81024_Auto_Edited.docx

WORD COUNT	3020	TIME SUBMITTED	15-DEC-2022 04:36PM
		PAPER ID	94024343

Name of Journal: *World Journal of Critical Care Medicine*

Manuscript NO: 81024

Manuscript Type: ORIGINAL ARTICLE

Prospective Study

Bedside ultrasonography of optic nerve sheath diameter for detection of raised intracranial pressure in nontraumatic neuro-critically ill patients

Madhura Bhide, Omender Singh, Deven Juneja, Amit Goel

Abstract

BACKGROUND

Delay in treatment of raised intracranial pressure (ICP) leads to poor clinical outcomes. Optic nerve sheath diameter (ONSD) by ultrasonography (US-ONSD) has shown good accuracy in traumatic brain injury and neurosurgical patients to diagnose raised ICP. However, there is a dearth of data in neuro-medical ICU where the spectrum of disease is different.

AIM

We conducted this study to validate the diagnostic accuracy of ONSD in non-traumatic neuro-critically ill patients.

METHODS

We prospectively enrolled 114 patients who had clinically suspected raised ICP due to non-traumatic causes admitted in neuro-medical ICU. US-ONSD was performed according to ALARA principles. A cut-off more than 5.7 mm was taken as significantly raised. Raised ONSD was corelated with raised ICP on radiological imaging. Clinical history, general and systemic examination findings, SOFA and APACHE 2 score and patient outcomes were recorded.

RESULTS

There was significant association between raised ONSD and raised ICP on imaging ($p<0.001$). The sensitivity, specificity, positive and negative predictive value at this cut-off was 77.55%, 89.06%, 84.44% and 83.82% respectively. The positive and negative likelihood ratio was 7.09 and 0.25. The AUROC was 0.844. Using Youden's index the best cut off value for ONSD was 5.75mm. Raised ONSD was associated with lower age ($P = 0.007$), poorer GCS ($P = 0.009$) and greater need for surgical intervention ($P = 0.006$) whereas no statistically significant association was found between raised ONSD and SOFA score, APACHE II score or ICU mortality. Our limitations were that it was a single centre study and we did not perform serial measurements or ONSD pre- and post-treatment or procedures for raised ICP.

CONCLUSION

ONSD can be used as a screening a test to detect raised ICP in a medical ICU and can used as a trigger to initiate further management of raised ICP. ONSD can be beneficial in ruling out a diagnosis in a low-prevalence population and rule in a diagnosis in a high-prevalence population.

INTRODUCTION

Raised intracranial pressure (ICP) is a dreaded complication in the intensive care unit (ICU) which may occur either as a result of primary neurological disorder or as a secondary complication in patients admitted due to other causes. Delay in detection of raised ICP can lead to poor clinical outcomes and increased mortality. The latest Brain Trauma Foundation (BTF) guidelines now recommend a cut off of 22 mmHg to initiate ICP lowering therapies[1]. Gold standard for measuring raised ICP is the intraventricular catheter. However, it is not widely available, requires expertise in insertion and maintenance and may be associated with many risks like infection,

collapse of ventricles and haemorrhage[2]. Hence, non-invasive methods like computed tomography (CT) scan or magnetic resonance imaging (MRI) are being increasingly used to diagnose raised ICP. However, they are associated with transport risk and radiation exposure, in case of CT scan, leading to logistical issues and limited repeatability.

Determination of optic nerve sheath diameter by ultrasonography (US-ONSD) is a simple bedside test, which has a small learning curve, low intra and interobserver variation and good repeatability[3,4]. Studies have shown good accuracy even when performed by non-radiologists[5]. In the modern ICUs, bedside ultrasonography is being integrated into routine clinical examination and hence, is easily available. ONSD is being frequently used across neuro-surgical ICUs as a tool for ICP monitoring and is particularly useful in patients in whom invasive ICP monitoring criteria is not met or is contraindicated. However, the spectrum of disease and comorbidities of patients admitted in neuro-medical ICUs are distinct from neurosurgical ICUs. There is a lack of effective bedside screening tool to timely detect raised ICP in neuro-medical ICUs and hence, we aimed to validate ONSD in neuro-medical ICU patients.

