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Original Article

Internal Medicine Section

Exploring Cerebral Perfusion Transcranial Doppler Parameters in Patients Admitted to Combined Medical Surgical Intensive Care Unit

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ABSTRACT

Introduction: Encephalopathy, a common complication in Intensive Care Unit (ICU) patients, is often linked to poor outcomes. Transcranial Doppler (TCD), a non-invasive tool assesses cerebral perfusion via the Pulsatility Index (PI), Resistivity Index (RI), and Time-Averaged Peak (TAP) or Mean Flow Velocity (MFV). These parameters may offer insights into cerebral perfusion and outcomes in encephalopathic patients.

Aim: To describe the PI, RI of the Middle Cerebral Artery (MCA), and MFV or TAP measured by TCD in patients admitted to the ICU, comparing those with and without encephalopathy at the time of admission.

Materials and Methods: This cross-sectional observational study was conducted from January 2019 to November 2020, in a combined medical-surgical ICU of a tertiary care hospital, involving 45 enrolled patients. Patients were evaluated within 24 hours of admission and subsequently every 24 hours until ICU discharge, death, or discharge against medical advice. Bilateral Middle cerebral artery TCD studies were conducted using a 1-5 MHz phased array probe or TCD mode through the transtemporal window. The PI, RI, and MFV were measured on both sides, with the higher value used for analysis, and all statistical analyses were performed using Statistics and Data 13 software.

Results: In the present study, 88% (n=40) of patients had encephalopathy (GCS <15 and RAAS less than or more than 0). The mean APACHE II score was 19 (14-25), indicating severe illness with a predicted mortality of 30-40%. Patients with encephalopathy had significantly higher APACHE II scores compared to those without (19.5 (16-25) vs 10 (4-19)). Although there was a trend towards a higher Pulsatility Index in encephalopathic patients at admission (1.11±0.378 vs 1.07±0.12, p=0.81), PI, RI, and TAP values did not significantly differ in non-survivors (1.12±0.49 vs 1.11±0.33, p=0.750). Persistent encephalopathy was associated with a trend towards higher PI at admission (1.05±0.24 vs 1.16±0.46; p=0.756), and a moderate correlation was found between decreasing PI and improvement in GCS (rho=-0.489, p=0.001).

Conclusion: PI, RI, and TAP at the time of admission were not found to be associated with occurrence and recovery of encephalopathy as well as mortality. The trend of change in PI moderately correlated with improvement in GCS suggesting the importance of trends rather than absolute values.

Keywords: Encephalopathy, Intensive care unit, Mean flow velocity, Pulsatility index, Resistivity index, Transcranial doppler

INTRODUCTION

Cerebral Blood Flow (CBF) and perfusion are autoregulated over a wide range of mean arterial pressure in health and are affected by age, hematocrit, partial pressure of carbon dioxide, temperature as well as disease states with loss of autoregulation. These physiological and pathological factors are also known to vary and are abnormal in critically ill patients who are admitted with several disease states. The disease entities can be either structural or non-structural. Structural causes are those due to Traumatic Brain Injury (TBI), ischemia stroke, Intracerebral bleed (ICH), Subarachnoid Hemorrhage (SAH), or due to Space-occupying Lesions (SOL). Non-structural causes are due to a variety of causes including metabolic, septic, toxic, and infective causes. The changes in CBF and CVR have been studied in these clinical situations, especially traumatic brain injury, Hepatic Encephalopathy (HE), and Sepsis-associated Encephalopathy (SAE) [1,2].

Clinical surrogates of these abnormalities in the form of global cerebral dysfunction manifest as encephalopathy with variation in level of consciousness, and altered sensorium- hyperactive or hypoactive. Such encephalopathy is identified in critically ill patients by variation in Glasgow Coma Scale (GCS), agitation scores such as Richmond Agitation Sedation Score (RASS), or delirium identification scores such as CAM-ICU score [3-6]. Such changes in consciousness or sensorium have been identified as markers of increased mortality and morbidity in this cohort of patients. The pathophysiology behind these changes has been attributed to neuroregulatory dysfunction as well as cerebral circulatory disturbances.

