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ORIGINAL ARTICLES

Bedside Ultrasonographic Assessment of the Optic Nerve Sheath Diameter to Assess Intracranial Pressure in Patients Given Ketamine in Emergency Department

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Abstract

Background: There is an ongoing debate if ketamine exerts any effect on intracranial pressure (ICP). ICP can be evaluated noninvasively by means of optic nerve sheath diameter (ONSD) measurement. In the present study, we aimed to determine if ketamine has any perceivable effect on ICP using ONSD.

Material and Methods: In this single-center observational study, we prospectively enrolled patients who were admitted to the ED and received intravenous ketamine for induction, analgesia, procedural sedation for any procedure (ie, fracture reduction, laceration repair, pacemaker implantation). ONSD was used to rate ICP changes noninvasively both before and after ketamine application.

Results: There were a total of 75 patients with a mean age of 59.8 ± 20.5 years. The majority of patients were applied Procedural Sedation (53.3%). In patients who were administered ketamine for induction, the median ONSD before and after ketamine were 5.10 (IQR: 1) mm and 5.00 (IQR: 1.30) mm, respectively. There occurred no significant diameter change (p=0.832). In patients who were administered ketamine for analgesia, the median ONSD 3.70 (IQR: 0.40) mm and 3.65 (IQR: 0.23) mm prior to and after the procedure, respectively. There occurred no significant diameter change (p=0.549). In patients who were administered ketamine for procedural sedation, the median ONSD before and after the procedure were 4.05 (IQR:0.67) mm and 3.97 (IQR: 0.69) mm, respectively. This time, however, ONSD was significantly reduced after ketamine administration (p=0.001).

Conclusions: In this patient population, ketamine did not cause any incremental effect on ONSD, a surrogate marker of ICP.

Keywords: Intracranial pressure; ketamine; sedation; ultrasound; optic nerve

Introduction

In the emergency care setting, ketamine is the most commonly employed drug for the purposes of procedural sedation, rapid sequence intubation (RSI), and analgesia [1]. An anesthetics agent that possesses dissociative properties, ketamine antagonizes central N-methyl-D-aspartate receptors but leaves protective airway reflexes, spontaneous respirations, and cardiovascular tone relatively intact [2]. Praised by such favorable overall side effect profile, however, there is ongoing debate if it elevates intracranial pressure (ICP) [3, 4]. During 70s, when first case series had been published, it was suggested that ketamine has an untoward effect of suddenly elevating ICP among patients with impedance to cerebrospinal fluid (CSF) circulation. Fortunately, however, this effect was not observed in those with unimpeded CSF flow [4]. Hence, *Green et. al.* [5] suggested that ketamine should not be avoided in procedural sedation, RSI, and analgesia in the ED, provided that the patient has no hydrocephalus.

Elevations in ICP are best reflected by invasive ICP monitoring [6]. Nevertheless, invasive ICP measurement can cause catastrophic hazards, including bleeding and infection, and the clinical condition of some patients may not be suitable for this method [7]. Thus, preferably bedside techniques that allow safe, simple, rapid, noninvasive, and reproducible ICP monitoring should be introduced into clin-

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ical practice [8]. Thanks to its steep learning curve, rapid, noninvasive, bedside nature, and reproducible results, ultrasonography (USG) has been widely utilized in the emergency departments (ED) worldwide [9]. It is used to evaluate abdominal, thoracic, cardiac cavities as well as bone, soft tissue, and eye in the ED [10, 11]. Ocular USG has been recently introduced and widely utilized to measure ONSD to determine ICP increase [12, 13].

Subarachnoid space is in direct continuation with the space beneath the optic nerve sheath and above the nerve; this explains the increase in the diameter of the retrobulbar sheath as a reflection of increased ICP (9,12). This expansion can be readily detected by B-scan USG (14).

It is a applicable method for unstable patients in the emergency room, intensive care unit (ICU) and and remote care facilities [15]. Studies conducted so far on the effect of ketamine on ICP have utilized invasive techniques.

In the present study, we investigated whether ketamine would increase ICP by measuring ONSD both before and after ketamine administration using bedside USG, a noninvasive technique, in patients who received ketamine in the ED. To our best knowledge, this is the first study of its kind in the literature.

Materials and Methods

Study design

This study was an observational study conducted in a single center in a prospective fashion between September 2021 and May 2022. It was approved by the local ethics committee at Health Sciences University Antalya Training and Research Hospital (02 September 2021, No:2021-259).

