

Randomized Control Trial For Transcranial Doppler monitoring in patients with Traumatic Brain Injury.

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Method Article

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Abstract

Traumatic Brain Injury is the leading cause of disability and mortality throughout the world. It temporarily or permanently impairs the brain function. Primary injury is induced by mechanical forces and occurs at the moment of injury while secondary brain damage may occur hours or even days after the traumatic event. This injury may result from impairment or local decline in the cerebral blood flow. Decreases in cerebral blood flow are the result of local edema, hemorrhage or increased intracranial pressure. Although major progress has been made in understanding of the pathophysiology of this injury, this has not yet led to substantial improvements in outcome. Traumatic Brain Injury is associated with various complications including raised intracranial pressure, midline shift due to worsening of the volume of intracranial hematoma, cerebral vasospasm in traumatic sub arachnoid hemorrhage.

Transcranial Doppler (TCD) has been utilized as a monitoring tool in the neurocritical care unit since it is non-invasive tool and that can be brought to bedside.

However, its utility in using as a protocol in management of traumatic brain injury patients has not been studied.

We hypothesized that daily TCD followed by early performance of Neuroimaging (CT scan) and Neurosurgical intervention will lead to improvement in clinical outcome.

Our study's design is Randomized Controlled Trial with neurosurgical intervention based upon the Intervention Group as the TCD-Monitoring/Neuroimaging vs Control Group as the Clinical Imaging/Neurological status. Our study's outcome is 90 days' clinical outcome (modified rankin scale) and Glasgow Coma Outcome Scale.

Introduction

Background

Each year 200 per 100,000 people suffer from traumatic brain injury leading to mortality and morbidity worldwide. Early assessment and neurosurgical intervention can improve the clinical outcome of the patient and prevent long term morbidity. TCD is also called as "stethoscope for the brain." It is inexpensive, reproducible, and portable, which is particularly useful in a neurointensive care setting².

The role of TCD in Trauma Unit:

Transcranial Doppler ultrasound (TCD) is a tool that has been increasingly used in cerebrovascular haemodynamic monitoring since 1982 (1). It measure different haemodynamic parameters such as, 1) brain flow velocity, 2) estimation of vascular brain resistance, and 3) brain perfusion pressure¹. The number one indication of TCD is for the detection and monitoring of vasospasm in patients with aneurysmal and traumatic subarachnoid hemorrhage. In addition, TCD is being studied as a non-invasive estimator of intracranial pressure (ICP) and cerebral perfusion pressure (CPP) in patients with severe traumatic brain injury. TCD-based assessment of cerebral pressure autoregulation and CO₂ reactivity has been shown to have prognostic implications and holds the potential to allow for individualization of therapy. In addition, TCD is a

non-invasive means of monitoring for vasospasm, stenosis, stroke, ICP or cerebral circulatory arrest⁴. Traumatic brain injury (TBI) may lead to hypoperfusion (day 0), hyperaemia (days 1–3), vasospasm (days 4–15), and raised ICP¹⁴. TCD can noninvasively identify such complications and provide prognostic information¹⁵

The role of TCD in Monitoring Intracranial Pressure:

TCD may be used as a noninvasive tool to screen for the development of elevated ICP in the first 24 hours following injury³. TCD cannot replace invasive ICP monitoring⁵ but may also be used to roughly predict ICP⁶ as well characterize the alterations in blood flow that occur during intra-cranial cerebral circulatory arrest from severely raised ICP⁷

TCD can be used to give a rough estimate for ICP, to help rule-in high ICP, but not as a surrogate for accurate invasive ICP monitors. As ICP increases, flow in intra-cranial vessels changes. Initially, systolic velocity increases (i.e., systolic peak flows) as increased ICP causes cerebral vessels to narrow from external pressure in the MCA. During diastole, diastolic flow becomes decreased/blunted, as raised ICP becomes the predominant external pressure opposing forward MCA flow during diastole. Raised ICP can also exceed normal forward flow during diastole, leading to diastolic flow reversal¹³.

Raised ICP can be estimated using the Gosling's pulsatility index, which is a reflection of peripheral resistance, which is equal to the difference between the peak systolic velocity (PSV) and end-diastolic velocity (ESV), divided by the mean velocity (MV)¹³. Bellner et al. correlated pulsatility index (PI) to ICP in clinical practice¹³.

