessed. At our institution, during the study period, sedations were performed by dedicated sedating physicians whose only responsibility was to monitor the patient and provide repeat ketamine doses throughout the sedation. Though we believe that the sedating physicians in our ED would administer repeat ketamine doses at appropriate times to prevent patients from becoming undissociated, it is impossible to know the extent to which this did or did not actually occur. As such, our study describes the ketamine dosages that patients received but does not conclusively demonstrate dosing requirements needed to maintain the dissociated state. Repeat doses were given at the sedating physician's discretion. At our institution, there is not a standardized

Table 3. Differences in Ketamine Dosages by Body Mass Index Class* (n = 363)

Body Mass Index Class	Underweight (n = 18)	Normal Weight (n = 229)	Overweight/Obese (n = 116)	*p* Value†
Time between doses in minutes, median (IQR)	7.0 (5.0–11.0)	7.0 (5.0–11.0)	7.5 (5.0–12.0)	0.74
Standardized repeat dosage in mg/kg/h, median (IQR)	2.4 (1.5–4.3)	2.2 (1.5–3.4)	2.1 (1.3–3.0)	0.12

IQR = interquartile range.
* Among patients who received repeat doses.
† Kruskal–Wallis test.

protocol on ketamine initial and repeat dosing, and providers vary on their choice of dosages. Although we excluded patients who we believed did not receive an appropriate initial first dose of ketamine (<1.0 mg/kg for patients weighing <50.0 kg or <50.0 mg for patients weighing ≥50.0 kg), provider variation and the lack of standardization of both initial and redosing serve as additional limitations.

In addition, because the present study was conducted at a single center, the results of this study may not be generalizable to other institutions, particularly those with differing racial or ethnic patient populations. Finally, because of small sample numbers in some of the subcategories, we were unable to control for procedure type. As shown in Table 1, the most common types of procedures performed differed across the age groups. Though we did not control for type of procedure per se, by using a standardized hourly ketamine dosage we accounted for differences in sedation times that are typically seen with these different types of procedures.

CONCLUSIONS

Initial dosing regimens for pediatric procedural sedation with ketamine have been well described in previous studies but repeat dosing to maintain dissociation has not yet been examined. This study found a standardized repeat dosage of 2.2 mg/kg/h across all age groups for patients who received at ≥1 repeat dose of ketamine. Children <3 years of age received more frequent ketamine doses as well as a higher standardized repeat dose in comparison to older children. Ketamine repeat dosing does not appear to be significantly different in children of differing BMI classes. The results of this study will be useful to emergency physicians when anticipating the need and timing for repeat doses during procedural sedation with ketamine. Future prospective studies are warranted to confirm these findings.

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ARTICLE SUMMARY

1. Why is this topic important?

Procedural sedation with ketamine is commonly performed by physicians in pediatric emergency departments. Initial dosing regimens are well established in current literature; however, repeat dosing to maintain the dissociated state has not been well described.

2. What does this study attempt to show?

We conducted a retrospective chart review to characterize the time interval and frequency of repeat ketamine dosing in children. We also explored the effects of age and body mass index on repeat dosing of ketamine.

3. What are the key findings?

This study found that most patients (86.6%) received $\geq$1 repeat dose of ketamine to maintain sedation for a median sedation time of 33.0 min and a standardized repeat dosage of 2.2 mg/kg/h across all age groups. In addition, we found that children <3 years of age received more frequent dosing of ketamine and a higher standardized repeat dosage when compared with older children.

4. How is patient care impacted?

These results will be helpful to emergency department providers when anticipating the need and timing of repeat doses when performing procedural sedation with ketamine in pediatric patients. Sedating physicians should anticipate administering repeat ketamine doses at relatively short time intervals, particularly to children <3 years of age.