These cerebral-circulatory disturbances in the form of variation in CBF and hence velocity as well as cerebrovascular resistance resulting in changes in Cerebral Perfusion Pressure (CPP) have been assessed by several invasive and non-invasive techniques. Among the non-invasive methods to study these parameters non-invasively are imaging techniques such as computed tomography, magnetic resonance imaging, sonology based Transcranial Doppler sonography (TCD), and Optic Nerve Sheath Diameter (ONSD) as well as near-infrared spectroscopy, visual-evoked potentials, etc., [7-9]. Each of these provides intuitive information on CBF and cerebral blood flow as well as cerebral auto-regulation. Among these methods, TCD provides direct as well as indirect information on cerebral hemodynamics in the setting of traumatic brain injury by measuring the flow velocities in proximal intracranial arteries [10].

TCD is non-invasive, repeatable, real-time imaging of basal cerebral arteries especially the Middle Cerebral Artery (MCA) usually through a transtemporal window. Spectral analysis of the doppler waveform helps derive blood flow velocity which includes Peak Systolic Velocity (PSV), End-diastolic Velocity (EDV), and Mean Flow Velocity (MFV) measured as Time-averaged Peak or Mean (TAP/TAM). It also gives unitless indices based on the velocity measurements Pulsatility Index (PI) and Resistivity Index (RI) [11-13].

These parameters have been used to describe cerebral hemodynamic abnormalities in various diseases. Although several cross-sectional studies have described abnormalities in the TCD flow parameters, none have described their distribution and variation in the trend of PI, RI, and TAP values over time in ICU patients [14]. It is still not

known whether these parameters vary among patients in ICU with the presence or absence of encephalopathy, and whether in patients with encephalopathy are these parameters different in those who have resolution or persistence of encephalopathy. The ability of these parameters to predict other clinically relevant outcomes is also not well studied. A description of these parameters could provide insight into pathological changes in cerebral circulation such as hypoperfusive, hyperemic, or vasospastic pathologies with increased or decreased velocity and variation in PI or RI among these patients and whether it corresponds to clinical changes observed in the sensorium or altered level of consciousness. In the present study among patients being admitted to the ICU, the authors described TCD parameters of velocity, PI, and RI and evaluated their association with encephalopathy, level of consciousness, and changes in consciousness during their stay in the ICU.

MATERIALS AND METHODS

This was a cross-sectional observational study conducted from January 2019 to November 2020, at St John's Medical College Hospital Bengaluru, Karnataka, India. This study was approved by the Institutional Ethical Committee (IEC) (No. IEC/1/015/2019 dated 9 January 2019).

Inclusion criteria: Those patients aged 18 years and above and admitted to the medical ICU were included in the study.

Exclusion criteria: Consisted of age less than 18 years, known severe carotid stenosis (>50%) or occluded carotid arteries, inadequate transcranial Doppler window, patients with a history of mental retardation, patients not expected to survive for >24 hours in the ICU, cardiac arrhythmias at the time of measurement, penetrating trauma to the head or significant ocular trauma, and refusal of consent were excluded from the study.

Sample size estimation: was based on a two-sample comparison of means from a pilot study done by the principal investigator in medical ICU among 4 encephalopathic and 5 non-encephalopathic patients where TCD measurements of PI, PSV, EDV, MFV (TAP), and ONSD were calculated for a total of 27 times among these patients. Assuming a two-sided alpha error of 0.05 for a power of 80% the number needed was 11 patients with encephalopathy and 44 patients without encephalopathy. Accounting for dropouts and patients with inadequate sonographic windows a sample size of 60 has been selected. However, the final sample size was restricted to 45 given constraints of time.

Procedure

Patients were assessed within 24 hours post-admission and subsequently every 24 hours till discharge from ICU or death. Patients were included in the study only after obtaining informed consent. All transcranial doppler and other ultrasound-based evaluations such as optic nerve sheath diameter and echocardiography were performed by the principal investigator and one coinvestigator under supervision. All TCD, ONSD, and Echocardiographic measurements were taken sequentially within 30 minutes of each other for a patient. To avoid bias the TCD and ONSD measurements were taken before transcribing patient data on the data entry form.