Gosling's pulsatility index (PI) provides information on downstream cerebral vascular resistance and is equal to $(PSV-EDV)/MFV$ [27]. PI is normally 0.5 to 1.19¹⁶. Proximal stenosis or occlusion may lower the PI below 0.5 due to downstream arteriolar vasodilation whilst distal occlusion or constriction may increase the PI above 1.19¹⁷. A PI less than 0.5 may also indicate an arteriovenous malformation as vessel resistance in proximal vessels is reduced due to continuous distal venous flow¹⁸. PI positively correlates with ICP; a PI change of 2.4% is reflected by a 1 mmHg change in ICP¹⁸.

The Pourcelot resistivity index (RI) is equal to $(PSV-EDV)/PSV$ with values 0.8 indicating increased downstream resistance. Derangements of RI reflect similar disease patterns as observed with an abnormal PI¹⁵.

Previous work with invasive ¹³³Xe clearance methods has shown that the extent of hypoperfusion in the acute setting after TBI correlates with outcome at 6 months based on the Glasgow Outcome Scale (GOS)¹⁹. TCD can avoid use of invasive CBF measurement techniques and provide similar prognostic information. A low-flow velocity state defined as an MCA MFV of <35 cm/s within 72 hours of head injury has been shown to predict unfavourable outcome at 6 months (GOS score 1–3: death, vegetative state, or severe disability) with an odds ratio of 3.9 (CI 1.2–13)²⁰. However, on multivariate analysis, this association was significantly less (OR 1.2 CI: 0.25–5.9), with initial GCS being a stronger predictor of outcome.

On TCD, raised ICP exhibits a sequential waveform, beginning with an increased PI and decreased MFV and EDV, followed by zero diastolic flow²¹. A significant correlation between PI and ICP (correlation coefficient 0.938) was demonstrated in a group of 81 patients who underwent TCD MCA PI measurements combined with invasive ICP measurements⁶. A regression line was derived as $ICP = (11.1 PI) - 1.43$, which could determine an ICP via the PI within ± 4.2 mmHg of the actual ICP, which is reasonably accurate. Using this regression line, an ICP of >20 mmHg could also be determined with 89% sensitivity and 92% specificity⁶. Furthermore, in a study of 125 patients with severe TBI, poor outcomes (GOS 1–3) were associated with a significant rise in MCA PI (1.56 versus 1,) within 24 hours of injury²². Additionally, a $PI \geq 1.56$ predicted 83% of patients who had a poor outcome at 6 months, whereas a $PI \leq 1$ identified 71% of patients with a good outcome (GOS 4–5)²².

The role of TCCD in determining the Midline shift:

As ultrasound technology has improved, the same transcranial acoustic windows used for the Doppler assessment of the cerebral circulation may also be used to achieve two-dimensional (2D) images of the brain parenchyma. Though anatomic detail is inferior to CT imaging, resolution is sufficient to answer emergent bedside questions such as mass effect leading to midline shift⁸

Seidel et al. illustrated the use of ultrasonography for the measurement of midline shift. Reproducibility of MLS via ultrasound corresponded to 0.3 ± 0.2 mm in ten volunteers⁹. Measurements on ultrasound have correlated well with CT findings¹⁰, and have been predictive of poor outcome from midline shift secondary to pathologies such as stroke, hemorrhage (subdural, epidural, subarachnoid), and traumatic brain injury¹⁰.

The role of TCD in deterring the Cerebral Vasospasm:

Transcranial Doppler has been studied extensively as a validated screening tool for diagnosing vasospasm¹¹, aiding in the management of subarachnoid hemorrhage (SAH) patients. The severity of vasospasm may also predict outcome on the GOS; in a study of 116 SAH patients, moderate BA vasospasm (MFV >60 cm/s) was associated with permanent neurological deficit, and severe BA vasospasm (MFV >85 cm/s) was associated with vegetative state²³. However, no relationship between the severity of MCA vasospasm and clinical outcome was demonstrated [89]. In a separate study of 50 patients with head injury who underwent TCD insonation of the MCA, ACA, and BA in the first 7 days after TBI, significantly more patients in the vasospasm and hyperaemia groups experienced a poor outcome at 6 months (GOS 1–3) compared to those without any significant flow velocity change²⁴. The highest MFV recorded, independent of vasospasm or hyperaemia, was also predictive of outcome with those in the poor outcome group (GOS 1–3) having a significantly greater highest MFV²⁴. The Lindegaard ratio (LR) allows differentiation between hyperdynamic flow and vasospasm and is defined as $MCA\ MFV / \text{extracranial ICA MFV}$ [30]. In the context of a high MFV, an LR >3 indicates hyperdynamic flow and <3 indicates vasospasm [31]. A modified LR (BA MFV/average of left and right extracranial VA MFV) and Sloan's hemispheric ratio (ACA MFV/ECICA MFV) can be similarly applied to the BA and ACA, respectively.

In HMC, TCD is used for assessment of patients with brain aneurysm only. This study will help in determination of blood flow velocity, raised ICP and traumatic vasospasm at an early stage. Therefore, early

diagnosis will lead to early management; thus improving the prognosis of patients with traumatic brain injury. In addition, our study will help in global use of TCD in TBI, thus will be added as a protocol in the management of TBI.

Objectives

OBJECTIVES:

Objectives of this study

The primary objectives of our study:

Primary objectives:

1. Daily screening patients with TCD in traumatic brain injury will improve the clinical outcome by detecting early increase of ICP or VSP
2. Modified rankin scale at discharge

Secondary objectives:

1. Modified rankin scale at 3 months
2. Length of Hospital stay
3. Number of interventions

Indicate if this is a retrospective data review

Retrospective Chart/data Review (Retrospective means the data is already in existence when the project is submitted to the IRB for initial review.

Provide the date range of the chart review (if this is a retrospective chart review, the end date must come before the submission date): mm/dd/yyyy to mm/dd/yyyy

Patients And Methods

PICOT:

P: population: Patients with traumatic brain injury

I: Intervention: TCD-monitoring group daily TCD from within 24 hours of trauma, CT neuroimaging/neurosurgical management when TCD reveals Pulsatility index greater than 1.2, Resistivity Index greater than 0.8, MFV (MCA > 150, ACA PCA ICA > 120 and VA BA > 100 cm/sec) with Lindegaard ratio greater than 3

C: Control: TBI with standard care (ICP placement and monitoring; CT scan if there is drop in GCS, changes in the size of pupils, further neurological decline; Mannitol/hypertonic saline in case of signs of raised ICP)

O: Outcome: mRS and GCOS at discharge and 3 months, length of hospital stay and number of interventions.

T: Time: symptoms onset to 90 days follow up

However, there is no specific rationale to do TCD in TBI. Therefore, we will continue it for 18 days as it the chances of traumatic vasospasm is very high till day 21 (max between 3–14 days)

Study Population and Study Setting/ Location

Patients who will be admitted with traumatic brain injury to HMC hospital will be enrolled in the study if willing to participate. This study will be conducted in the TRAUMA CENTER OF HAMAD GENERAL HOSPITAL; 1 Resident from Neurosurgery and 1 Senior Consultant from Neurology will be leading the research. TCD will be performed by sonologist, who has experience of TCD for more than 2 years. This will be double-checked by Dr. Maher Saqqur, who has certification in US and Sonology in Neurology. The hospital ethics review board will review and approve the study.

Inclusion Criteria:

1. Patient age 18 and older
2. Patient with moderate and severe traumatic brain injury (GCS 3-13)
3. Patient with TBI within 12 hours of injury

Exclusion Criteria:

1. GCS 3 with absent Brainstem reflexes
2. Pregnant
3. Preexisting neurological disability that would confound outcome
4. Patient with lack of temporal window for TCD testing.
5. Severe Other Injuries based on the trauma surgeon opinion

Randomization:

Patient who is admitted to the hospital with moderate and severe Traumatic Brain Injury will be randomized by the block randomization method (300 patients in total) so equal number of 150 treatment and 150 control arms can be assured in 2 groups (moderate and severe Head Injury based upon the Glasgow Coma Scale) in Hamad General Hospital. The TCD arm will be assigned even number and the control odds ones in a randomization box in each block group.

Study procedures

Study Duration and Timelines

Approximately 6 months for data collection and 2 months for manuscript writing.