Data collection

This study included patients who were admitted to the ED and received ketamine for induction, analgesia, procedural sedation for any procedure (i.e., fracture reduction, laceration repair, pacemaker implantation). There was no specific age limit for study entry. All participants or their relatives gave informed consent for study participation. The following exclusion criteria were used to exclude subjects: eye and orbital diseases, optic nerve tumors, orbital mass, history of neurosurgical procedures, history of head trauma, and refusal of the study participation.

Study Protocol

The following demographic and clinical data of the patients were collected: age, sex, type of the procedure (induction, procedural sedation, analgesia), initial ketamine dose, any maintenance ketamine dose, and timing of ketamine application. Simultaneously with the ONSD measurements, vital signs were also measured and included the following: heart rate, blood pressure, respiratory rate, oxygen saturation (SpO2), Glasgow Coma Scale (GCS) score. The patient outcomes in the ED (discharge, hospital admission, ICU admission, death) were recorded on a pre-prepared Study Form.

After the decision was made by the ED Physician to administer ketamine after initial evaluation, bedside ONSD measurement was done. Another physician, namely the treating physician, performed IV ketamine administration after determining the medication dose and timing. ONSD was measured 1 to 2 minutes before and 10 minutes after a single dose of 0.5–2 mg/kg IV of racemic mixture of ketamine. Because ketamine has a short duration of action (~ 10 minutes), no other treatment was administered, nor drug change made for a 10-minute waiting time [16].

ONSD Measurement

After the principle emergency physician performed a clinical assessment of all patients, they all underwent bedside USG examination according to the study protocol. The USG examinations were carried out by 4 emergency physicians working in the ED, who had at least 2-year experience in USG and were certified for basic USG and advanced USG including ONSD assessment. Briefly, ONSD measurement was performed with the patient in supine position with both eyes shut, and a small volume of ultrasound gel was applied on both eyelids.

This was followed by determining the site of the optic disk using a 7.5 MHz linear ultrasound probe (Mindray Medical, Germany). First, both eyes were examined both vertically and horizontally; then, the optic disk was directly visualized. As stated elsewhere, ONSD measurement was carried out both in transverse and sagittal planes, from a point that was 3 mm proximal to the optic disk. ONSD was measured in reference to the width of the hypoechoic area used as a guide (Figure 1). Two separate measurements in terms of millimeter (mm) were taken from both the coronal and longitudinal planes and averaged to yield the mean ONSD value.

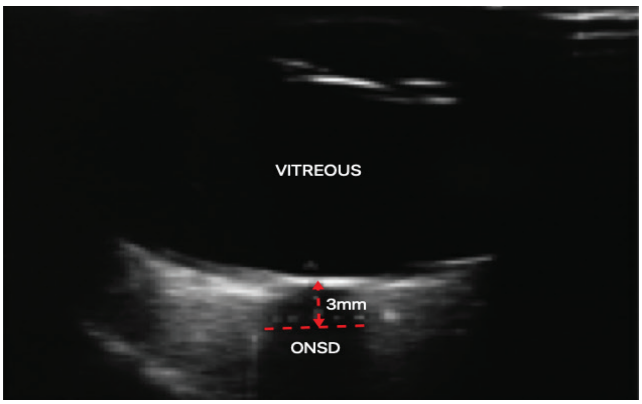

Figure 1. ONSD Measurement technique: transverse measurement of optic nerve, at a site 3 mm proximal from the optic disk, with closed eyelids.

Statistical Analysis

Study data were analyzed with SPSS (Statistical Package for the Social Sciences) 23.00 for Windows statistical software package (version 23.0; SPSS, Chicago, IL). Descriptive data included number (n) and percentage (%) of patients,

and interquartile range (IQR) for continuous variables. Fischer's Exact Test was used to compare categoric variables. The distribution of continuous variables was tested using Kolmogorov-Smirnov test. Sign test was used for the comparison of the continuous variables in two dependent groups; Mann-Whitney U test was used to compare continuous variables between two independent groups. A p value of less than 0.05 was considered statistically significant.

Results

This study enrolled a total of 75 patients who were administered ketamine in the ED. Forty-four (58.7%) of them were male and 31 (41.3%) were female. Their mean age was 59.8 ± 20.5 years. Their comorbidities included HT in 42.7% (n=32) patients, DM in 22.7% (n=17), CAD in 17.3% (n=13), COPD in 10.7% (n=8), malignancy in 10.7% (n=8), CVD in 9.3% (n=7), and CRD in 6.7% (n=5). An analysis of their vital signs revealed a mean SBP of 120.93 ± 30.0 mmHg, mean DBP of 71.64 ± 19.3 mmHg, mean pulse rate of 95 ± 24.2 bpm, mean SpO2 of 93.74% ± 9.3%, and mean respiratory rate of 17.73 ± 5.9 breaths per minute. The demographic and clinical characteristics of the study population were shown on Table 1. The initial ketamine dose administered was 1.0 ± 0.4 mg/kg. Twelve participants received a second ketamine dose of 0.7 ± 0.1 mg/kg given 10 min after the first dose.

Variable	**% (n)**
Sex	
Male	58.7% (44)
Female	41.3% (31)
HT	42.7% (32)
DM	22.7% (17)
CAD	17.3% (13)
COPD	10.7% (8)
Malignancy	10.7% (8)
CVD	9.3% (7)
CRD	6.7% (5)
	Mean ± SD
Age	59.8 ± 20.5
HR	95 ± 24.2
SBP	120.93 ± 30.0
DBP	71.64 ± 19.3
SpO2	93.74 ± 9.3
RR	17.73 ± 5.9
Initial ketamine dose (mg/kg)	1.0 ± 0.4
Participants who received a second ketamine dose	12 (16%)
Second ketamine dose (mg/kg)	0.7 ± 0.1

Note: Data are presented as n (%), mean ± SD, or median [IQR]. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RR, respiratory rate; SpO2, pulse oximetry. HT: hypertension, DM: diabetes mellitus, CAD: Coronary artery disease, COPD: chronic obstructive pulmonary disease, CVD: Cerebrovascular disease, CRD: chronic renal disease

Table 1. Demographic and clinical characteristics of the study population

The indications of administration of ketamine in the ED included induction in 30.7% (n=23) patients, procedural sedation in 53.3% (n=40), and analgesia in 16% (n=12) *(Table 2)*.

Ketamine Indication	**% (n)**
Induction	30.7% (23)
Procedural Sedation	53.3% (40)
Analgesia	16% (12)
Total	100% (75)

Table 2. Ketamine Indication

An analysis of ONSD measurements carried out before and after ketamine administration showed that the minimum and maximum ONSD values before ketamine administration were 3.30 mm and 7.40 mm; after ketamine administration, the minimum and maximum ONSD values were 3.30 mm and 7.15 mm. ONSD measurements before and after ketamine administration were shown in *Figure 2* and *Figure 3*.

An analysis of the pre-procedural and post-procedural bedside ONSD measurements revealed that among patients who received ketamine for induction, pre-procedural median ONSD was 5.10 (IQR:1) mm and post-procedural ONSD was 5.00 (IQR:1.30) mm, and the difference was not statistically significant (p=0.832). Among those who received ketamine for analgesia, the corresponding values were 3.70 (IQR:0.40) mm and 3.65 (IQR:0.23) mm, and the difference was again statistically non-significant (p=0,549). Among those who received ketamine for procedural sedation, the corresponding measurements were 4.05 (IQR:0.67) mm, and 3.97 (IQR:0.69) mm, and the difference between the two measurements was statistically significant (p=0.001) (Table 3).

Ketamine indication	**ONSD**		**p value**
	Pre-procedural ONSD value (IQR)	Post-procedural ONSD value (IQR)	
Induction	5.10 (1.0) mm	5.0 (1.3) mm	**0.832**
Procedural Sedation	4.05 (0.67) mm	3.97 (0.69) mm	**0.001**
Analgesia	3.70 (0.40) mm	3.65 (0.23) mm	**0.549**

ONSD: Optic nerve sheath diameter, IQR: Median interquartile range, mm: Millimeter

Table 3. Pre-procedural and post-procedural bedside ONSD measurements of patients who received ketamine