TCD methods: All measurements were done with Sonosite ultrasound machine available in MICU using phased array low frequency Echocardiography probe 1-5 MHz in abdomen mode (penetration mode) or TCD mode with tissue harmonic imaging and multibeam set off or with TCD mode. The depth was set at 13-16 cm adequate to visualise the contralateral inner table of calvarium. The patient was positioned in the supine position with 30° head up for the transtemporal TCD window and for measurement of optic nerve sheath diameter. The transtemporal window, located above the zygomatic ridge between the lateral canthus of the eye and auricular pinna was used to insonate the proximal Middle cerebral artery. This was preceded by identifying on B-mode the butterfly-shaped midbrain or the lesser wing/sphenoid ridge. The depth was adjusted to 13-15 cm taking note of the probable depth at which the MCA is likely to be found (5-6 cm). Further optimisation was done by powering down the gain and switching to color doppler imaging to focus on the area anterior to the midbrain. Slowly increasing the color gain till it was over-gained and then bringing it down helped in getting the optimal color signal of the MCA where the flow was directed toward the probe (Red). A small color gate and slight free-hand adjustments of the probe help identify the best color flow and get the artery/vessel in line for pulse Doppler measurements. Once this was done pulse wave doppler was switched on to get a clear and crisp margin of spectra, with the maximum audio signal. The point of maximum deflection was taken for measurements. The maximum angle correction was less than 20°. Using the caliper controls the waveform was outlined manually or automatically to get the flow velocities, PI, and RI. These measurements were repeated on both sides. For analysis, the higher value of PI, and RI among the two sides was taken and the lower of the TAP was taken [15-17].

TCD calculations:

1) PI=(PSV-EDV)/MFV
2) RI=(PSV-EDV)/PSV
4) MFV=[PSV+(EDV×2)]/3

ONSD methods: ONSD measurements were done with a Linear high-frequency 6-13 MHz vascular probe in nerve mode. The patient was positioned supine or 30° heads up. The probe was placed longitudinally on the upper eyelid, slightly temporal to visualise the nerve with care to avoid the lens and avoid pressure on the orbit by resting the hand on the face. Measurements were taken 3 mm behind the globe (not the papilla) which has been shown to have the best contrast for measurements. ONSD measurement will be taken from inside the hyperechoic dural layer and perpendicular to the axis of the nerve [7,17].

Echocardiography methods: Patients were evaluated with a 1-5 MHz cardiac probe equipped with Doppler Imaging. The apical 5-chamber view was used for measuring the Left Ventricular Outflow Tract Velocity Time Integral (LVOT VTI) with a pulse doppler gate in between the LVOT distal to the aortic valve with minimal angle correction. LVOT Diameter was measured 0.5 cm below the level of the aortic valve at the point of maximum separation in the Parasternal Long Axis View (PLAX) view. LVOT VTI was measured in apical 5-chamber view (A5C) 0.5 cm below the level of the aortic valve [18].

An identification number and basic details of patients including age, sex, date of admission to hospital and ICU, duration and day of stay in ICU, source of ICU admission, date of discharge, outcomes, and cause of death were recorded from electronic patient information. Admission diagnosis and complications, co-morbidities (both with ICD code), Charleston co-morbidity index, and APACHE II score on the day of admission were also recorded. Clinical data such as GCS, RASS, presence of sepsis and probable focus, toxin exposure, type and toxidrome, CNS disease information, and use of drugs such as vasopressor and sedatives were also recorded from the patient admission sheet, flow chart, and drug chart on the day of admission and every 24 hours subsequently. Other relevant information such as hemodynamic data, data on mechanical ventilation at the time of TCD, and ABG values available nearest to the time of TCD were transcribed onto patient data form and were acquired from the patient charts and monitored at admission, and every 24 hours. Laboratory tests that were done as part of standard care such as Hemoglobin, LFT, and Creatinine as performed based on the discretion of the treating physician, were obtained from the patient's records as mentioned for other parameters. TCD-based data included pulsatility and resistivity index and flow velocities such as PSV, EDV, MFV, and ONSD measurements on both sides.

