

BRIEF RESEARCH REPORT

Pediatrics

Effect of ketamine on transcranial Doppler Gosling pulsatility index in children undergoing procedural sedation: A pilot study

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Funding and support: This project was supported in part by the National Institutes of Health (UL1-TR-001857).

Presented at the American College of Emergency Physicians (ACEP) Scientific Assembly, Virtual National Conference, October 28, 2020.

Abstract

Objectives: There has been controversy over whether ketamine affects intracranial pressure (ICP) in children. Transcranial Doppler ultrasound (TCD) is a validated technique used to assess ICP changes noninvasively. Gosling pulsatility index (PI) directly correlates with ICP changes. The objective of this study was to quantify PI changes as a surrogate marker for ICP changes in previously healthy children receiving intravenous ketamine for procedural sedation.

Methods: We performed a prospective, observational study of patients 5–18 years old who underwent sedation with intravenous ketamine as monotherapy. ICP changes were assessed by surrogate PI at baseline, immediately after ketamine administration, and every 5 minutes until completion of the procedure. The primary outcome measure was PI change after ketamine administration compared to baseline (denoted Δ PI).

Results: We enrolled 15 participants. Mean age was 9.9 ± 3.4 years. Most participants underwent sedation for fracture reduction (87%). Mean initial ketamine dose was 1.4 ± 0.3 mg/kg. PI decreased at all time points after ketamine administration. Mean Δ PI at sedation onset was -0.23 (95% confidence interval [CI] = -0.30 to -0.15), at 5 minutes was -0.23 (95% CI = -0.28 to -0.18), at 10 minutes was -0.14 (95% CI = -0.21 to -0.08), at 15 minutes was -0.18 (95% CI = -0.25 to -0.12), and at 20 minutes was -0.19 (95% CI = -0.26 to -0.12). Using a clinically relevant threshold of Δ PI set at $+1$ ($+8$ cm H₂O), no elevation in ICP, based on the PI surrogate marker, was demonstrated with 95% confidence at all time points after ketamine administration.

Conclusions: Ketamine did not significantly increase PI, which was used as a surrogate marker for ICP in this sample of previously healthy children. This pilot study demonstrates a model for evaluating ICP changes noninvasively in the emergency department.

KEYWORDS

intracranial pressure, ketamine, pulsatility index, sedation, transcranial Doppler, ultrasound

Supervising Editor: Sing-Yi Feng, MD.

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1 | INTRODUCTION

1.1 | Background

Ketamine is the most frequently used medication for procedural sedation in pediatric emergency departments (EDs).¹ It is a dissociative anesthetic that acts via antagonism of central N-methyl-D-aspartate receptors and maintains protective airway reflexes, spontaneous respirations, and cardiovascular tone.^{2,3} Despite these beneficial properties, there has been controversy over whether ketamine increases intracranial pressure (ICP).³⁻⁵ Initial case series in the 1970s showed that ketamine acutely elevated ICP in patients with obstructed cerebrospinal fluid (CSF) flow. However, ICP elevation has not been observed in patients with intact CSF flow.⁴ Green et al⁴ proposed that, except for hydrocephalus, there is no contraindication to using ketamine in procedural sedation, rapid sequence intubation, and analgesia in the ED.

1.2 | Importance

Nonetheless, research on ketamine's effect on ICP in children is lacking.³ Given concerns of the potential for ketamine to increase ICP, it is frequently avoided in the ED in pediatric patients with head trauma despite its hemodynamic advantages.

We investigated the relationship between ketamine and ICP in the pediatric ED setting using a surrogate marker measured by transcranial Doppler ultrasound (TCD). TCD is a technique used to assess changes in ICP noninvasively, and is well-established in neurosurgical and neurocritical care literature.⁶ Specifically, the Gosling pulsatility index⁷ (PI) measured using TCD has previously been shown to have a linear relationship with ICP changes.^{8,9} Prior research in children with hydrocephalus and severe head injury has supported this direct correlation between PI changes and ICP changes.^{10,11} PI is a function of peak systolic velocity minus end-diastolic velocity divided by the mean velocity. As intracranial pressure rises, intracranial systolic blood flow increases and intracranial diastolic blood flow decreases, thus increasing the PI.