Table (1): Schedule of assessment and tests in the TCD arm (TCD included) and control arm (no TCD test)

	Clinical assessment	mRS BI GCOS SF-36	TCD	Head CT	ICP Monitoring	Pulsatility Index	MFV	Comments
Day 1	X	X		X	X			
2	X		X					
3	X		X					
4	X		X					
5	X		X					
6	X		X	X	X	X		Pulsatility index greater than 1.2, Resistivity Index greater than 0.8, MFV (MCA > 150, ACA PCA ICA > 120 and VA BA > 100 cm/sec) with Lindegaard ratio greater than 3
7	X		X					
8	X		X					
9	X		X					
10	X		X					
11	X		X					
12	X		X	X				
13	X		X					
14	X		X					
15	X		X					
16	X		X					
17	X		X					
18	X		X					

Discharge	X	X
90 days	X	X +
		SF-36

Informed Consent

Patients/ relatives/ guardians will only be contacted by the consulting physician and if they agree, the research team can approach them to further explain the study and obtain consent. 3. Add that 3 copies of the ICF will be maintained 1 with the patient, 1 within medical records and 1 within the study site file

Risk

No risk expected from the tests.

Bio-Specimens & Sample Collection

None

Outcomes

Primary outcome

1. Good clinical outcome at discharge (mRS <3)
2. Management protocol based upon these of TCD would result in reduced mortality and improve clinical condition.

Secondary outcome:

1. Hydrocephalus/Cerebral edema/increased midline shift/enlargement of hematoma as evident on CT scan
2. Good long term clinical outcome at 90 days (mRS < 3) and Glasgow Coma Outcome Scale GOS
3. Length of hospital stay
4. Number of interventions

Modified rankin scale is the score to determine the neurological disability 0–2 means there is no-slight disability in carrying out activities, thus it's a good clinical outcome. On the other hand, 3–6 means moderate disability to death, thus it means it has a poor clinical outcome (25)

Data Collection & Confidentiality

All data will be managed by the Neurology/Neurosurgery Center research team. The electronic CRFs store data in the HGH stroke registry. The data will be entered by into the computer by a study coordinator. Only the

three Investigators and the coordinator will have access to enter and monitor the data. The data will be stored on a password protected laptop which will be kept under lock and key at the Neurology office.

Subject Withdrawal/ Withdrawal of Consent

If a subject withdraws from the study, their electronic information will be erased. We will destroy their records immediately, we will not use the collected data for our final analysis.

Statistical Consideration and Data Analysis

Demographic data will be calculated using descriptive analysis method. The sensitivity, specificity, positive predictive value (PPV), and Negative predictive value (NPV) will be calculated for screening TCD MFV/PI as compared to the ICP monitoring/serial CT scan head. The cut off for different criteria were selected based on the best accuracy parameters (P value > 0.001) and ROC curve analysis for each criteria (area under the curve ≥ 0.6).

Group sample sizes of 150 in TCD arm and 150 in the control one in order to achieve 80% power to detect a difference between the group proportions of -0.1000 . The proportion in group one (the treatment group) is assumed to be 0.3000 under the null hypothesis and 0.2000 under the alternative hypothesis. The proportion in group two (the control group) is 0.3000. The test statistic used is the two-sided Z test with pooled variance. The significance level of the test was targeted at 0.0500.

We do expect to recruit 5 patients per month. For that reason, in order to complete the trial in 10 months period

The study's analysis will be completed during the 3 months following completion of the study

The Transcranial Doppler will be performed by one sonographer and the TCD reading will be done by MS and NA in blind fashion to other neuroimaging result. The neuroimaging test (CT) will be read by 2 neuroradiologists (AZ, PG) and ICP monitoring (PG, Nurse) in blind fashion to the randomization arm and TCD result.

The Head CT will be stored in archived PIN file.

The clinical TCD and neuroimaging variables are listed in the data form sheet.

Adverse Event Reporting

The study is not testing any new drugs. This is an observational study evaluating the progression and recurrence of Stroke and TIA.

Since we are not prescribing any new medication nor procedures for the purpose of our study, we do not anticipate any adverse events as such. If there is any adverse events, it WILL BE REPORTED FIRST TO THE HOSPITAL AND THEN MRC

Ethical Consideration

“The study will only be conducted after review and approval from MRC”

Sponsor, Funding & Collaborator Information

MRC

Dissemination of Results and Publication policy

The data will be presented to the senior management of the HMC, at international conferences and submitted for publication to peer-review journals.