Echocardiographic data included LVOT VTI, LVOT diameter, and CO. All measurements were done sequentially within 30 minutes of each other to avoid discrepancies in values arising from global macrocirculatory changes.

Encephalopathy was diagnosed when GCS was less than 15/15 and a RASS score other than zero. Resolution of encephalopathy was considered when GCS improved to 15/15 with a RASS of 0.

Encephalopathy: GCS <15/15 and RAAS </>0

No encephalopathy: GCS 15/15 and RASS=0

Initial TCD parameters of PI, RI, and TAP were described in patients with or without encephalopathy at admission. The resolution of encephalopathy was analysed with trends of PI.

The GCS in intubated patients was corrected for verbal score to categorise into mild, moderate, and severe using imputation values for Verbal score based on E and M scores at the time of observation [19]. The imputation model was performed as well as a more complex model involving distinct combinations of eye and motor scores. This performed well when compared to actual verbal scores to determine prognosis in traumatic brain injury and neurosurgical patients when applied to the GCS-Pupils plus age plus CT findings (GCS-PA CT) prognostic model. The imputation model consisted of the following: EM scores 2-6, add 1; EM score 7, add 2; EM score 8 or 9, add 4; and EM score 10, add 5 to provide the GCS sum score. Modeling without information about the verbal score as per this method of imputation did not affect the predictive value of GCS when compared to scores with absolute values of the verbal score for GCS (Reduced the R2 from 32.1% to 31.4% and from 34.9% to 34.0% for predictions of death and favorable outcome at 6 months). Mild derangement in GCS was taken as scores of 13-15, moderate grades as scores of 9-12, and severe as less than 9. GCS grades at admission were described in patients with or without encephalopathy at admission. Improvement in GCS by a score of 2 during admission was analysed separately against the trend of the derived pulsatility index. Linear regression was done to analyse the absolute change in GCS from admission to discharge with change in PI values during ICU stay. Death and Discharge Against Medical Advice (DAMA) were considered together as mortality for analysis.

STATISTICAL ANALYSIS

The trend of TCD-based parameter PI was categorised on a Likert scale into decreasing, static, and increasing based on a 10 percent change from baseline at admission. Similarly, GCS was categorised into a Likert scale into mild, moderate, and severe after correction for the V score in intubated patients based on E and M scores. Also, encephalopathy was categorised into recovered and not recovered. Categorical and continuous variables were analysed using Chi-square, ANOVA, and Mann-Whitney U depending on the distribution of data. Spearman's correlation coefficient (bivariate analysis) was used to analyse the ordinal variables. This analysis was repeated after excluding non-encephalopathic patients. A bivariate logistic regression analysis was performed to identify factors associated with poor outcomes. Linear regression was done between the change in GCS and the change in PI. Statistical analyses were done using the STATA 13 statistical package (StataCorp, College Station, Texas, United States).

RESULTS

The enrolled 45 patients mean age was 46.71±19.3 years with the majority of the patients within the age group 45-65 years (35.6%). Males outnumbered the females by a ratio of 2.3:1. Of the total number of 45 patients 40 (88.9%) had encephalopathy and only 5 (11.1%) did not have encephalopathy. The distribution of GCS grades among these patients divided as mild, moderate, and severe was 33.3%, 28.9%, and 37.8 % respectively. The mean APACHE II score was 19.86±8.5 suggesting most patients were severely ill with predicted mortality of 30-40%. The mean duration of stay in ICU and of mechanical ventilation were 6±4.4 and 4±4.4 days respectively. Among all the patients studied 14 (31.1%) had poor outcomes (Death and DAMA). A total of (15.55%) underwent tracheostomy. A total of 12 (26.6%) had a shock at the time of TCD measurements. The mean PI at admission was 1.13±.34.

The mean APACHE-II (20.91.2±8.04 days vs 11.2±8.5, p=0.026), Length of ICU stay (6.3±4.5 days vs 3.2±1.3, p=0.05), and duration of mechanical ventilation (4.4±4.5 vs 0.6±1.34, p=0.01) were significantly different between patients with and without encephalopathy. Age, gender distribution, PI at admission, mortality, and need for tracheostomy were not significantly different between the two groups. All patients who did not have encephalopathy had only mild alternation in GCS whereas among the encephalopathic group, 25% were categorised as mild, 32.5% as moderate and 42.5% had severe alteration in GCS [Table/Fig-1].

The distribution of PI, RI, and TAP at admission was compared among all patients with different grades of GCS [Table/Fig-2].

	Total (n=45)		Encephalopathy		p-value
			YES (n=40)	NO (n=5)	
Males: Females ratio	2.3:1		2.07:1	4:1	1.00
Age (years)	46.71±19.3		47.22±18.6	42.6±26.7	0.57
Encephalopathy (%)			88.9	11.1	
Glasgow Coma Scale (GCS) Grade-N (%)	**Mild**	15 (33.3)	10	5	**0.04**
	Moderate	13 (28.9)	13	0	
	Severe	17 (37.8)	17	0	
APACHE II	19 (14-25)		19.5 (16-25)	10 (4-19)	**0.026**
Length of ICU stay (days)	4 (3-7)		5 (3-7.75)	3 (2-4.5)	**0.05**
Duration of MV (days)	3 (.25-5.75)		3 (2-6)	0.0 (.0-1.5)	**0.01**
Tracheostomy-N (%)	7 (15.55)		0 (0)	7 (17.5)	-
Shock at time of TCD-N (%)	12 (26.6)		0 (0)	12 (30)	0.30

[Table/Fig-1]: Demographic variables.
GCS Grade (Corrected for verbal score)-Mild: 13-15, Moderate: 8-12, Severe: <8

GCS Grade	Mild (n=15)	Moderate (n=13)	Severe (n=17)	p-value
PI (Mean±SD)	1.12±0.28	1.08±0.33	1.11±0.44	0.944
TAP (Mean±SD)	46.78±18.06	46.86±26.7	53.13±23.15	0.688
RI (Mean±SD)	0.64±0.09	0.63±0.06	0.63±0.11	0.944

[Table/Fig-2]: PI, RI, TAP among all patients with different grades of GCS at admission.
PI: Pulsatility index; TAP: Time-averaged peak velocity; RI: Resistivity index

The PI, RI, and TAP values at admission were compared among patients with encephalopathy against different grades of GCS. The PI and RI values between the groups were similar, whereas TAP values were high in patients with severe encephalopathy but it did not attain statistical significance [Table/Fig-3].

GCS Grade	Mild n=10	Moderate n=13	Severe n=17	p-value
PI (Mean±SD)	1.15±0.34	1.08±0.33	1.11±0.44	0.906
TAP (Mean±SD)	44.4±14.76	46.86±26.70	53.13±23.15	0.585
RI (Mean±SD)	0.64±0.10	0.63±0.06	0.63±0.11	0.91

[Table/Fig-3]: PI, RI, TAP in encephalopathic patients with different grades of GCS at admission.
PI: Pulsatility index; TAP: Time:averaged peak velocity; RI: Resistivity index

The values PI, RI, and TAP at admission among patients with encephalopathy and without encephalopathy during admission

were analysed. The mean PI in the encephalopathic and non-encephalopathic groups were 1.14±0.36 and 1.07±0.12 respectively (p-value=0.814). The mean TAP in the encephalopathy and nonencephalopathic group were 62.01±24.35 and 54.9±23.88 respectively, however, there was no statistical difference between the two groups [Table/Fig-4].

Encephalopathy	Yes (n=40)	No (n=5)	p-value
PI (Mean±SD)	1.14±0.36	1.07±0.12	0.814
TAP (Mean±SD)	62.01±24.35	54.9±23.88	0.957
RI (Mean±SD)	0.63±0.09	0.63±0.5	0.127

[Table/Fig-4]: TCD parameters in patients with or without encephalopathy at admission to ICU.
PI: Pulsatility index; TAP: Time:averaged peak velocity; RI: Resistivity index

The TCD parameters PI, RI, and TAP were compared between survivors and non-survivors in patients with encephalopathy. Although PI (1.12±0.49 vs 1.11±0.33, p=0.750), RI (0.64±0.14 vs 0.63±0.07, p=0.915) values were higher; TAP (47.45±20.54 vs 49.46±23.45, p=0.844) values were lower in non-survivors it did not reach statistical significance [Table/Fig-5].

TCD parameters at admission	Encephalopathy (n=40)		p-value
	Survivors (n=29)	Non-survivors (n=11)	
PI (Mean±SD)	1.11±0.33	1.12±0.49	0.750
TAP (Mean±SD)	49.46±23.45	47.45±20.54	0.844
RI (Mean±SD)	0.63±0.07	0.64±0.14	0.915

[Table/Fig-5]: TCD parameters among Survivors vs non-survivors (with encephalopathy).
PI: Pulsatility index; TAP: Time:averaged peak velocity; RI: Resistivity index

Among patients with encephalopathy, PI, RI, and TAP were not statistically different between patients who had improved GCS and those who did not improve their GCS during their stay in ICU [Table/Fig-6].

TCD parameters	Improved GCS (n=27)	GCS Not improved (n=13)	p-value
PI (Mean±SD)	1.1±0.39	0.99±0.31	0.214
TAP (Mean±SD)	47.96±24.56	50.88±18.01	0.427
RI (Mean±SD)	0.64±0.08	0.61±0.11	0.452

[Table/Fig-6]: Improvement versus no improvement in GCS (with encephalopathy).
PI: Pulsatility index; TAP: Time:averaged peak velocity; RI: Resistivity index

Among patients with encephalopathy, TCD parameters PI, RI, and TAP were compared between patients in whom encephalopathy resolved vs those in whom persisted. Although PI (1.16±0.46 vs 1.05±0.24, p=0.756), RI (0.65±0.11 vs 0.61±.05, p=0.225) values were higher; TAP (47.88±21.46 vs 50.45±25.50, p=0.234) values were lower in patients in whom encephalopathy persisted but it did not reach statistical significance [Table/Fig-7].

TCD parameters	Resolved encephalopathy (n=20)	Not resolved (n=20)	p-value
PI (Mean±SD)	1.05±0.24	1.16±0.46	0.756
TAP (Mean±SD)	50.45±25.50	47.88±21.46	0.234
RI (Mean±SD)	0.61±.05	0.65±0.11	0.225

[Table/Fig-7]: TCD parameters in those with Resolution vs persistence of encephalopathy.
PI: Pulsatility index; TAP: Time:averaged peak velocity; RI: Resistivity index

The trend of decreasing PI correlated with improvement in GCS suggested by moderate correlation (rho=-0.379, p=0.010). This was even more significant when only encephalopathic patients were taken for analysis (rho=-0.489, p=0.001). The trend of decreasing PI did not however correlate with resolution of encephalopathy (rho=-0.262, p=0.097. The same was observed despite taking only patients with encephalopathy (rho -0.259, p=-0.085).

Logistic regression analysis was done between important TCD parameters at admission and clinically relevant outcomes of presence of encephalopathy [Table/Fig-8], against the presenting GCS [Table/Fig-9] and mortality [Table/Fig-10]. There was no clinically significant association between any of the TCD parameters at admission in terms of the aforementioned outcomes or variables.

TCD parameters	Odds ratio	Sig.	95% CI	
			Lower	Upper
PI (Mean±SD)	84.98	0.517	0	5.84
TAP (Mean±SD)	3.07	0.301	3.52	2.67
RI (Mean±SD)	0.972	0.372	0.913	1.035

[Table/Fig-8]: Logistic (Binary) regression between TCD parameters and the presence of encephalopathy at admission.
PI: Pulsatility index; TAP: Time:averaged peak velocity; RI: Resistivity index

TCD	Regression coefficient	SE	p-value
PI (Mean±SD)	-6.77	4.332	0.12
TAP (Mean±SD)	-0.03	0.02	0.29
RI (Mean±SD)	35.41	19.25	0.07

[Table/Fig-9]: Logistic regression between TCD parameters and GCS at admission.
PI: Pulsatility index; TAP: Time:averaged peak velocity; RI: Resistivity index

TCD	Odds ratio	Sig.	95% CI	
			Lower	Upper
PI (Mean±SD)	34.926	0.522	0.001	1.837E+06
TAP (Mean±SD)	1833.90	0.557	2.43E-08	1.382E+14
RI (Mean±SD)	0.997	0.875	0.961	1.035

[Table/Fig-10]: Logistic (Binary) regression between TCD parameters and mortality at admission.
PI: Pulsatility index; TAP: Time:averaged peak velocity; RI: Resistivity index

Logistic regression analysis was done between important TCD parameters at admission and clinically relevant outcomes of resolution of encephalopathy and improvement in GCS. There was no clinically significant association between any of the TCD parameters at admission in terms of the aforementioned outcomes or variables.