MATERIALS AND METHODS

We conducted a prospective study in 114 patients for determining the diagnostic accuracy of ONSD in adult non-traumatic neuro-critically ill patients after approval from institutional ethics committee. Our inclusion criteria were patients with age more than 18 years admitted in neuro-medical ICU with signs and symptoms suggestive of raised ICP. Our exclusion criteria were previous known history of neurological conditions like chronic hydrocephalus, in situ ventriculo-peritoneal shunt, known ocular mass, ocular trauma, conjunctival edema, orbital edema, cavernous sinus pathology or arachnoid cysts, and patients having optic nerve disease. Additionally, patients in whom CT/MRI could not be performed within 24 h of US-ONSD, were also excluded from the analysis.

We serially enrolled patients who fulfilled the inclusion criteria. After a written informed consent was obtained, ocular USG was done by critical care specialists, trained in critical care ultrasonography, using 7-15 MHz ultrasound probe in B mode to determine the ONSD 3 mm distal to optic disc in both the eyes. Two readings were taken for each eye and a mean value was calculated to represent the final ONSD. ONSD more than 5.7 mm was taken as a threshold for determining raised ICP.[3] CT/MRI scans of brain were done within 24 h of US-ONSD and the images were reviewed for signs of raised ICP. Raised ICP or non-traumatic radiographic cerebral edema [NTRCE] was defined on imaging as presence of significant brain edema, midline shift, compression of basal cisterns or ventricles, effacement of sulci, insufficient grey/white differentiation and transfalcine herniation. Clinical history, general and systemic examination findings, SOFA and APACHE 2 scores and patient outcomes were also recorded.

Statistical analysis

The collected data were transformed into variables, coded and entered in Microsoft Excel. Data were analysed and statistically evaluated using SPSS-PC-25 version. Quantitative data were expressed in mean ± standard deviation (SD) or median with interquartile range (IQR) and depending upon normality distribution, difference between two comparable groups were tested by student's t-test (unpaired) or Mann Whitney 'U' test. Qualitative data were expressed in percentage and statistical differences between the proportions were tested by chi square test or Fisher's exact test, as appropriate. For all statistical tests, the p-value less than 0.05 was taken as valid evidence for statistical significance of the data.

Performance of the diagnostic tests was estimated using 2x2 contingency tables to calculate sensitivity, specificity overall diagnostic accuracy, positive and negative predictive value, likelihood ratios (LRs) and 95% confidence intervals (CI). Post-test probability was determined using Bayes's nomogram. Discrimination was tested using

the receiver operating characteristic (ROC) curves. The best cut off value for ONSD was calculated by using Youden's index.

RESULTS

A total number 114 patients with signs and symptoms suggestive of raised ICP were included in the analysis. Out of these, raised ONSD (> 5.7 mm) was found in 45 (39.5%) patients. The mean age of patients in our study cohort was 64.05 (±16.80) years with predominantly male population (59.3%). Table 1 shows that the patient comorbidities, clinical symptoms and signs, except Glasgow Coma Scale (GCS), on admission were comparable across both groups. Poor GCS was significantly associated with raised ICP (P = 0.009). Raised ICP on imaging was seen in 49 patients (43%). Most common feature of raised ICP patients on imaging was diffuse cerebral edema (38.1%) followed by effacement of sulci (32.7%), insufficient grey/white differentiation (30.1%), compression of ventricles (21.2%), midline shift (20.4%) and transfalcine herniation (1.8%).

There was statistically significant correlation between raised ONSD and increased ICP features on CT/MRI scan ($p<0.001$). As shown in table 2, the sensitivity, specificity, positive and negative predictive value at this cut-off was 77.55%, 89.06%, 84.44% and 83.82% respectively. The AUROC was 0.844. The best cut off value for ONSD calculated by using Youden's index was 5.75mm.

