Published in final edited form as:

Ann Emerg Med. 2015 June ; 65(6): 640–648.e2. doi:10.1016/j.annemergmed.2014.12.011.

“Rapid administration technique of ketamine for pediatric forearm fracture reduction- a dose finding study”

Sri S Chinta, MBBS,

Department of Pediatrics, Washington University in St Louis School of Medicine, St Louis Children's Hospital, St Louis, MO, United States

Charles R Schrock, MD,

Department of Anesthesiology, Washington University in St Louis School of Medicine, St Louis Children's Hospital, St Louis, MO, United States

John D McAllister, MD,

Department of Anesthesiology, Washington University in St Louis School of Medicine, St Louis Children's Hospital, St Louis, MO, United States

David M Jaffe, MD,

Department of Pediatrics, Washington University in St Louis School of Medicine, St Louis Children's Hospital, St Louis, MO, United States

Jingxia Liu, PhD, and

Division of Biostatistics, Washington University in St Louis School of Medicine, St Louis, MO, United States

Robert M Kennedy, MD

Department of Pediatrics, Washington University in St Louis School of Medicine, St Louis Children's Hospital, St Louis, MO, United States

Abstract

© 2014 by the American College of Emergency Physicians. All rights reserved.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Meetings:

Oral presentation of preliminary data by the first author at Pediatric Academic Society Meeting in Washington DC in May, 2013.

Oral presentation of preliminary data by the first author at the Society of Academic Emergency Medicine meeting in Atlanta, GA in May, 2013.

Oral presentation by the last author at American Academy of Pediatrics National conference and Exhibition in San Diego, CA in October, 2014.

ClinicalTrials.gov identifier: NCT01669642

Conflicts of Interests: None

Author contributions: All authors were involved in conceiving and designing the study. SSC, DMJ and RMK obtained funding for the study. SSC enrolled the patients and collected data. All the authors were involved in data analysis, article preparation and final article revisions. SSC takes responsibility for the paper as a whole.

Study Objective—To estimate the minimum dose and total sedation time of rapidly infused ketamine that achieves 3-5 minutes of effective sedation in children undergoing forearm fracture reduction in the emergency department.

Methods—We used the Up-Down method to estimate the median dose of intravenous ketamine infused over 5 sec that provided effective sedation in 50% (ED₅₀) and 95% (ED₉₅) of healthy children aged 2-5, 6-11 or 12-17 years undergoing forearm fracture reduction. Most were pretreated with opioids. Three investigators blinded to ketamine dose independently graded sedation effectiveness by viewing a video recording of the first 5 minutes of sedation. Recovery was assessed by Modified Aldrete score.

Results—We enrolled 20 children in each age group. The estimated ED₅₀ was 0.7, 0.5 and 0.6 mg/kg and the estimated ED₉₅ was 0.7, 0.7 and 0.8 mg/kg for the 2-5, 6-11 and 12-17 years age groups, respectively. For the 2-5 years age group, an empirically derived ED₉₅ was 0.8 mg/kg. All who received the empirically derived ED₉₅ in the 2-5 years group or the estimated ED₉₅ in the 6-11 and 12-17 years group had effective sedation. The median total sedation time for the three age groups respectively, was 25, 22.5 and 25 minutes if one dose of ketamine was administered and 35, 25 and 45 minutes if additional doses were administered. No participant experienced serious adverse events.

Conclusions—We estimated ED₅₀ and ED₉₅ for rapidly infused ketamine for three age groups undergoing fracture reduction. Total sedation time was shorter than most previous studies.

Introduction

Background

Ketamine is one of the most common drugs administered to sedate children for painful procedures in the emergency setting¹⁻⁴. A recent clinical practice guideline for emergency department ketamine sedation⁴ recommends an intravenous loading dose of 1.5- 2 mg/kg, administered over 30-60 seconds for children of all ages. This regimen achieves effective sedation for 5-10 minutes but is associated with variably defined recovery to discharge readiness times ranging from 16 to 110 minutes⁵⁻⁸. The prolonged recovery found in most studies strains emergency department staffs and work flow. We therefore were interested in determining whether an alternative ketamine administration technique might provide a sufficient period of effective sedation but result in more rapid recovery without an increase in adverse events.

We believe that rapid infusion of smaller doses of ketamine achieves clinical effectiveness because it likely results in adequate ketamine concentrations at the site of action in the brain^{9,10}. Since we use a smaller dose, recovery is faster due to rapid redistribution.

The goal of this investigation was to estimate the ED₅₀ and ED₉₅ (effective dose in 50% and 95% of patients respectively) of rapidly infused ketamine for fracture reductions in children.

Importance

Rapid infusion of a small ketamine dose is a novel, simple procedural sedation technique that achieves brief effective sedation with rapid recovery. This study is designed to establish a starting dose of ketamine for this alternate technique for brief procedures.

Methods

Study design

We used the Up- Down method to estimate ED₅₀ and ED₉₅. ED₅₀ is the median effective dose; the dose of rapidly infused ketamine that achieves effective sedation in 50% of children and ED₉₅ is the dose of ketamine effective for 95% of children. We studied a cohort of children of different cognitive and developmental stages who were undergoing procedural sedation with ketamine for forearm fracture reduction.

Setting—The study was done in the pediatric emergency department of St. Louis Children's Hospital, a tertiary care pediatric trauma center with an annual ED census of 54,000 visits/year. XXX's institutional review board (IRB) approved the study. We registered our trial in www.clinicaltrials.gov (ClinicalTrials.gov identifier: XXXX).

Selection of Participants—A convenience sample of healthy children who were American Society of Anesthesiology (ASA) physical status I and II, between the ages of 2 and 17 years and required sedation for forearm fracture reduction in the emergency department were enrolled. Patients were identified from the emergency department electronic patient tracking board as study candidates after the treating physician had decided that ketamine sedation was indicated. Patients were enrolled in the study when the principal investigator (SSC) was available. The PI obtained signed consent from the patients' parents and assent from cognitively capable children who were older than 5 years. Exclusion criteria included temperature $\geq 38^{\circ}\text{C}$ due to upper respiratory infection, obesity defined as Body Mass Index (BMI) $>2\text{SD}$ for age and gender or undernourishment defined as BMI $<2\text{SD}$ for age and sex, psychiatric diagnosis with the patient currently under the care of a psychiatrist and/or taking psychiatric medication with the exception of patients with Attention Deficit Hyperactivity Disorder who were not excluded, previous adverse reactions with ketamine sedation, multiple fractures requiring reduction, non-English speaking parents, foster care or previous participation in the current research project.

Methods and Measurements

The PI performed all sedations to ensure quality and adherence to the research protocol. On call orthopedic residents who were in their 2nd or higher year of residency training at Washington University in St Louis performed the fracture reductions. Children received opioid analgesia at the discretion of the treating physician at or after the time of triage for pre-procedural fracture related pain. No patient was pre-treated or concurrently treated with midazolam or other sedative. All children were monitored by direct observation and standard cardio-respiratory monitoring (Phillips IntelliVue MP30[®] patient monitor) including continuous monitoring of heart rate with ECG, respiratory rate, oxygen saturation with pulse oximetry, and end-tidal CO₂ by nasal capnography (Phillips EGM[®] gas

monitor). Supplemental oxygen was not administered except in response to an adverse clinical event. Blood pressure was recorded before and 2 minutes after giving ketamine and then every 5 minutes. Parental presence throughout the sedation, procedure and recovery was permitted. The standard St. Louis Children's Hospital procedural sedation record was used to document pre-sedation evaluation, patient monitoring during the procedural sedation and post-sedation recovery. Adverse events/effects as defined in consensus-based recommendations¹¹ were documented for each patient. Ondansetron was administered in response to nausea and/or vomiting but not as prophylaxis.

We targeted a sedation score of 2 on the Children's Hospital of Wisconsin (CHW) Sedation Scale¹² (Appendix table 3) for intended depth of sedation. The modified Aldrete score (Appendix table 4) was used to assess recovery¹³. An Aldrete score of 10 and a CHW sedation score of 5 indicated sufficient recovery (readiness) for hospital discharge. After completion of the fracture reduction, the PI assessed the patient at 5-minute intervals to determine the degree of recovery from sedation. A patient was considered fully awake (Aldrete criteria for consciousness) if he or she was able to sit unassisted, hold and eat a popsicle, respond appropriately to simple questions and had minimal or no dizziness (in patients who could express dizziness). Total sedation time included both the procedure and post-sedation recovery time periods, and was defined as beginning with administration of the 1st dose of ketamine and ending when the patient achieved an Aldrete score of 10 and a sedation score of 5. Procedure time was defined as starting with the initial fracture reduction attempt (one minute after ketamine infusion) and ending with completion of the fracture reduction. A nurse or a medic trained in procedural sedation monitored all patients independently to document vital signs and adverse events.

At the time of discharge, the PI asked patients (or their parents for younger children) if they experienced any itchiness, rash, double vision, abdominal pain, dizziness or shivering during or after recovery. He also inquired whether the patient had any unpleasant recall of the procedure and patient and family preference to receive similar sedation in the future, should the need arise. The PI called the family within 2 weeks to inquire about any adverse events after discharge, including whether the patient had had dry mouth, dizziness, balance problems, nausea, headache, vomiting, nightmares or pleasant dreams, hallucinations, excessive sleepiness or difficulty falling asleep, pain after discharge or any other symptoms, and whether the patient had missed school or the caretaker had missed work to care for the patient. We compared the frequency of adverse events in our study to a recent meta-analysis that reported the type and frequency of adverse events associated with ketamine sedations in children^{14,15}.