Linear regression was done by comparing the absolute change in GCS with the change in PI values and it was not statistically significant (p-value=0.076).

DISCUSSION

The occurrence of acute brain dysfunction or encephalopathy, manifesting as an altered level of consciousness and awareness, is grossly under-reported and even by conservative estimates ranges from 50-80% among critically ill patients [20]. The presence of altered mental status has been associated with disease severity and poor outcomes in various disease states [21]. This has been widely recognised and therefore has been included as an essential component of various disease severity scores such as APACHE II and sequential organ failure score (SOFA) [22,23]. Cerebral circulatory abnormalities seen in encephalopathy are associated with changes in TCD parameters such as PI, MFV as well as RI. Such variations have been described in various conditions including TBI, hepatic encephalopathy, septic encephalopathy, toxic and metabolic encephalopathy such as myxoedema, and diabetic emergencies such as hyper oncotic nonketotic coma [24,25]. Abnormally high values of PI and low values of MFV have been seen in patients with TBI and other non-structural causes of encephalopathy and have correlated with worsening levels of consciousness and poorer outcomes in TBI as well as hepatic encephalopathy [24,26]. Most of these studies done previously have attempted to describe and characterise these alterations of cerebral circulation in pre-defined specific populations such as in head injury or hepatic encephalopathy. Whereas the changes in the cerebral circulation are dynamic in such patients and vary over time most studies have either looked at

one-time measurements at admission or at prespecified discontinuous time points.

In the present study, the authors included a mixed population of patients being admitted to our ICU to describe and decipher whether PI, MFV, and RI were associated with encephalopathy, variation in level of consciousness, or could predict outcomes such as mortality and resolution of encephalopathy or improvement in level of consciousness (GCS). The authors here also measured daily trends in PI and compared them against trends in GCS and the resolution of encephalopathy.

The mean age of the present study population was 46.71±19.3 years with no significant difference in the distribution among patients with encephalopathy and those without. In the study done by Chan KH et. al. among patients with TBI, the mean age was 30-49 years probably reflecting the occurrence of TBI in at-risk groups with lower age [27]. Whereas in a study by Pierrakos C et. al. among patients with sepsis and septic encephalopathy the mean age was 67±11 years probably reflecting similar demographics in a combined ICU [28]. In the present study, males (68.9%) were the predominant group and similar observations have been reported in other studies [29-31]. A total of 88% of patients in this study were encephalopathic as defined by GCS<15 and RAAS less than or more than 0 which is higher than that reported by Spronk PE et al., from a similar ICU in the Netherlands [20]. The mean APACHE II score in the study population was 19 (14-25) suggesting most patients were severely ill with predicted mortality of 30-40% which was similar in other studies by Pierrakos among septic patients [15]. There was a significant difference in APACHE II score between patients with encephalopathy and those without [median and IQR, 19.5 (16-25) vs 10 (4-19)] which suggests encephalopathy was associated with severity of illness, a finding consistently seen in other study population such as in TBI and hepatic encephalopathy. The predominant cause of encephalopathy was tropical fever (n=8), sepsis (n=8), and CVA (n=7), followed by uraemia (n=3), hepatic encephalopathy (n=3) and post-cardiac arrest encephalopathy (n=3) among others, suggestive of heterogeneous ICU population [32].