The commonest diagnosis was septic/metabolic encephalopathies (27.4%). Other diagnosis were acute intracranial bleed (21.2%), acute ischaemic stroke (20.4%), meningoencephalitis (13.3%), super refractory status epilepticus (4.4%), newly diagnosed space occupying lesion (1.8%), cerebral venous sinus thrombosis (CVST) (1.7%) and hypoxic-ischaemic encephalopathy (1.7%).

Patient outcomes including ICU length of stay (LOS) and ICU mortality were comparable across both groups as shown in table 3. Raised ONSD had statistically higher requirement of surgical intervention (P = 0.006). The surgical procedures done were decompressive craniotomy in 6 patients, ventriculo-peritoneal shunt (VP shunt) in

3 patients and extra-ventricular drain (EVD) insertion in 2 patients. One patient underwent EVD followed by VP shunt with Omaya reservoir.

DISCUSSION

Invasive ICP monitoring is not widely available across the ICUs, especially in resource limited settings. An internet-based survey of critical care physicians in India in 2013 showed that only 36.42% had access to exclusive neurocritical care units and 63.4% consultants did not monitor ICP. Amongst the physician who monitored for raised ICP, 60.32% CT / MRI scans, 28.57% intraventricular catheter with external transducer and 11.11% used Codman microsensor[6]. This shows the extent of deficit in terms of advanced neuro-monitoring facilities across ICUs in resource limited settings. US-ONSD provides a lucrative alternative to the available methods for ICP monitoring. We conducted a prospective study with the primary objective of validating ONSD by bedside ultrasound in comparison to features of raised ICP on CT/MRI brain. Our study found significant association between raised ONSD (> 5.7 mm) and findings of raised ICP on imaging. The sensitivity and specificity, at this cut-off was 77.55% and 89.06% with an AUROC was 0.844. The positive and negative predictive values were 84.44% and 83.82% respectively. The best cut off value for ONSD determined by Youden's index was 5.75 mm.

Physical findings of raised ICP are nonspecific and lack accuracy to diagnose raised ICP. Glasgow Coma Scale is commonly used for monitoring of neuro-critically ill patients. Poor motor performance has been associated with raised ICP and poor prognosis[7]. In our study, the most common symptom in patients with suspected raised ICP was altered mental status and poor GCS score was significantly associated with raised ONSD. This was in accordance with a study of patients with traumatic brain injury (TBI) where raised ONSD was compared to 3 groups of GCS 3-5, 6-8, >8 and a statistical significance was found between poor GCS and raised ONSD[8]. In patients in whom GCS cannot be assessed due to ongoing sedatives or paralytic agents, raised

ONSD can be used an indicator for raised ICP warranting further evaluation. However, further studies are required to establish any linear relationship between deteriorating GCS and increasing ONSD.

Out of our entire study population, 49 patients (42.98%) showed presence of NTRCE. In a study in general medical ICU by Salahuddin *et al*, NTRCE was found to be 30.4%[9]. Higher prevalence of NTRCE in our study can be explained by the fact that it was done in a neuro-medical ICU patients with suspected raised ICP, as opposed to the above mentioned study which was done in a general medical ICU.

For over 10 years the upper limit of normal for US-ONSD was considered to be 4.5 to 5.0 mm. However, recent studies have shown a higher threshold. Geeraerts *et al*, reported that with an ONSD cut-off 5.7 to 5.8 mm could exclude raised ICP with a sensitivity and negative predictor value of >90%. If the ONSD was < 5.7 mm the probability of ICP above 20 mmHg was less than 5%[10]. Another study conducted on 100 stroke patients with mass effect compared US-ONSD with signs suggestive of raised ICP on CT scan of brain, and showed that an ONSD cut-off of > 5.7 mm had positive correlation with CT scan findings[11]. In the present study, we found best cut-off for ONSD using Youden's index as 5.75 mm which is in accordance with the recent data[11].