1.3 | Goals of this investigation

The objective of this study was to quantify ICP changes by the surrogate marker PI after ketamine administration in previously healthy children receiving intravenous ketamine monotherapy for procedural sedation. We hypothesized that ketamine administration would not cause an increase in ICP, as measured at multiple time points after administration using the TCD PI.

2 | METHODS

2.1 | Study design

We performed a prospective, observational study measuring PI by TCD in pediatric patients who underwent procedural sedation with intra-

The Bottom Line

The use of ketamine has been controversial due to its theoretical increase of intracranial pressure. The authors of this study try to debunk this theory with the use of transcranial Doppler ultrasound in patients undergoing ketamine sedation. Although their numbers of participants are low, this study is important in making sure that the emergency medicine practice is truly evidence based.

venous ketamine as monotherapy. This study was approved by our local institutional review board. Written consent was obtained from the parent/guardian of all participants enrolled, with assent obtained from all participants.

2.2 | Selection of participants

We recruited participants from a convenience sample of patients ages 5–18 years at an urban tertiary pediatric ED who were undergoing procedural sedation for any procedure (ie, fracture reduction, laceration repair). Patients with head trauma were excluded.

2.3 | Measurements

TCD was performed using standardized methods as described by Aaslid et al¹² and Lindegaard et al.¹³ With the patient supine, we insonated the right transtemporal window (Figure S1) and right neck at the following time points: baseline prior to sedation, immediately after ketamine administration upon sedation onset (indicated by nystagmus) and every 5 min after sedation onset until completion of the procedure. We calculated the Gosling PI of the middle cerebral artery as (peak systolic velocity – diastolic velocity)/mean velocity. To evaluate for any effect of vasospasm on PI, we recorded the Lindegaard ratio (LR = mean velocity in the middle cerebral artery/mean velocity in the ipsilateral extracranial internal carotid artery). Scans were performed with a 2-Mhz transducer (Terumo PMD150 Digital Transcranial Doppler System/Trifid 33-Gate Technology, Spencer Technologies, Seattle, WA). A single individual (C.T.S.) performed all TCD scans using identical technique. A separate investigator (J.R.B.) with greater than 20 years of TCD experience provided training and quality assurance review of TCD waveforms. Ketamine was administered by the treating physician, who was not the same individual performing TCD measurements. The treating physician determined the dose and timing of ketamine administration.

We recorded demographic and clinical characteristics of the study population including age, sex, race, weight, procedure type, initial ketamine dose, any subsequent ketamine doses, and timing of medication administration. We recorded vital signs at the same intervals as TCD measurements, including heart rate, blood pressure, respiratory

rate, oxygen saturation (SpO₂), and partial pressure of exhaled carbon dioxide (CO₂) (NICO/NM3 Capnostat CO₂ Sensor, Model 7900, Philips, Pittsburgh, PA).

2.4 | Outcomes

The primary outcome measure was the PI change after ketamine administration compared to baseline (denoted Δ PI). The clinically relevant threshold was set at Δ PI of +1. Prior research indicates that Δ PI of +1 above baseline corresponds to an ICP increase of 7.1–8.0 cm H₂O (5.2–5.9 mmHg).¹⁴ Therefore, we determined that Δ PI less than +1 corresponds to an ICP increase of less than 8 cm H₂O and would likely represent a clinically insignificant ICP change.

2.5 | Analysis

We were unable to perform a power analysis or sample size estimate given the absence of literature available for serial PI measurements in healthy children. We analyzed our primary outcome (Δ PI) with descriptive statistics and reported the mean change in PI from baseline with 95% confidence intervals for all time points of interest: at sedation onset and every 5 minutes after sedation onset until completion of the procedure. To evaluate if Δ PI would exceed +1 for any of the time points, we conducted a paired t-test at each time point.