Up - Down Method

We used the Up - Down method of Dixon¹⁶ to estimate the ED₅₀ and ED₉₅ for each age group. Based on pharmacodynamic studies¹⁷ and our experience, we used the following starting ketamine doses for the initial patient in each patient cohort: 1.0 mg/kg for the first patient aged 2-5 years, 0.6 mg/kg for the first patient aged 6-11 years and 0.5 mg/kg for the first patient aged 12-17 years. Within each cohort, the subsequent patient's initial ketamine dose was determined by the effectiveness of the previous patient's initial ketamine dose.

Effectiveness of each patient's initial dose was independently assessed by three independent reviewers as detailed below. If the prior patient's initial ketamine dose was deemed ineffective, the subsequent patient's initial ketamine dose was incremented upward by 0.1 mg/kg. Likewise, if the prior patient's initial ketamine dose was deemed effective, the subsequent patient's initial ketamine dose was incremented downward by 0.1 mg/kg. This process was continued serially for 20 participants within each of the age groups. This up-down incremental series of doses with associated success or failure brackets the median effective dose (ED₅₀) for that population. We used racemic ketamine hydrochloride for this study (Ketalar 10mg/ml by JHP Pharmaceuticals LLC).

Ketamine followed by a 5 ml normal saline flush was infused intravenously in 5 sec. One minute later the fracture was manipulated. We assessed the depth of sedation at this point using the CHW Sedation Scale¹². *A priori*, we defined the criteria for effective sedation (Appendix table 5). At any time during the procedure, if the participant verbalized significant pain, showed significant distress, resisted the procedure or required restraint, additional ketamine was administered to complete the procedure. The amount of ketamine for the additional dose was determined by the sedation provider based on the response to the previous dose and was administered by rapid infusion technique. Only the first ketamine dose and initial reduction attempt were considered in assessing the dose's sedation efficacy. A reduction attempt was defined as contiguous manipulations by the orthopedic surgeon to realign the fracture with confirmation by bedside fluoroscopy.

All reductions were video recorded by the PI onto DVDs from pre-sedation state to complete recovery. Discrete and waveform form data from the patient's bedside monitor were synchronously video recorded in a picture-in-picture format with the view of the patient throughout the sedation, procedure and recovery. Data elements included heart rate, blood pressure, respiratory rate (by impedance plethysmography and by end-tidal capnography), O₂ saturation, end-tidal CO₂ and capnography. This recording and the monitoring nurse's or medic's hand written procedural sedation record along with the PI's direct observations were available to assess for cardiopulmonary depression or other adverse events.

Effectiveness of sedation from the initial ketamine dose was determined after the patient's discharge by soliciting the opinions of three expert reviewers who each independently reviewed a 5 minute segment of each patient's audio-video recording. The segment began with administration of the pre-determined initial ketamine dose and included the first fracture reduction attempt. The PI transmitted this 5 minute audio-video segment to a secure web-based Dropbox[®] and notified the three reviewers (JDM, CRS and RMK) by email of each new recording.

These reviewers then independently accessed the Dropbox[®] to view the recording to assess the sedation effectiveness of each patient's initial ketamine dose using the criteria for effective sedation (Appendix table 5). All reviewers were blinded to the dose administered and did not participate in the fracture reduction or sedation. Their independent assessments were transmitted by email to the PI. The initial ketamine dose was deemed effective if at least two reviewers agreed that the sedation was effective. If only two reviewers were

available to review a video and agreed on the effectiveness, it was considered 100% agreement.

We created an independent data safety monitoring board comprised of a pediatric anesthesiologist, pediatric intensivist and a pediatric hospitalist, all of whom were not study investigators, to review any major adverse events. A data safety-monitoring plan was established prior to the start of the study. Study stopping criteria included laryngospasm, apnea, or respiratory depression requiring positive pressure ventilation in 2 or more patients.

Outcomes

The primary outcome for this study was to find the ED₅₀ and ED₉₅ (effective dose in 50% and 95% of patients respectively) of rapidly infused ketamine for each age group. The secondary outcomes were total sedation time, frequency of adverse events in the emergency department and patient/parent satisfaction.

Analysis

A sample size of 20 per group is based on previous studies that used the Up-Down Method in which typical samples of 20-40 were used¹⁸. The logistic regression Model was used to estimate ED₅₀ and ED₉₅, and dose response curves based on dose were analyzed^{19,20}. The 95% confidence intervals for the ED₅₀ and ED₉₅ were calculated using the profile penalized likelihood approach. All analyses were conducted using SAS (SAS Institute, Cary, NC) at the two-sided 5% significance level. Kappa (κ) statistics were calculated for consensus decisions and individual graders to reflect agreement²¹.

Results

Characteristics of study subjects

Sixty-two patients were enrolled between May 2012 and September 2013. Two patients in the 12-17 years group were excluded from analysis after enrollment due to errors in the initial dose of ketamine administered. Sixty five percent of fractures were displaced (full cortical disruption); in 25% the fragments were overriding. Patient characteristics are detailed in Table 1.

Main results

The calculated estimate of the ED₉₅ for the 2-5 years fracture group was 0.7 mg/kg. However, review of the data suggested an empiric estimate of 0.8 mg/kg. All patients who received the empirically derived ED₉₅ in the 2-5 years group and the estimated ED₉₅ in the 6-11 and 12-17 year group had effective sedation with the first dose of ketamine. The median total sedation time for the three age groups respectively, were 25, 22.5 and 25 minutes when only one dose of ketamine was administered and somewhat longer if additional doses of ketamine were needed (Table 2).

All sedations were reviewed by at least two reviewers; 74% were reviewed all three. Reviewers had 100% agreement (2/2 or 3/3) for 51 procedures (85%). The kappa statistic for consensus decisions and each individual grader were 0.90, 0.85 and 0.90.

None of the patients had a major adverse event including apnea, laryngospasm or oxygen desaturation requiring intervention. One patient (5%) in each of the 3 age groups vomited before discharge. Of the 56 patients reached by telephone for follow-up, post-discharge vomiting occurred in 32% in the 2-5 years age group and in 17% and 16% in the 6-11 and the 12-17 years age groups, respectively. Three patients in the 12-17 years age group had mild dysphoria consisting of tearfulness and minimal agitation, which required no interventions. One patient in the 2-5 years age group received midazolam for significant agitation. Six of the 60 patients had some but not unpleasant awareness of the fracture reduction. Fracture reductions were unsuccessful for 3 patients, all in the 12-17 years group. All 3 had unstable mid shaft fractures of radius and ulna and underwent operative reduction and pinning. Parent satisfaction was high in all age groups.

Limitations

Our estimated ED₉₅ was not precise because of small sample size and limited dose range. We studied a small sample of healthy children in an inner city emergency department undergoing forearm fracture reductions. We may not necessarily be able to generalize our ED₅₀ and ED₉₅ to other painful procedures and different populations. While the adverse event profile in this study is encouraging, the small sample size limits our ability to claim safety. Most of the patients were pretreated with opioids, which may have affected the ED₅₀, but it is a common practice to administer opioid pain medication for painful conditions such as fractures while awaiting diagnosis and treatment. Our sedation effectiveness criteria were not previously validated. Finally, the PI's determination of the time of full of recovery had potential for bias but a standardized recovery assessment tool was used to minimize this possibility.

Discussion

Many painful procedures necessary in the care of acutely injured children are brief. In our study, the median times to complete fracture reductions were 2.5-4 minutes, consistent with Sharieff, et al²². Our rapid administration of smaller intravenous ketamine doses achieved brief effective sedation for fracture reductions with full recovery within 30 minutes or less, significantly faster than the 45 minutes to 84 minutes reported in other studies that used larger, more slowly administered doses of ketamine^{5,6,23}. Patients requiring additional doses of ketamine also had shorter total sedation time that ranged 25-45 minutes (Table 2). When additional ketamine is necessary to achieve or maintain effective sedation, rapid infusion of smaller doses enables rapid titration to the desired effect.

Importantly, no patient in our study had a significant cardiopulmonary adverse event or unpleasant recall of the procedure. We have been using the rapid infusion technique prior to the start of the study and have noticed a similar safety profile. Confirmatory studies with large sample sizes are necessary to fully evaluate the safety of this approach. The frequencies of minor adverse events such as vomiting and recovery dysphoria were low except for the higher frequency of emesis after discharge noted in the 2-5 years groups.

In the 2-5 years group, 9 patients received a dose of 0.7 mg/kg but only 5 of them achieved effective sedation. Seven patients received 0.8mg/kg or higher and all of them achieved

effective sedation. Although the calculated ED₉₅ is 0.72 mg/kg, based on our data, 0.8 mg/kg is more reflective of ED₉₅ and consistently achieved effective sedation. Two patients in the 6-11 years group and 1 patient in the 12-17 years age group received doses equivalent to or higher than ED₉₅ and had effective sedation. Further studies are needed to determine a more precise ED₉₅. It should be noted that 40/60 patients received additional doses of ketamine. This is to be expected with the Up-Down method in which the effective dose for only 50% of patients (ED₅₀) is being estimated. In addition, some of the forearm fracture reductions were more difficult and required more prolonged sedation. Orthopedic residents in different years of training participated in the fracture reduction, which can impact the number of attempts and length of sedation. Additional doses of ketamine were also administered to approximately 30% of patients in other studies that used larger initial doses.^{6,23} Sedation providers may still choose to select the ED₉₅ as a starting dose anticipating that additional ketamine may be necessary for some reduction attempts. When dealing with displaced fractures that might require multiple reduction attempts, the length of sedation can be extended using the rapid infusion technique to administer additional doses of ketamine, titrating to effect. Patient's responsiveness and depth of sedation are the key determinants of the need for and amount of additional doses of ketamine. The pharmacokinetic modeling of recovery from ketamine sedation by Dallimore suggests that recovery is more rapid when repeated smaller doses are administered instead of a large initial dose that achieves the same length of effective sedation time.²⁴

We estimated the minimum dose of ketamine infused over less than 5 seconds that is expected to provide 3-5 minutes of effective sedation for children undergoing fracture reduction to be 0.8 mg/kg for 2-5 years, 0.7 mg/kg for 6-11 years and 0.8 mg/kg for 12-17 years age groups. These ketamine doses are smaller than those used in most clinical studies in children^{1,3,4,6-8,23} and what is recommended in a widely accepted clinical practice guideline⁴. We believe that similar to propofol and other intravenous anesthetic induction drugs, rapid infusion of smaller doses of ketamine achieves clinical effectiveness because it likely achieves a similar ketamine concentration at the site of action in the brain as larger doses more slowly infused^{9,10} and rapid re-distribution of this smaller dose of drug out of the brain leads to shorter recovery. Because most sedative drugs cause respiratory depression and hypotension when rapidly infused, this technique is undesirable for patients undergoing brief sedation in the emergency department. Ketamine, however, is associated with minimal cardiopulmonary depression^{14,25-33}.

No widely accepted and validated criteria for effective sedation currently exist^{34,35}. To the best of our knowledge, this is the first study that has defined criteria for clinical effectiveness of sedation, which is one of the six objective measures for quality of sedation.³⁴ We created a simple tool to standardize a more uniform determination of clinically effective sedation (Appendix table 4). Our criteria were similar to those recently proposed by the Society for Pediatric Sedation (SPS)³⁴. These criteria focus on maximizing the patient's comfort and create optimal operative conditions while minimizing adverse events throughout the procedure. Our kappa statistic value of >0.8 for consensus decisions and each individual grader indicate near perfect agreement between our expert video reviewers using these criteria²¹.

Overall, 15 (20%) of the participants vomited either in the emergency department or after discharge. We note, but do not have a clear explanation for, a higher frequency of vomiting in the 2-5 years age group (35% either in the ED or after discharge) than previously reported pediatric ketamine studies (18-25%)^{3,36,37}. During triage, we routinely offer and administer oral opioid analgesia to children likely to have fractures. More than 90% in this study received opioids prior to procedural sedation in contrast with 30-40% reported in previous studies^{36,37}. Opioids are likely to increase the risk of emesis; a disproportionately higher frequency is noted in the 2-5 years age group.

Our novel technique is significantly different from the current practice of administering 1.5-2 mg/kg ketamine over 30-60 seconds. A rationale for slow administration of ketamine over 30-60 seconds is the concern for respiratory depression noted in early studies. In some of these studies, patients received higher doses of ketamine (2 mg/kg)^{5,38} and in other studies there were anecdotal reports of respiratory depression without mention of the dose administered^{39,40}. Green et al¹⁴, in their meta-analysis concluded that intravenous doses of ketamine 2.5 mg/kg or total doses 5.0 mg/kg are independent predictors of airway and respiratory adverse events with ketamine sedation. We believe rapid administration of ketamine is safe at smaller doses. However, an assessment of airway and respiratory adverse events in a large cohort of patients is required to clarify safety of this technique. As with all procedural sedation techniques, providers should be prepared for unanticipated adverse events when using the rapid infusion, small dose ketamine technique.

We conclude that rapid infusion of small doses of ketamine achieves effective brief sedation and rapid recovery; the adverse events frequency and severity appear to be comparable to those reported in previous studies. We estimated the ED₅₀ and ED₉₅ for our rapid infusion technique of ketamine in 2-17 years old healthy children undergoing brief forearm fracture reductions.

Acknowledgments

Funding and support:

This project was supported by a T32 grant (T32HD049338-01A2), Postdoctoral program at Washington University in St Louis (UL1TR000448) Clinical and Translational Science Award (CTSA) and Ken Graff Young Investigator award from the Section on Emergency Medicine of the American Academy of Pediatrics. We would like to thank William Waldrop MD, John Lin MD and Michael Turmelle MD for serving in the data safety monitoring board for the study.

Appendix

Appendix table 3

The Children's Hospital of Wisconsin (CHW) Sedation Scale¹²

Sedation Classification	Sedation Score	Description
Inadequate	6	Anxious, agitated, or in pain
Minimal-conscious	5	Spontaneously awake without stimulus
Conscious-moderate	4	Drowsy, eyes open or closed, but easily arouses to consciousness with verbal stimulus

Sedation Classification	Sedation Score	Description
Moderate-deep	3	Arouses to consciousness with moderate tactile or loud verbal stimulus
Deep	2	Arouses slowly to consciousness with sustained painful stimulus
	1	Arouses, but not to consciousness, with painful stimulus
Anesthesia	0	Unresponsive to painful stimulus

The CHW sedation scale was modified from the Ramsay scale to provide additional behavioral anchors in the useful range of moderate sedation.