In this study Pulsatility index at admission was higher in patients with encephalopathy compared to patients without encephalopathy but it did not attain statistical significance (1.11±0.378 vs 1.07±0.12, p-value- 0.81). Studies done among cirrhosis patients have shown that those with Hepatic Encephalopathy (HE) had significantly higher PI and RI as compared to those without HE [24,30]. In another study, PI and RI were significantly different between sepsis patients with and without Sepsis-Associated Encephalopathy (SAE). These results suggest the presence of increased cerebral vascular resistance and decreased blood flow velocity in patients with HE and SAE. In the present study, such an observation could not be replicated and could be due to variable etiological diagnosis and a smaller number of patients in the non-encephalopathy group.

In this study, the authors found that MFV measured as TAP at admission was higher in patients with severe encephalopathy but it was not statistically significant. Whereas in another study done in the UK in TBI patients TAP at the time of admission was significantly lower in severe TBI when compared to mild or moderate TBI which is contradictory to these findings. This could be explained by variable cerebral hemodynamic alteration in TBI which is predominantly hypoperfusive state in severe TBI as compared to hyperaemic response seen in septic patients who comprised the predominant group in our study [27,33].

In the present study, PI and RI values were higher and TAP values were lower in non-survivors but did not reach statistical significance. A similar finding was observed in a study by Chan KH et al., in the UK among patients with TBI where TAP of less than 28 cm/s correctly predicted 80% of the early deaths [27]. Another study done in India showed higher mortality (35% vs 14%) in patients with PI <1.1 and MFV <35 cm/sec when compared to those with normal TCD parameters [34]. Yet another study from Turkey among cirrhotics showed PI and RI were correlated with the Model for End-stage Liver Disease (MELD) scores suggestive of higher mortality [29].

In the present study PI at admission was higher in patients with persistent encephalopathy but it did not attain statistical significance (1.05±0.24 vs 1.16±0.46; p=0.756). A similar observation was found in another study from France among patients with mild to moderate TBI, PI at admission predicted the development of late-onset neurological deterioration (1.04 vs 1.24; p=0.05). Though the PI at admission was higher in patients who did not recover from encephalopathy in this study it did not attain statistical significance as the present population predominantly included tropical fever and sepsis including the lesser sample size achieved [35].

In the present study trend of decreasing PI moderately correlated with improvement in GCS (rho=-0.489, p=0.001). In a study among TBI from the UK a significant in increase MFV (TAP) from baseline at admission (36.2 vs 47.8 cm/s) in patients who made a good recovery or had moderate disability as per GOS score at 6 months compared to those who were severely disabled [27]. These findings are congruent with the present implicating that as the cerebral hemodynamics improve with reversal of cerebral vasoconstriction it could also predict improvement in sensorium and resolution of altered brain function.

Previous studies have shown that TCD parameters at the time of admission in prespecified groups of patients (TBI, HE, Sepsis) were associated with the severity of encephalopathy and subsequent worsening of encephalopathy [2,15,24,30,34,36]. In the present study which included a heterogenous ICU population, the authors did not find similar observation, which could be explained by variable pathological changes in cerebral hemodynamics. However, trends in PI were correlated with improvement in GCS. This highlights the fact that rather single measurement of TCD parameters at the time of admission, flowing-up trends in TCD are of higher clinical utility.

Limitation(s)

Being an observational study it was not adequately powered to predict outcomes. The authors here were not able to achieve a pre-defined sample size due to the unprecedented present situation. Though trends are of more value in these clinical situations, obtaining daily trends is cumbersome. Further, also it might miss out on certain situations that might have changed the hemodynamics in the cerebral circulation. Our definition of encephalopathy based on GCS and RAAS scores was not validated compared to other scoring systems such as the CAM-ICU score. This could have possibly affected the results of the study. Also, TCD values are likely to be of more value if taken together with other parameters as part of multimodal neuromonitoring.

CONCLUSION(S)

In this prospective observation, the authors here looked at the utility of TCD parameters at admission and their trends in predicting occurrence and recovery of encephalopathy. The present results suggest that PI, RI, and TAP at the time of admission were not found to be associated occurrence and recovery of encephalopathy as well as mortality. The trend of change in PI moderately correlated with improvement in GCS suggesting the importance of trends. Further studies with adequate sample size are required to find the utility and place of TCD monitoring in a mixed population of critically ill patients.

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