We summarized demographics, clinical characteristics, and secondary outcomes including heart rate, blood pressure, respiratory rate, SpO₂, exhaled CO₂, and Δ LR using descriptive statistics. We presented continuous variables as mean \pm SD or median [IQR] as appropriate. We reported categorical variables as frequencies and percentages. Analyses were conducted using R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria; <https://www.R-project.org/>).

3 | RESULTS

3.1 | Characteristics of study participants

We enrolled 15 participants. The mean age was 9.9 ± 3.4 years and 47% were female. Most participants underwent sedation for fracture reduction (87%). Demographic and clinical characteristics are displayed in Table 1. The baseline PI was 0.88 ± 0.13 . The initial ketamine dose administered was 1.4 ± 0.3 mg/kg. Seven participants received a second ketamine dose of 0.9 ± 0.1 mg/kg given 11.9 ± 6.4 min after the first dose.

3.2 | Main results

In all participants, mean Δ PI was negative at all time points after ketamine, indicating that there was a reduction in PI after ketamine (Figure 1). Using a clinically relevant threshold set at +1 PI unit, no

TABLE 1 Demographic and clinical characteristics

Age (y)	9.9 \pm 3.4
Female sex	7 (47%)
Race	
White	13 (87%)
Asian	2 (13%)
Weight (kg)	40.0 (23.8–54.9)
Procedure requiring sedation	
Fracture reduction	13 (87%)
Laceration repair	2 (13%)
Initial PI	0.88 \pm 0.13
Initial ketamine dose (mg/kg)	1.4 \pm 0.3
Participants who received a second ketamine dose	7 (47%)
Second ketamine dose (mg/kg)	0.9 \pm 0.1

Note: Data are presented as n (%), mean \pm SD, or median [IQR]. PI, pulsatility index.

increase (no significant elevation in ICP measured by PI surrogate) was demonstrated with 95% confidence at all time points after ketamine administration. Secondary outcome measures are reported in Table 2

We were unable to assess PI in 1 participant at sedation onset and at 20 min due to difficulty finding the middle cerebral artery by TCD at those time points. Sedation was completed before 15 min in 2 participants and was completed prior to 20 min in 6 additional participants. All other participants had measurements recorded at all time points until conclusion of the procedure.

4 | LIMITATIONS

The findings in this study are subject to limitations. This was a small sample size in a pilot study enrolled via convenience sampling, and future studies should enroll a larger population. Our study population was limited to children over 5 years of age because baseline TCD ultrasounds before sedation would be technically challenging in children under 5 years due to movement.

This study was limited by reliance on PI as a surrogate marker for ICP, rather than a gold standard method. Direct measurement via intracranial pressure monitoring or lumbar puncture in otherwise healthy children would not be feasible. TCD PI correlation with ICP has been inconsistent across prior studies.¹⁵ In particular, measurement of a single PI value is not consistently reliable in predicting ICP. On the other hand, multiple studies have shown good correlation between PI and ICP when serial values are assessed over time.^{8,16,17} To that effect, many authors agree that the trend in PI is a useful and accurate reflection of ICP change.^{18,19} The 2019 Brain Trauma Foundation Guidelines for severe pediatric TBI call for consideration of TCD ultrasound velocity measurements of the middle cerebral artery as a tool to guide titration of ICP lowering therapy.²⁰ Additionally, Cardim et al¹⁵ have suggested that TCD predicts ICP change most reliably

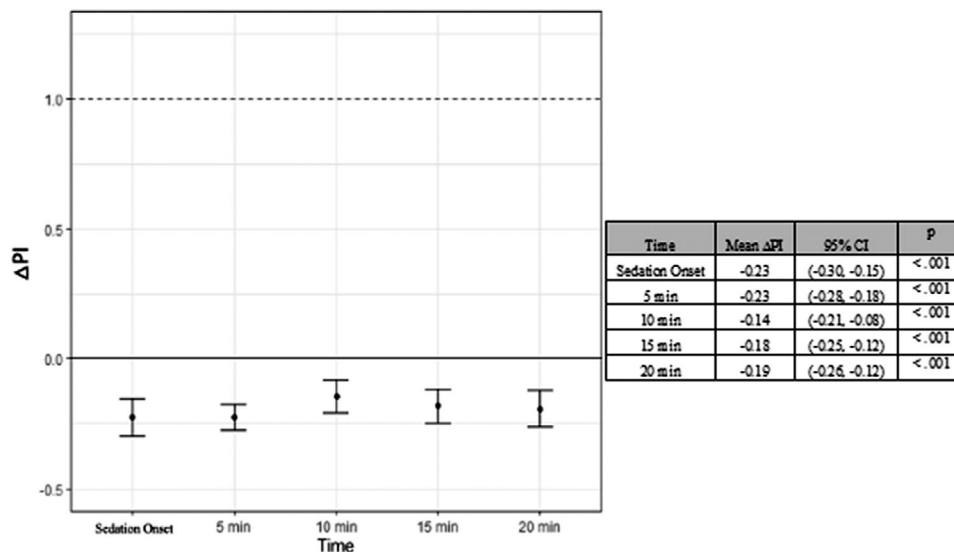


FIGURE 1 Change in pulsatility index from baseline (Δ PI) over time. Bars indicate 95% confidence intervals. Dashed line indicates clinically relevant threshold of Δ PI + 1. (See Section 2.4 for definition of clinically relevant threshold.)

TABLE 2 Secondary outcome measures at each time point

Time	HR	SBP	DBP	RR	CO ₂	SpO ₂	Δ LR
Baseline	90 \pm 12	124 \pm 15	68 \pm 7	21 \pm 4	39 [35–40]	99 [99–100]	N/A
Sedation onset	97 \pm 19	135 \pm 24	70 \pm 11	23 \pm 8	36 [35–39]	99 [98–100]	0.15 \pm 0.45
5 min	106 \pm 19	145 \pm 21	76 \pm 11	23 \pm 4	38 [34–38]	99 [97–99]	0.20 \pm 0.50
10 min	104 \pm 18	140 \pm 15	74 \pm 11	24 \pm 5	36 [34–38]	99 [98–99]	0.33 \pm 0.67
15 min	106 \pm 16	141 \pm 16	71 \pm 7	25 \pm 5	36 [34–38]	98 [98–99]	0.23 \pm 0.32
20 min	107 \pm 11	134 \pm 17	68 \pm 8	26 \pm 6	36 [36–38]	99 [97–100]	0.18 \pm 0.23

Note: Data are presented as mean \pm SD or median [IQR]. PI, pulsatility index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RR, respiratory rate; CO₂, exhaled carbon dioxide; SpO₂, pulse oximetry; Δ LR, change in Lindegaard ratio from baseline.

when ICP changes due to vasogenic effects. Ketamine tends to increase heart rate and blood pressure.² Therefore, if ketamine were to cause any ICP change, it may be due to its vasogenic effects, which would lend reliability to our study's TCD assessment model of ketamine. Although, research suggests that the PI trend correlates with ICP changes in children with hydrocephalus and severe head injury,^{10,11} we extrapolated this correlation to healthy participants enrolled in this study.

Our study showed that the PI of healthy children who received ketamine did not increase. This finding may not be directly applied to children with head injury. Further research is needed to evaluate ketamine's effect on PI in children with TBI, especially at the extremes of cerebral autoregulation.

We believe that the range of ketamine doses administered in this study provides adequate analgesia during painful procedures.² However, it is possible that ICP and PI may have been affected by pain response during the procedures (ie, pain with fracture reduction, cast molding, and laceration repair). Pre-sedation and post-sedation pain scores, which were not recorded, could potentially confound assessment of ketamine's effect on ICP. Despite this limitation, the conditions

of this study represent a real-life situation because intubation, bag-valve mask ventilation, and other procedures requiring the use of ketamine have similar potential for pain and discomfort.