Appendix table 4

The Modified Aldrete Scoring System for Determination of Patient readiness for Discharge from Post-anesthesia Care

Activity: able to move voluntarily or on command	
4 extremities	2
2 extremities	1
0 extremities	0
Respiration	
Able to deep breathe and cough freely	2
Dyspnea, shallow or limited breathing	1
Apneic	0
Circulation	
BP $\pm$ 20 mm of pre-anesthetic level	2
BP $\pm$ 20-50 mm of pre-anesthetic level	1
BP $\pm$ 50 mm of pre-anesthetic level	0
Consciousness	
Fully awake	2
Arousable on calling	1
Not responding	0
O ₂ saturation	
Able to maintain O ₂ saturation > 92% on room air	2
Needs O ₂ inhalation to maintain O ₂ saturation > 90%	1
O ₂ saturation < 90% even with oxygen saturation	0

BP = blood pressure

Appendix table 5

Criteria used for effectiveness of sedation

<p>Presence of any of the following indicates an ineffective sedation:</p> <ol style="list-style-type: none"> 1. Patient purposefully resisted the procedure (withdrew the body part or tried to move away from the performer). 2. Significant restraint was required to accomplish the procedure. 3. Patient verbalized significant pain (clear comments about hurting such as "stop that"). 4. Patient demonstrated significant distress (agitation, thrashing or vigorous crying).

Bibliography

1. Kennedy RM, Porter FL, Miller JP, Jaffe DM. Comparison of fentanyl/midazolam with ketamine/midazolam for pediatric orthopedic emergencies. *Pediatrics*. Oct; 1998 102(4 Pt 1):956–963. [PubMed: 9755272]
2. Godambe SA, Elliot V, Matheny D, Pershad J. Comparison of propofol/fentanyl versus ketamine/midazolam for brief orthopedic procedural sedation in a pediatric emergency department. *Pediatrics*. Jul; 2003 112(1 Pt 1):116–123. [PubMed: 12837876]
3. Luhmann JD, Schootman M, Luhmann SJ, Kennedy RM. A randomized comparison of nitrous oxide plus hematoma block versus ketamine plus midazolam for emergency department forearm fracture reduction in children. *Pediatrics*. Oct; 2006 118(4):e1078–1086. [PubMed: 16966390]
4. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. *Annals of emergency medicine*. May; 2011 57(5):449–461. [PubMed: 21256625]
5. Green SM, Rothrock SG, Harris T, Hopkins GA, Garrett W, Sherwin T. Intravenous ketamine for pediatric sedation in the emergency department: safety profile with 156 cases. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*. Oct; 1998 5(10):971–976. [PubMed: 9862587]
6. Sherwin TS, Green SM, Khan A, Chapman DS, Dannenberg B. Does adjunctive midazolam reduce recovery agitation after ketamine sedation for pediatric procedures? A randomized, double-blind, placebo-controlled trial. *Annals of emergency medicine*. Mar; 2000 35(3):229–238. [PubMed: 10692189]
7. Shah A, Mosdosy G, McLeod S, Lehnhardt K, Peddle M, Rieder M. A blinded, randomized controlled trial to evaluate ketamine/propofol versus ketamine alone for procedural sedation in children. *Annals of emergency medicine*. May; 2011 57(5):425–433. e422. [PubMed: 20947210]
8. Ramaswamy P, Babl FE, Deasy C, Sharwood LN. Pediatric procedural sedation with ketamine: time to discharge after intramuscular versus intravenous administration. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*. Feb; 2009 16(2):101–107. [PubMed: 19076105]
9. Krejcie TC, Avram MJ. What determines anesthetic induction dose? It's the front-end kinetics, doctor! *Anesthesia and analgesia*. Sep; 1999 89(3):541–544. [PubMed: 10475278]
10. Ludbrook GL, Upton RN. A physiological model of induction of anaesthesia with propofol in sheep. 2. Model analysis and implications for dose requirements. *British journal of anaesthesia*. Oct; 1997 79(4):505–513. [PubMed: 9389271]
11. Bhatt M, Kennedy RM, Osmond MH, et al. Consensus-based recommendations for standardizing terminology and reporting adverse events for emergency department procedural sedation and analgesia in children. *Annals of emergency medicine*. Apr; 2009 53(4):426–435. e424. [PubMed: 19026467]
12. Hoffman GM, Nowakowski R, Troshynski TJ, Berens RJ, Weisman SJ. Risk reduction in pediatric procedural sedation by application of an American Academy of Pediatrics/American Society of Anesthesiologists process model. *Pediatrics*. Feb; 2002 109(2):236–243. [PubMed: 11826201]
13. Aldrete JA. The post-anesthesia recovery score revisited. *J Clin Anesth*. Feb; 1995 7(1):89–91. [PubMed: 7772368]
14. Green SM, Roback MG, Krauss B, et al. Predictors of airway and respiratory adverse events with ketamine sedation in the emergency department: an individual-patient data meta-analysis of 8,282 children. *Annals of emergency medicine*. Aug; 2009 54(2):158–168. e151–154. [PubMed: 19201064]
15. Green SM, Roback MG, Krauss B, et al. Predictors of emesis and recovery agitation with emergency department ketamine sedation: an individual-patient data meta-analysis of 8,282 children. *Annals of emergency medicine*. Aug; 2009 54(2):171–180. e171–174. [PubMed: 19501426]
16. Dixon W. The Up-and-down method for small samples. *J Am Stat Assoc*. 1965; 60:967–978. 1965.

17. Herd D, Anderson BJ. Ketamine disposition in children presenting for procedural sedation and analgesia in a children's emergency department. *Paediatric anaesthesia*. Jul; 2007 17(7):622–629. [PubMed: 17564643]
18. Pace NL, Stylianou MP. Advances in and limitations of up-and-down methodology: a precis of clinical use, study design, and dose estimation in anesthesia research. *Anesthesiology*. Jul; 2007 107(1):144–152. [PubMed: 17585226]
19. WJ, D.; Massey, FJ. Introduction to statistical analysis. McGraw-hill book co; New York: 1957.
20. Agresti, A. Categorical data analysis. 3rd ed.. Wiley; Hoboken, NJ: 2013.
21. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. Mar; 1977 33(1):159–174. [PubMed: 843571]
22. Sharieff GQ, Trocinski DR, Kanegaye JT, Fisher B, Harley JR. Ketamine-propofol combination sedation for fracture reduction in the pediatric emergency department. *Pediatric emergency care*. Dec; 2007 23(12):881–884. [PubMed: 18091596]
23. Wathen JE, Roback MG, Mackenzie T, Bothner JP. Does midazolam alter the clinical effects of intravenous ketamine sedation in children? A double-blind, randomized, controlled, emergency department trial. *Annals of emergency medicine*. Dec; 2000 36(6):579–588. [PubMed: 11097698]
24. Dallimore D, Herd DW, Short T, Anderson BJ. Dosing ketamine for pediatric procedural sedation in the emergency department. *Pediatric emergency care*. Aug; 2008 24(8):529–533. [PubMed: 18645539]
25. Green SM, Johnson NE. Ketamine sedation for pediatric procedures: Part 2, Review and implications. *Annals of emergency medicine*. Sep; 1990 19(9):1033–1046. [PubMed: 2203290]
26. White PF, Way WL, Trevor AJ. Ketamine--its pharmacology and therapeutic uses. *Anesthesiology*. Feb; 1982 56(2):119–136. [PubMed: 6892475]
27. Drummond GB. Comparison of sedation with midazolam and ketamine: effects on airway muscle activity. *British journal of anaesthesia*. May; 1996 76(5):663–667. [PubMed: 8688266]
28. Hamza J, Ecoffey C, Gross JB. Ventilatory response to CO₂ following intravenous ketamine in children. *Anesthesiology*. Mar; 1989 70(3):422–425. [PubMed: 2493753]
29. Mankikian B, Cantineau JP, Sartene R, Clergue F, Viars P. Ventilatory pattern and chest wall mechanics during ketamine anesthesia in humans. *Anesthesiology*. Nov; 1986 65(5):492–499. [PubMed: 3777478]
30. Tokics L, Strandberg A, Brismar B, Lundquist H, Hedenstierna G. Computerized tomography of the chest and gas exchange measurements during ketamine anaesthesia. *Acta anaesthesiologica Scandinavica*. Nov; 1987 31(8):684–692. [PubMed: 3434162]
31. Shulman DL, Bar-Yishay E, Godfrey S. Respiratory mechanics and intrinsic PEEP during ketamine and halothane anesthesia in young children. *Anesthesia and analgesia*. Jul; 1988 67(7):656–662. [PubMed: 3382039]
32. Morel DR, Forster A, Gemperle M. Noninvasive evaluation of breathing pattern and thoraco-abdominal motion following the infusion of ketamine or droperidol in humans. *Anesthesiology*. Oct; 1986 65(4):392–398. [PubMed: 3767037]
33. Joly LM, Benhamou D. Ventilation during total intravenous anaesthesia with ketamine. *Canadian journal of anaesthesia = Journal canadien d'anesthesie*. Mar; 1994 41(3):227–231.
34. Connors JM, Cravero JP, Kost S, Laviolette D, Lowrie L, Scherrer PD. Great Expectations-Defining Quality in Pediatric Sedation: Outcomes of a Multidisciplinary Consensus Conference. *Journal for healthcare quality : official publication of the National Association for Healthcare Quality*. Aug 26.2013
35. Crellin D, Sullivan TP, Babl FE, O'Sullivan R, Hutchinson A. Analysis of the validation of existing behavioral pain and distress scales for use in the procedural setting. *Paediatric anaesthesia*. Aug; 2007 17(8):720–733. [PubMed: 17596217]
36. Langston WT, Wathen JE, Roback MG, Bajaj L. Effect of ondansetron on the incidence of vomiting associated with ketamine sedation in children: a double-blind, randomized, placebo-controlled trial. *Annals of emergency medicine*. Jul; 2008 52(1):30–34. [PubMed: 18353503]
37. Roback MG, Wathen JE, MacKenzie T, Bajaj L. A randomized, controlled trial of i.v. versus i.m. ketamine for sedation of pediatric patients receiving emergency department orthopedic procedures. *Annals of emergency medicine*. Nov; 2006 48(5):605–612. [PubMed: 17052563]

38. Corssen G, Miyasaka M, Domino EF. Changing concepts in pain control during surgery: dissociative anesthesia with CI-581. A progress report. *Anesthesia and analgesia*. Nov-Dec;1968 47(6):746–759. [PubMed: 5749338]
39. Hollister GR, Burn JM. Side effects of ketamine in pediatric anesthesia. *Anesthesia and analgesia*. Mar-Apr;1974 53(2):264–267. [PubMed: 4856136]
40. Young RA, Epker BN. Ketamine hydrochloride in outpatient oral surgery in children. *J Oral Surg*. Oct; 1971 29(10):703–705. [PubMed: 4255301]

Figure 1.

Sequence of patients in 2-5, 6-11 and 12-17 years fracture groups showing first dose of ketamine ($\diamond$), total amount of ketamine for procedure completion($\times$) and Wisconsin sedation score at 1 minute(–). Patients received pre specified first dose of ketamine based on the response of the previous patient in the group. For the 20th patient, the first dose of ketamine was effective in the 2-5 and 6-11 years groups and was ineffective in 12-17 years group. Wisconsin sedation score 2 is assigned when patient under sedation slowly arouses to consciousness with sustained painful stimulus.

Table 1

Characteristics of the 60 patients enrolled

Age group	2-5 years (n=20)	6-11 years (n=20)	12-17 years (n=20)
Median (range) age in years	4.8 (2.9-6.9)	9.2 (6.0-11.9)	13.7 (12.6-16.9)
Male	11	14	19
Race: African-American	5	2	8
Caucasian	13	17	10
Other	2	1	2
Opioids prior to sedation	19/20	18/20	19/20
Oxycodone	11	9	11
Morphine	7	8	6
Other	1	1	2
Median time (minutes) between opioid administration and start of sedation: median, (range)	116 (20-383)	96 (1-251)	129 (27-401)
Fracture characteristics			
Non-displaced	10	2	9
Displaced but not overriding	6	11	7
Displaced and Overriding	4	7	4

Table 2

Primary and secondary outcomes

	2-5 years (n=20)	6-11 years (n=20)	12-17 years (n=20)
ED ₅₀ (mg/kg [95% CI])	0.7 *	0.5 [0.4-0.6]	0.60 [0.5-0.7]
ED ₉₅ (mg/kg)	0.7 [#]	0.7	0.8
Number of effective sedations at			
0.5 mg/kg	NA	3/8	1/5
0.6 mg/kg	0/4	5/7	4/8
0.7 mg/kg	5/9	2/2	4/5
0.8 mg/kg	5/5	NA	1/1
0.9 mg/kg	2/2	NA	NA
Median length of procedure in minutes (median [range])	2.5 [1-5]	3 [1-9]	4 [2-22]
Number of participants with Wisconsin sedation score of 2 at 1 min after first dose of ketamine	12	9	10
Total sedation time in minutes (median [range])			
Patients requiring only a single dose of ketamine	25 [15-30] (9/20 patients)	22.5 [15-31] (6/20 patients)	25 [25-30] (5/20 patients)
Patients requiring additional doses of ketamine	35 [25-85] (11/20 patients)	25 [15-50] (14/20 patients)	45 [20-80] (15/20 patients)
Vomiting, n (%)			
in the ED	1/20 (5)	1/20 (5)	1/20 (5)
after discharge	6/19 (32)	3/18 (17)	3/19 (16)
Parent and/or participant satisfaction: "Prefer this type of sedation for similar procedure in the future" [@]	18/19	18/19	15/20

* Insufficient ED₅₀ doses tested to calculate confidence interval.

[#] Estimated ED₉₅. Based on patient dose responses, empirical ED₉₅ was 0.8 mg/kg.

Denominator is the number of patients able to be contacted.

[@] Denominator is the number of parent and/or participants who answered the question.