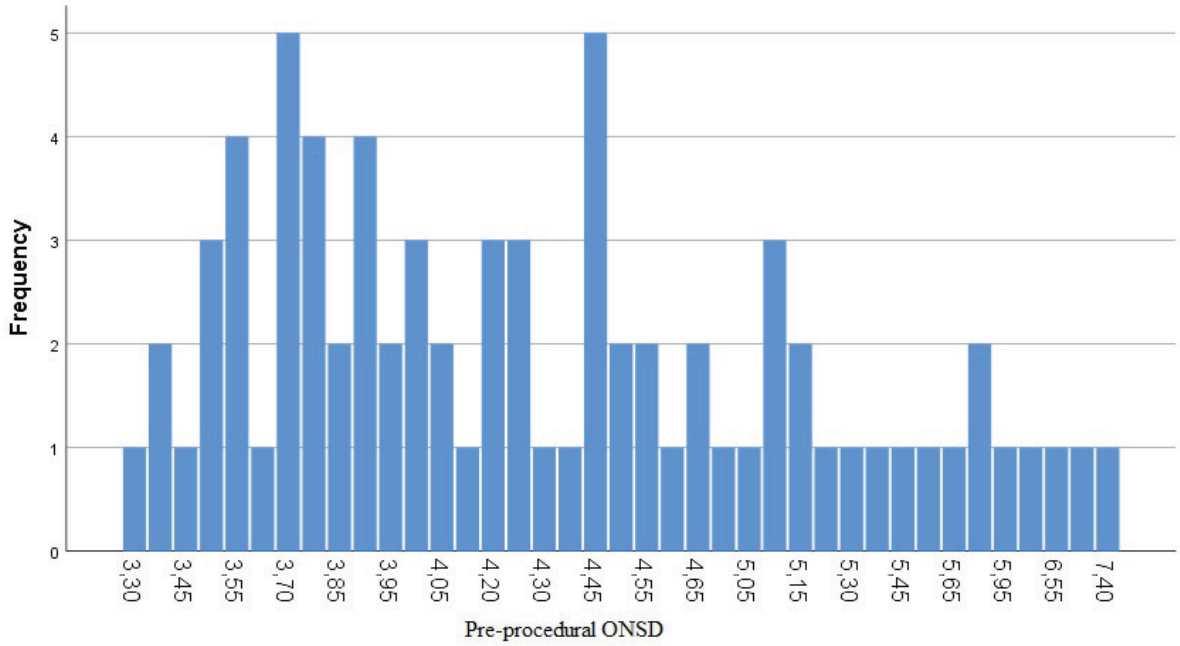

Figure 2. Pre-procedural ONSD measurements

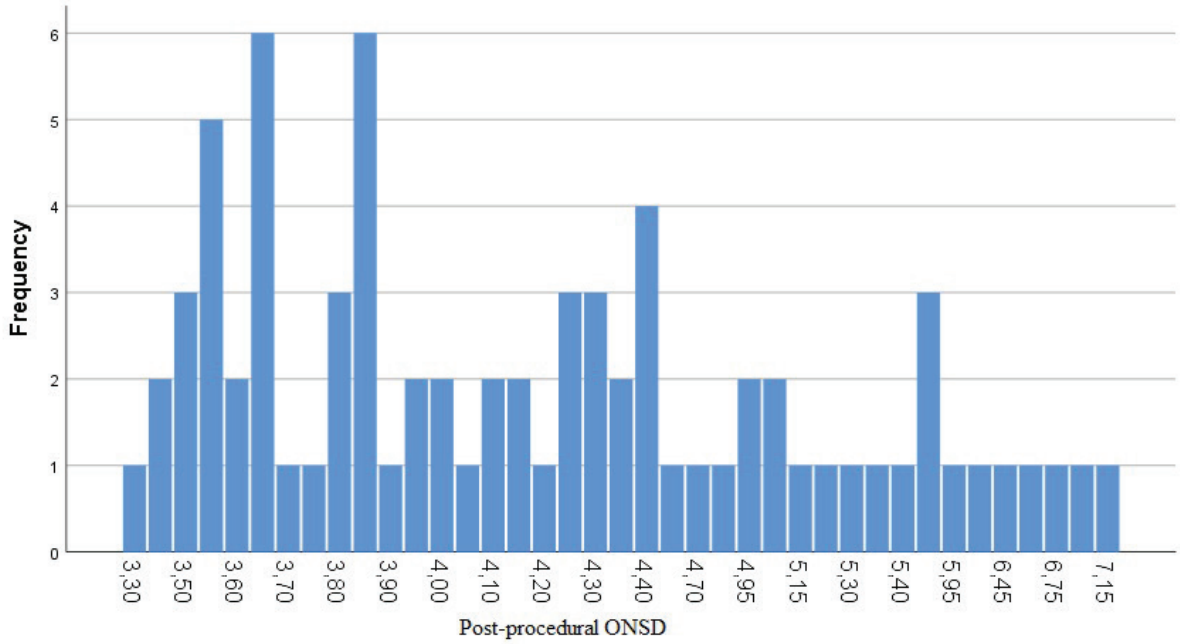

Figure 3. Post-procedural ONSD measurements

An analysis of patient's outcomes revealed that 29.3% (n=22) of patients were discharged from the emergency department; 16% (n=12) were admitted to hospital; 53% (n=40) were admitted to ICU; and 1.3% (n=1) died (Table 4).