5 | DISCUSSION

In this cohort of previously healthy pediatric patients, ketamine did not increase PI. In fact, we observed a small decline in PI in all participants after ketamine administration, as the observed confidence intervals for Δ PI at all time points were less than 0.

Furthermore, the maximum PI decline in this study was relatively small. The maximum PI decline within the confidence intervals was -0.30 . Based on available literature,¹⁴ this corresponds to an ICP decrease of 2.5 cm H₂O (1.8 mm Hg) or less. This likely represents a clinically insignificant ICP decline after ketamine administration.

Our results are likely applicable to the ED population for several reasons. First, the participants in this study represented the broad range of ages encountered in a pediatric ED. Second, the initial dose range in this study reflects the ketamine dose typically used for procedural sedation

and rapid sequence intubation. Third, our sample included participants who received multiple doses of ketamine.

These findings are notable because ketamine's effect on ICP has been controversial as noted above. Although this study does not provide information on ketamine's effect at the extremes of cerebral autoregulation, these findings contribute to the literature evaluating the effect of ketamine on ICP, adding data on the in vivo use of ketamine as monotherapy in children. Before this, no studies assessed ketamine's effect on PI.

More recent studies challenge the dogma that ketamine should not be used for sedation or rapid sequence intubation in head-injured patients. A systematic review of 10 studies by Cohen et al²¹ found that ketamine caused no change or a small reduction in ICP in critically ill patients, including those with TBI. Bar-Joseph et al⁵ investigated the effect of ketamine on ICP in children with intracranial hypertension in the critical care setting, including children with trauma and intracranial hemorrhage. They found that ICP, measured by intracranial pressure monitors, decreased with the administration of ketamine while maintaining blood pressure and cerebral perfusion pressure.⁵ Still, it is not entirely clear if the critical care literature can be directly applied to the pediatric ED population, as patients receiving critical care frequently receive additional sedative and analgesic medications which exert their own effects on ICP, thus confounding the assessment of ketamine's effect.

Although ICP is often measured directly in the critical care setting, this is not feasible in the ED. Therefore, a non-invasive technique for tracking ICP changes in the ED may be valuable for both clinical decision-making and research. TCD offers a noninvasive method of assessing ICP changes using the PI as a surrogate marker for ICP. This study demonstrates the feasibility of tracking serial PI changes over time in the ED, specifically to evaluate ketamine's effect on ICP in children. While additional research may be needed to establish the reliability of PI as a surrogate marker for ICP change in healthy children, we found that ketamine exerted a small and clinically insignificant PI decrease in this small sample.

In this prospective, observational study of previously healthy children undergoing procedural sedation, ketamine administration led to a small decrease in PI, a surrogate marker for ICP. Future research may investigate ketamine's effect on PI and ICP in patients with head injury.

ACKNOWLEDGMENTS

The authors would like to thank Philip Grosse, PhD, and Li Wang, MS, for their contribution to the statistical analysis.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Christopher T. Stem performed data acquisition. Christopher T. Stem, Sriram Ramgopal, Robert W. Hickey, Mioara D. Manole, and Jeffrey R. Balzer contributed to study concept and design, analysis and interpretation of the data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical expertise.

REFERENCES

- Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. *Ann Emerg Med.* 2011;57(5):449-461.
- Mion G, Villeveille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). *CNS Neurosci Ther.* 2013;19(6):370-380.
- Kochanek PM, Tasker RC, Carney N, et al. Guidelines for the management of pediatric severe traumatic brain injury, third edition: update of the brain trauma foundation guidelines. *Pediatr Crit Care Med.* 2019;20(3S Suppl 1):S1-82.
- Green SM, Andolfatto G, Krauss BS. Ketamine and intracranial pressure: no contraindication except hydrocephalus. *Ann Emerg Med.* 2015;65(1):52-54.
- Bar-Joseph G, Guilburd Y, Tamir A, Guilburd JN. Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension. *J Neurosurg Pediatr.* 2009;4(1):40-46.
- White H, Venkatesh B. Applications of transcranial Doppler in the ICU: a review. *Intensive Care Med.* 2006;32(7):981-994.
- Gosling RG, King DH. Arterial assessment by Doppler-shift ultrasound. *Proc R Soc Med.* 1974;67(6 Pt 1):447-449.
- Bellner J, Romner B, Reinstrup P, Kristiansson K-A, Ryding E, Brandt L. Transcranial Doppler sonography pulsatility index (PI) reflects intracranial pressure (ICP). *Surg Neurol.* 2004;62(1):45-51.
- Moreno JA, Mesalles E, Gener J, et al. Evaluating the outcome of severe head injury with transcranial Doppler ultrasonography. *Neurosurg Focus.* 2000;8(1):1-7.
- Nadvi SS, Du Trevo MD, Van Dellen JR, Gouws E. The use of transcranial Doppler ultrasonography as a method of assessing intracranial pressure in hydrocephalic children. *Br J Neurosurg.* 1994;8(5):573-577.
- Sanker P, Richard KE, Weigl HC, Klug N, van Leyen K. Transcranial Doppler sonography and intracranial pressure monitoring in children and juveniles with acute brain injuries or hydrocephalus. *Childs Nerv Syst.* 1991;7(7):391-393.
- Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *J Neurosurg.* 1982;57(6):769-774.
- Lindgaard KF, Nornes H, Bakke SJ, Sorteberg W, Nakstad P. Cerebral vasospasm diagnosis by means of angiography and blood velocity measurements. *Acta Neurochir.* 1989;100(1-2):12-24.
- Gura M, Elmaci I, Sari R, Coskun N. Correlation of pulsatility index with intracranial pressure in traumatic brain injury. *Turk Neurosurg.* 2011;21(2):210-215.
- Cardim D, Robba C, Bohdanowicz M, et al. Non-invasive monitoring of intracranial pressure using transcranial doppler ultrasonography: is it possible? *Neurocrit Care.* 2016;25(3):473-491.
- Chan KH, Miller JD, Dearden NM, Andrews PJ, Midgley S. The effect of changes in cerebral perfusion pressure upon middle cerebral artery blood flow velocity and jugular bulb venous oxygen saturation after severe brain injury. *J Neurosurg.* 1992;77(1):55-61.
- Asil T, Uzunca I, Utku U, Berberoglu U. Monitoring of increased intracranial pressure resulting from cerebral edema with transcranial Doppler sonography in patients with middle cerebral artery infarction. *J Ultrasound Med.* 2003;22(10):1049-1053.
- Wakerley BR, Sharma VK. Transcranial Doppler derived pulsatility index in the assessment of intracranial pressure: the trend is your friend. *Neurosurgery.* 2013;72(2):E319-E320.
- Zweifel C, Czosnyka M, Smielewski P. In reply. Transcranial Doppler derived pulsatility index in the assessment of intracranial pressure: the trend is your friend. *Neurosurgery.* 2013;72(2):E320.
- Kochanek PM, Tasker RC, Bell MJ, et al. Management of pediatric severe traumatic brain injury: 2019 consensus and guidelines-based algorithm for first and second tier therapies. *Pediatr Crit Care Med.* 2019;20(3):269-279.

21. Cohen L, Athaide V, Wickham ME, Doyle-Waters MM, Rose NGW, Hohl CM. The effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes: a systematic review. *Ann Emerg Med.* 2015;65(1):43-51.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Stem CT, Ramgopal S, Hickey RW, Manole MD, Balzer JR. Effect of ketamine on transcranial Doppler Gosling pulsatility index in children undergoing procedural sedation: A pilot study. *JACEP Open.* 2022;3:e12760. <https://doi.org/10.1002/emp2.12760>