In our study, there was statistically significant association between raised ONSD (> 5.7 mm) compared to raised ICP on CT/MRI brain. Raised US-ONSD was shown to be a good screening tool for raised ICP with the sensitivity and specificity was 77.55% and 89.06%, respectively and AUROC was 0.844. However, the terms sensitivity and specificity do not take into account disease prevalence and are hence, are more applicable at a population level. LRs are dependent on disease prevalence and therefore, can be used to quantify the probability of disease in an individual patient. In our study, the positive and negative LR was 7.09 and 0.25. The disease prevalence (raised ICP) in our study was 43%. Using Baye's nomogram, this suggests that if ONSD is more than 5.7 mm there is 84% probability of patient having raised ICP. On the other

hand, if ONSD is less than 5.7 mm the probability of raised ICP is only 16% (CI:10-24%). Hence, in neuro-medical ICUs where raised ICP has high prevalence, ONSD is a good screening test to detect raised ICP but may not be accurate enough to rule out raised ICP. When the same LRs are applied to a low prevalence population like in a study by Tayal *et al* where raised ICP was found to be prevalent in only 14% of patients presenting to the emergency department with a suspected acute head injury requiring CT, the positive post-test possibility was 54% and negative post-test probability was less than 4%[12]. Therefore, in a population with a low prevalence of raised ICP, the optic nerve sheath diameter maybe good for ruling out the diagnosis of raised ICP.

Most of the studies related to ICP monitoring and US-ONSD have been conducted in neurosurgical ICU where trauma and strokes form the bulk of the disease. Primary pathology of neurocritical illness is different in medical ICUs[3,4]. A previous study of ONSD in a medical ICU found that the common causes of coma were septic or metabolic encephalopathy (25.4%) followed by new intracranial vascular event (17.6%) anoxic brain injury (4.9%), hepatic encephalopathy (21.5%), intracranial malignancy (8.8%) and others (intracranial infection, reversible posterior leukoencephalopathy syndrome (RPLS), subclinical seizures) in 21.5%[9]. Similarly our study also found septic/ metabolic encephalopathy to be the commonest cause. This gives an insight into the spectrum of diseases causing signs and symptoms of raised ICP in a neuro-medical ICU.

To summarize, US-ONSD was found to be a good screening tool to detect raised ICP in high prevalence population and to rule out raised ICP in low prevalence population. Thus, ONSD can act as a bridge in between clinical suspicion of raised ICP and definitive tests for raised ICP and can be used as a trigger to start more aggressive monitoring and therapy. There was no statistically significant difference between raised ONSD and SOFA score and APACHE II score. The severity of disease seems to have no impact on ONSD. The hospital LOS, ICU LOS, ICU mortality did not show any statistical corelation with ONSD. Hence, ONSD may not be a good test for prognostication in a neuro-medical ICU. However, patients with raised ONSD had

statistically higher rate of surgeries in our study and raised ONSD may indicate the need for surgical intervention.

There are several strengths in our study. We included a fairly large number of patients. This was a prospective study with a well-defined study protocol. Study was done in single centre so the ICU admission protocol, management strategies were uniform and standardised. We used CT/MRI brain as the gold standard for comparison with US-ONSD. We acknowledge the inferiority of CT/MRI to invasive gold standard measures of raised ICP. However, as invasive ICP monitoring is not readily available using CT/MRI shows a more real-life situation and may have better external validity, especially in resource poor settings. Limitations were that all data were obtained from a single centre database, which may result in concerns regarding the generalization of the conclusions. We did not perform serial ONSD measurements or ONSD pre and post treatment or procedures undertaken for raised ICP. Hence, the effect of therapeutic strategies on delta ONSD is not available.

CONCLUSION

Given the good sensitivity, positive LR and AUROC, ONSD can be used as a screening a test to detect raised ICP in a neuro-medical ICU where the prevalence of raised ICP is high and can used as a trigger to initiate further investigations and management of raised ICP. This can help in decreasing the time gap between the episode of raised ICP and initiation of treatment.