Patient Outcome	% (n)
Discharge from ED	29.3% (22)
Hospital admission	16% (12)
ICU	53.3% (40)
Dead	1.3% (1)

Table 4. Patient Outcomes

Discussion

Early ketamine studies have implicated its use with temporary increments in ICP [17]. Initially, *Shapiro et.al.* [18] reported temporary ICP increase independent of alterations of partial pressure of oxygen (PaO2) or partial pressure of carbon dioxide (PaCO2). It was suggested that ICP increase is probably dependent on cerebral blood flow swings. These early observations have caused hesitancy among physicians about the use of ketamine in patients with neurological conditions for a long time. Although several publications have challenged this notion, precluded use of ketamine for patients with neurological conditions has remained a norm. In contrast to this widespread belief, a systematic review of 16 articles involving 127 adults refuted ICP increase in patients with atraumatic brain conditions receiving ketamine [19]. Furthermore, a more recent systematic review of 11 studies dealt with the issue and stated that while only slight ICP increase was observed in two of the studies, two other small studies actually reported a decrease in ICP after ketamine application [20]. In all of these studies ICP measurements have been carried out using invasive methods. Nevertheless, invasive ICP monitoring is not free of complications; bleeding, infections and other potentially dangerous complications may develop, and not all patients are suitable for undergoing invasive ICP monitoring [9].

ONSD measurement with POCUS is considered a safe, noninvasive tool for rapid determination of ICP and can be readily performed at bedside, allowing earlier implementation of appropriate therapy [18]. We also investigated if ketamine used for various indications in the ED increased ICP using ONSD measurement, a noninvasive tool. We have come across no study in the literature that specifically studied ICP changes using ONSD measurements in patients who received ketamine.

We observed no significant changes regarding ONSD between pre-procedural and post-procedural measurements in patients who received ketamine for induction and analgesia (p= 0.832 and 0.549 respectively). In patients who received ketamine for procedural sedation, on the other hand, there was a significant difference between pre-procedural median ONSD and post-procedural median ONSD (4.05 (IQR:0.67) mm vs 3,97 (IQR:0.69) mm, p=0.001).

Our study results suggest that, let alone increasing ICP, ketamine actually reduced ICP in a statistically significant manner when administered for procedural sedation (p=0.001). Ketamine interferes with the presynaptic catecholamine uptake and its effect starts within 30 seconds. It then rapidly enters the central nervous system owing to its high lipophilic character (distribution half-life of 10 min) [21, 22]. Its usual dose is between 1 and 5 mg/kg/h [22]. We also administered ketamine at a dose range of 0.5-2 mg/kg. Additionally, 12 patients needed an extra dose of ketamine.

Our study results can be generalized to ED patients for a number of reasons. First of all, our study population included a wide range of age groups admitted to ED in daily routine. Secondly, we used an initial ketamine dose that is conventionally used for anesthesia induction, analgesia and procedural sedation. Thirdly, our patients were administered more than one ketamine dose. Despite the fact that our study made no observation about ketamine's effects in settings where cerebral autoregulation was pushed to its limits, it still provides valuable information about ketamine monotherapy's effects on ICP, both in adults and children. Our study is the first to provide an insight on ketamine's effect on ONSD.

Conclusions

An overview of the results of our analyses using ONSD, a noninvasive bedside tool, suggest that ketamine is a medication that does not cause any increase in ICP when given for various indications in the ED. There is a need for future studies to specifically investigate ketamine's effects on ONSD when administered for a range of indications in the ED.

Author Contributors

FY, EA and BB performed data acquisition. FY, EA, CK, IT, IB and EDA 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.

Declaration of conflicting interests

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Informed consent

All patients provided written informed consent prior to study participation.

Ethical approval

This study was initiated in the ED of a tertiary hospital following ethics committee approval.

Availability of data and materials

All materials taken from other sources (including our own published writing) were clearly cited.

Human rights

Our work does not infringe on any rights of others, including privacy rights, and intellectual property rights. There is no human rights violation in our manuscript.

Abbreviations:

RSI - Rapid Sequence Intubation; ICP - Intracranial Pressure; CSF - Cerebrospinal Fluid; USG - Ultrasonography; ED - Emergency Departments; ONSD - Optic Nerve Sheath Diameter; SpO2 - Oxygen Saturation; GCS - Glasgow Coma Scale; ICU - Intensive Care Unit; IQR - Interquartile

Range; SPSS - Statistical Package for the Social Sciences; HR - Heart Rate; SBP - Systolic Blood Pressure; DBP - Diastolic Blood Pressure; RR - Respiratory Rate; HT – Hypertension; DM - Diabetes Mellitus; CAD - Coronary Artery Disease; COPD - Chronic Obstructive Pulmonary Disease; CVD -Cerebrovascular Disease; CRD - Chronic Renal Disease; PaO2 - Partial Pressure of Oxygen; PaCO2 - Partial Pressure Of Carbon Dioxide;

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