Abbreviations

TBI Traumatic Brain Injury

TCD Transcranial Doppler

CVS Cerebral Vasospasm

mRS Modified Rankin Scale

SAH Subarachnoid Hemorrhage

PI Pulsatility Index

RI Resistivity Index

GOS Glasgow Coma Outcome Scale

Declarations

Competing interests: The authors declare no competing interests.

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Figures

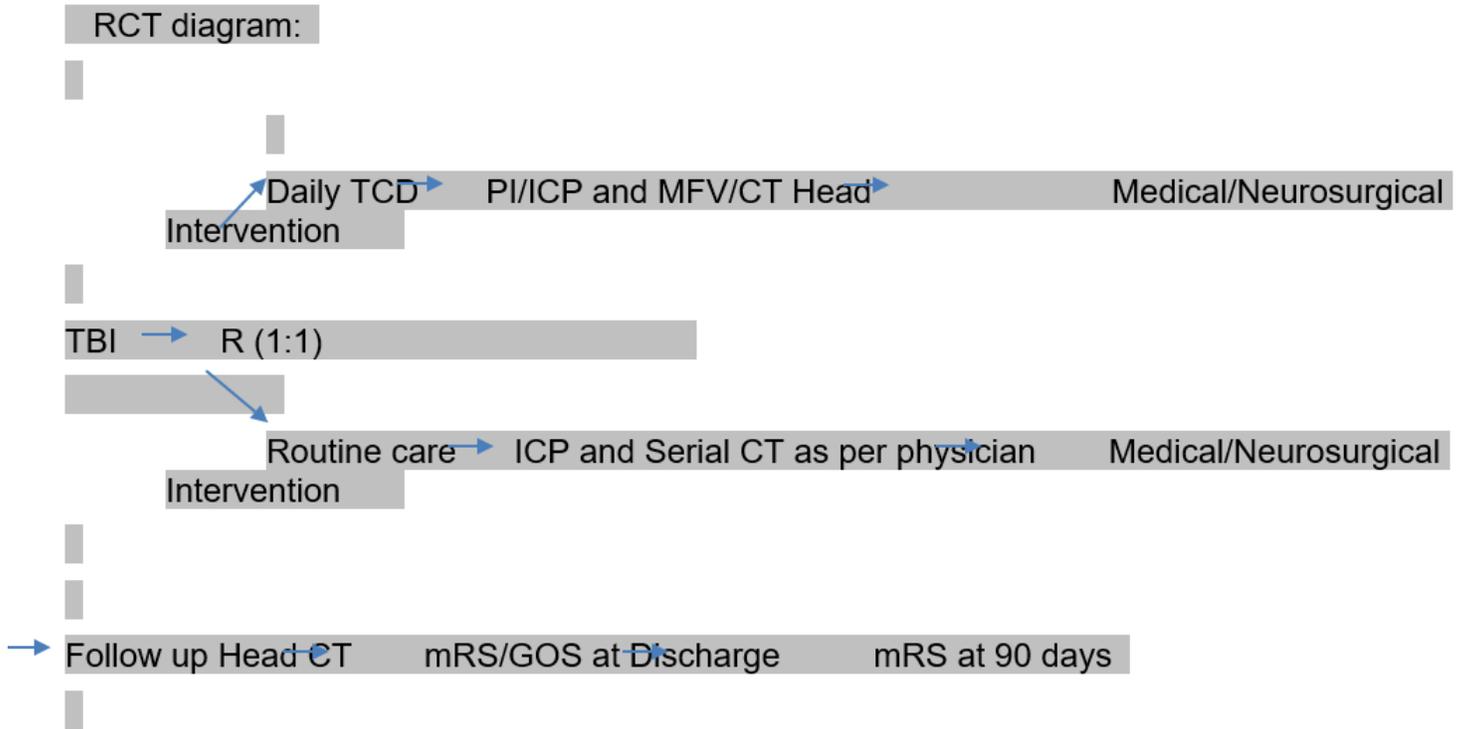


Figure 1

RCT diagram