ARTICLE HIGHLIGHTS

Research background

Delay in treatment of raised intracranial pressure (ICP) leads to poor clinical outcomes.

Research motivation

Optic nerve sheath diameter (ONSD) by ultrasonography (US-ONSD) has shown good accuracy in traumatic brain injury and neurosurgical patients to diagnose raised ICP. However, there is a dearth of data in neuro-medical ICU where the spectrum of disease is different.

Research objectives

We conducted this study to validate the diagnostic accuracy of ONSD in non-traumatic neuro-critically ill patients.

Research methods

We prospectively enrolled 114 patients who had clinically suspected raised ICP due to non-traumatic causes admitted in neuro-medical ICU. US-ONSD was performed according to ALARA principles. A cut-off more than 5.7 mm was taken as significantly raised. Raised ONSD was correlated with raised ICP on radiological imaging. Clinical history, general and systemic examination findings, SOFA and APACHE 2 score and patient outcomes were recorded.

Research results

There was significant association between raised ONSD and raised ICP on imaging ($p<0.001$). The sensitivity, specificity, positive and negative predictive value at this cut-off was 77.55%, 89.06%, 84.44% and 83.82% respectively. The positive and negative likelihood ratio was 7.09 and 0.25. The AUROC was 0.844. Using Youden's index the best cut off value for ONSD was 5.75 mm. Raised ONSD was associated with lower age ($P = 0.007$), poorer GCS ($P = 0.009$) and greater need for surgical intervention ($P = 0.006$) whereas no statistically significant association was found between raised ONSD and SOFA score, APACHE II score or ICU mortality. Our limitations were that it was a single centre study and we did not perform serial measurements or ONSD pre- and post-treatment or procedures for raised ICP.

Research conclusions

ONSD can be used as a screening a test to detect raised ICP in a medical ICU and can used as a trigger to initiate further management of raised ICP. ONSD can be beneficial in ruling out a diagnosis in a low-prevalence population and rule in a diagnosis in a high-prevalence population.

Research perspectives

Large scale studies need to be performed to assess the utility of ONSD in specific sub-groups of critically ill patients with neurological derrangements.

81024_Auto_Edited.docx

ORIGINALITY REPORT

10%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.jultrasoundmed.org Internet	106 words — 3%
2	www.alliedacademies.org Internet	58 words — 2%
3	link.springer.com Internet	39 words — 1%
4	D. W. Potgieter, A. Kippin, F. Ngu, C. McKean. "Can Accurate Ultrasonographic Measurement of the Optic Nerve Sheath Diameter (a Non-Invasive Measure of Intracranial Pressure) be Taught to Novice Operators in a Single Training Session?", Anaesthesia and Intensive Care, 2019 Crossref	26 words — 1%
5	Anisha Beniwal, Omender Singh, Deven Juneja, Hemant Kumar Beniwal, Sahil Kataria, Madhura Bhide, Devraj Yadav. "Clinical course and outcomes of cancer patients admitted in medical ICU with sepsis", Journal of the Intensive Care Society, 2022 Crossref	25 words — 1%
6	Ana B. Maldonado-Cárceles, José García-Medina, Alberto M. Torres-Cantero. "Performance of physical examination versus ultrasonography to detect stenosis in haemodialysis arteriovenous fistula", The Journal of Vascular Access, 2018	20 words — 1%

Crossref

7	Thomas Geeraerts. "Theme: Neurology - Optic nerve sheath diameter measurement as a risk marker for significant intracranial hypertension", Biomarkers in Medicine, 04/2009 Crossref	13 words — < 1%
8	f6publishing.blob.core.windows.net Internet	13 words — < 1%
9	drbillsukala.com Internet	12 words — < 1%
10	www.plamj.org Internet	12 words — < 1%
11	www.thieme-connect.com Internet	12 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS