VOL 12, ISSUE 1 | Winter 2017

JHNJOURNAL

a publication of the **Vickie and Jack Farber Institute for Neuroscience at Jefferson**

Neurocritical Care

Vickie and Jack Farber Institute for Neuroscience™ at Jefferson

(Left to Right): Jack Jallo, MD, PhD; Matthew Vibbert, MD; David Wyler, MD; M. Kamran Athar, MD;

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 ISSN 1558-8726

Jefferson.edu/Neurosurgery

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CS 17-0334

Jack Jallo, MD, PhD, FACS

Dear Reader,

Welcome to the second neurocritical care special issue of *JHN Journal*. Since our publication last year, our program has grown to continue to serve the needs of our patients.

We have long offered a UCNS-accredited, two-year fellowship in neurocritical care for graduates of neurology, internal medicine and anesthesia residencies. This year, SNS/CAST awarded us accreditation for a one-year neurocritical care fellowship to be offered to neurosurgeons. This is a reflection of the intrinsically multidisciplinary nature of our field.

A further demonstration of this point lies with the appointment of David Wyler, MD, Assistant Professor of Anesthesiology and Neurological Surgery. Dr. Wyler, who is trained in both anesthesiology and neurocritical care, will spend half of his time providing intraoperative services and the remainder of his time as an attending in one of our two neuroscience ICUs. The faculty members of our division now come from four distinct backgrounds: neurology, neurosurgery, internal medicine and, now, anesthesiology.

A few years ago, our group was asked to provide tele-ICU coverage to Kennedy University Hospital, Washington Township, where Jefferson neurosurgeons operate. The partnership was positive and we will soon be offering similar services at Bryn Mawr Hospital, part of Main Line Health. Like our program at Kennedy, we will work collaboratively with neurologists, neurosurgeons and critical care physicians to provide specialized care to critically ill patients with neurological disease or injury.

This September, Jefferson was the proud host of the 6th International Hypothermia and Temperature Management Symposium. These meetings, held every two years, are international in the truest sense of the word: our meeting's attendees came from a total of eleven countries. Hosting this event was an honor that recognized our institution's influence in the world of critical care.

The articles in this issue demonstrate the breadth and depth of our faculty's expertise. I hope you find them as interesting as I do.

Best regards,

Jack Jallo, MD, PhD

Professor of Neurological Surgery
Division Director, Neuro-Trauma and Critical Care
Vice Chair of Academic Services

NEUROCRITICAL CARE AT JEFFERSON

Thomas Jefferson University Hospital is a major referral for stroke and critically ill neurology and neurosurgery patients for the tri-state area. Thomas Jefferson University Hospital and Jefferson Hospital for Neuroscience (JHN) have a total of 40 Neurointensive care unit beds and one of the largest Neurocritical Care programs in the country. JHN is the only dedicated hospital for neuroscience in the Philadelphia region. Jefferson neurosurgery and endovascular neuroradiology treats the highest volume of patients with aneurysms, brain AVMs, angioplasty and stenting occlusive carotids in the region. Our neurocritical units are staffed by Neurocritical Care specialists who have been highly-trained to meet the specific, often dire needs of critically ill neurological patients. The units are equipped with advanced neuromonitoring tools and newer technologies have been incorporated into our practice over time. These include the following:

- **Advanced Intracranial Monitoring (Brain Tissue Oxygenation)**
- **Intracranial Pressure Monitoring**
- **Arterial Pressure Monitoring**
- **Central Venous Pressure Monitoring**
- **Noninvasive Cardiac Output Monitoring - pulse contour analysis and transpulmonary thermodilution**
- **Hypothermia devices - intravascular catheters and body surface cooling**
- **Transcranial Doppler Ultrasound**
- **Continuous and Quantitative Video EEG**
- **Direct and Video Laryngoscopy and Adjunctive Airway Management Tools**
- **Bronchoscopy**
- **Comprehensive Ultrasonography for Volume Status and Cardiopulmonary Assessment, and Vascular Access**
- **EMG**
- **Evoked Potential Assessment**
- **Telemedicine**

As part of our commitment to education, we also offer fellowship training in the discipline of Neurocritical care, which is accredited by United Council for Neurologic Subspecialties (UCNS). This program provides core clinical training in neurocritical care in the Neuro-ICU and general critical care in the SICU, MICU, CCU, CTICU, as well as formal procedural training done in a one-on-one environment. Our fellows also engage in a clinical research training curriculum and present their findings at a national level.

Jefferson has a strong engagement with the entire regional medical community and is actively expanding access to our expertise via telemedicine. Jefferson neuroscience has taken the vanguard in these efforts and provides advice to emergency room physicians treating patients with acute stroke via a telemedicine system that serves over 30 area hospitals. The Neurocritical Care team at Jefferson has expanded this model to provide support via telepresence to the medical intensivists providing care to critically ill neurologically injured patients in the Kennedy Health System. Now in its third year, this program has enhanced the already high quality care delivered at Kennedy and has been well received by physicians, nursing, patients, and families.

This special edition of the *JHN journal* highlights various facets of neurocritical care. The authors report on diseases most commonly encountered in the neurologic ICU, such as Intracerebral hemorrhage, as well as more unusual conditions such as an unusual presentation of Brugada syndrome. Recent literature on the management of severe traumatic brain injury is also reviewed, as well as the emerging role of biomarkers in brain injured patients. The challenges of diagnosing brain death in ECMO patients are also discussed. Taken as a whole, this edition of the *JHN Journal* offers a glimpse of the complexities and challenges encountered by practitioners in this exciting and rapidly evolving critical care specialty.

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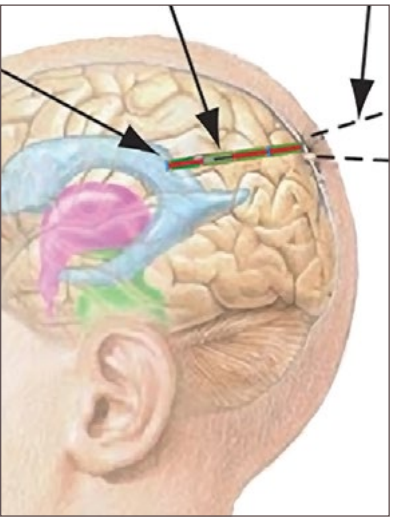

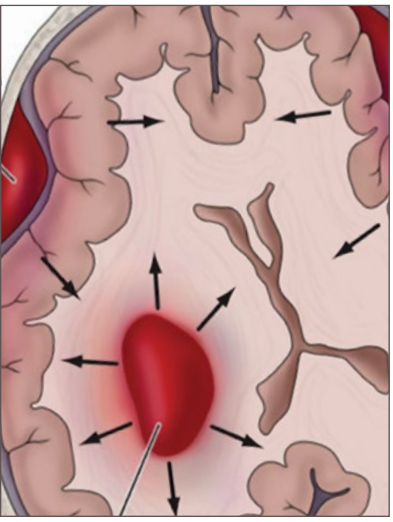

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Phenotype Variant Brugada Pattern: An Early Sign of Propofol Infusion Syndrome

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ABSTRACT

This report demonstrates the first case of inferior phenotype variant Brugada Pattern (BP) as the presenting sign of Propofol Infusion Syndrome (PRIS). A 65-year-old male in respiratory failure receiving four consecutive days of high dose propofol developed ST elevations, hyperkalemia, and lactatemia. ST elevations noted were sharply down-sloping presenting in inferior leads.[1] Hyperkalemia was treated and propofol discontinued. This therapy resulted in improvement in EKG and favorable outcome. This case supports three conclusions: the existence of inferior variant BP, BP may be a strong initial sign of PRIS, and early recognition and action stopping propofol leads to favorable outcome in PRIS.[1-4]

INTRODUCTION

Propofol Infusion Syndrome (PRIS), once thought only to occur in children, has gained popularity in recent years due to its high morbidity and mortality in adults as well. Due to heightened awareness and detection bias, the incidence of PRIS is increasing. The cause of PRIS, hypothesized to be either by direct mitochondrial chain inhibition or dysfunctional fatty acid metabolism, remains unclear.[3] Since the infancy of the syndrome, cardiac conduction abnormalities and refractory bradycardia hhave been its hallmarks. Case reports have in fact linked PRIS to the sodium channelopathy Brugada Syndrome (BS) known to cause malignant dysrhythmias and sudden death.[2,4] ST elevation in a sharp down-sloping so called Brugada like pattern may be a strong initial sign of PRIS.[3] Many different presentations of PRIS have been described in the literature but the most consistent known finding is the use of high dose propofol infusion for long duration.[5] This risk factor often occurs in critically ill patients requiring propofol therapy for increased intracranial pressure.[2,5] Other known findings include metabolic acidosis, lactemia, Acute Renal Failure (ARF), hyperkalemia, elevated triglycerides (TAG), and rhabdomyolysis.[5] Early detection and cessation of propofol is the only known method to improve outcome in PRIS.[6] Therefore, discovering methods for early detection is imperative.

CASE FINDINGS

A 65-year-old Caucasian male presented to the Surgical ICU intubated for respiratory failure preoperatively for open lung biopsy. A CT scan from an outside hospital demonstrated pan-bronchiolitis and apical cavitation suspicious for Tuberculosis (TB). Arriving with significant bronchospasm, the patient required around the clock bronchodilators and deep propofol sedation up to institutional maximum dose of 80 mcg/kg/min. Steroids were held at that time until TB and other infectious causes ruled out. Pulmonary consultation recommended bronchoscopy, an additional Acid-Fast Bacilli smear (AFB) to complete the work up for TB, and viral cultures. On the next hospital day, propofol wean was attempted unsuccessfully. Subsequently, on hospital day three, ketamine and muscle paralysis were added to reduce propofol requirements. Propofol 80 mcg/kg/min was still required to maintain oxygen saturations of 89% while permissive hypercapnia continued. Since bronchospasm continued and TB ruled out, intravenous steroids were initiated.

On hospital day four, after several days of maximum dose propofol, the ICU nurse noted changes in the telemetry strip that were concerning. The bizarre telemetry strip led to the 12 lead EKG seen in Figure 1A. Labs were drawn and the patient was found to be in ARF with acidosis (PH=7.21) and hyperkalemia of 6.5. The hyperkalemia protocol was initiated which included calcium gluconate, D50/insulin combination, albuterol, and kayexalate. Sodium bicarbonate was withheld for concern of worsening acidosis since ventilation was suboptimal. The arterial blood gas (ABG) at that time showed that the once compensated hypercapnic respiratory failure now was decompensated with new onset metabolic derangement and an elevated lactate of 2.2. Lasix was given in favor of hemodialysis since urine output was adequate. Cardiac enzymes were negative for MI, and thus EKG changes were attributed to ARF. Since the patient's condition had not improved, another set of cardiac enzymes were done and a chest wall echocardiogram was performed. Negative enzymes and an echocardiogram that showed no regional wall or structural abnormalities, ruled out myocardial infarction. Hyperkalemia, acidemia, and elevated lactate however persisted. The repeat EKGs seen in Figures 1B-1D were becoming more bizarre and paroxysmal atrial fibrillation was reported.

PRIS was discussed and propofol was discontinued in spite of normal creatinine phosphokinase (CPK) and (TAG) at that time. Aggressive diuresis with Lasix and Diuril in favor of hemodialysis was continued since urine output remained robust. Six hours after repeat diuretics were given and propofol discontinued, the hyperkalemia and acidosis improved. The 12-lead EKG returned to baseline morphology as seen in Figure 1E. Since the patient made dramatic improvement, he was transferred to Medical ICU for further pulmonary treatments. EKG

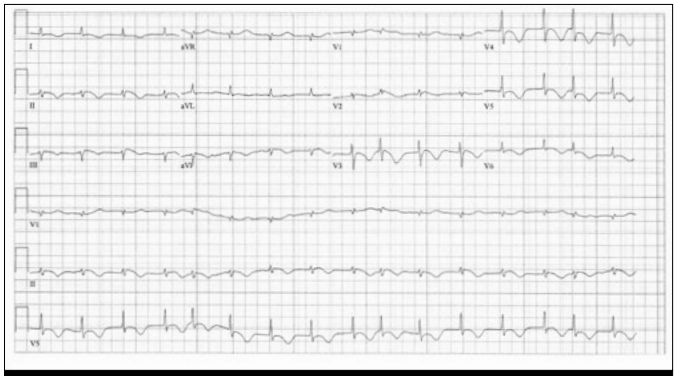
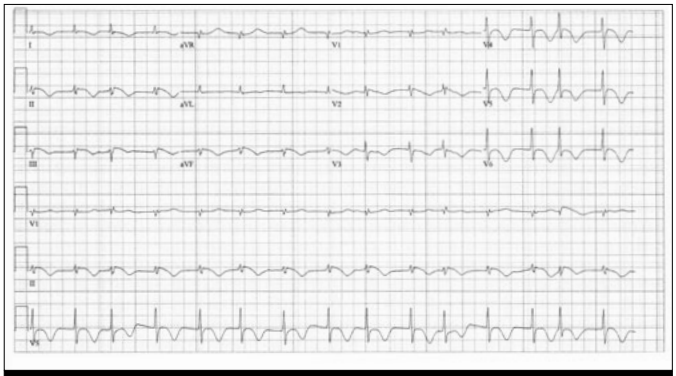


Figure 1A.



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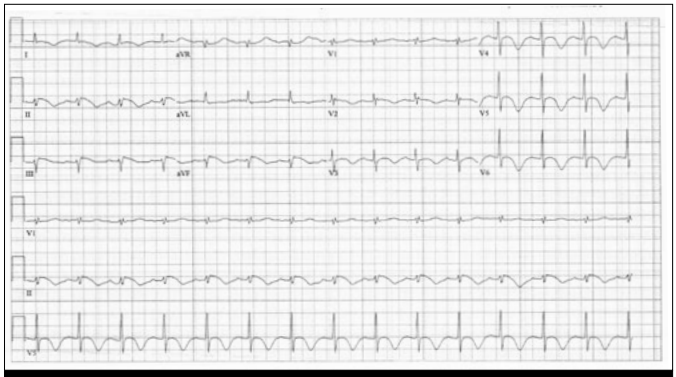

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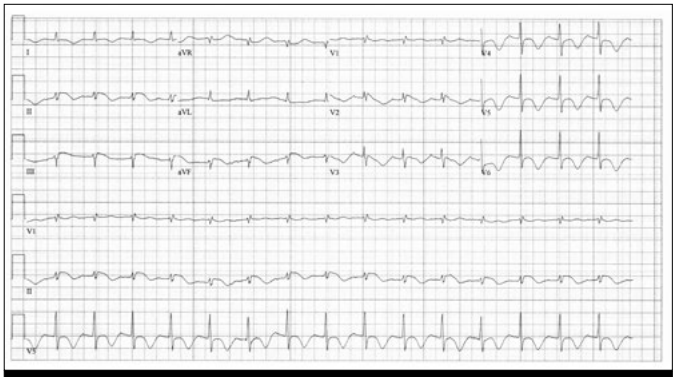

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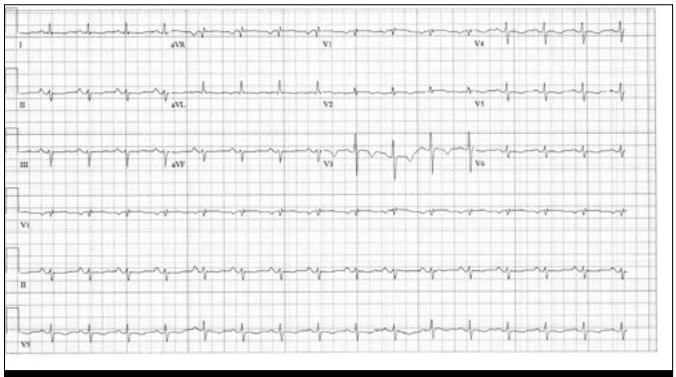

Figure 1E.

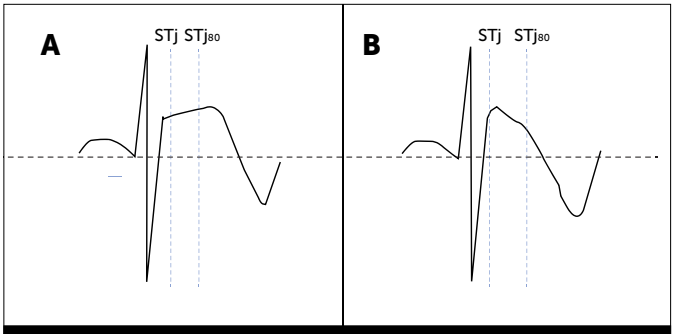

Figure 2.
Comparison between ST elevation in Early Repolarization (A) with Brugada Syndrome (B)

evolution was sent to the electrophysiology department for further analysis so that follow up with the patient could be maintained.

DISCUSSION

ST elevation (STE) is common in the ICU and includes an extensive differential. STE is considered to reflect acute transmural ischemia caused by an occlusion of a coronary artery by a thrombus until proven otherwise.[7] As per the 2013 ACCF/AHA Management Guidelines, STEMI is a clinical syndrome that comprises of typical symptoms of acute ischemia of the heart muscle in conjunction with elevation of the ST segment and increased blood levels of biomarkers that indicate necrosis of the cardiac muscle.[8] Therefore, it is recommended that patients with suspected acute STEMI receive immediate revascularization therapy to the occluded artery by either percutaneous coronary intervention or fibrinolysis. The decision to proceed with angiography or give thrombolytic

is made based on symptoms and STE analysis, and is usually reached before biomarkers such as troponins are detectable in the blood.[7] Symptoms however often present atypically; or as in this case, a patient may be sedated and intubated precluding the ability to elicit the classic ischemia symptoms. A detailed list of non-ischemic causes of ST elevation can be found in Table 1.[9]

Table 1. List of non-ischemic causes for ST elevation

1	ST elevation secondary to LVH
2	ST elevation secondary to conduction defect (such as left bundle branch blockage and non-specific intracardiac conduction delay)
3	Early repolarization pattern (notched J-point typically in anterollateral leads
4	Hypercalcemia Normal variant of ST elevation (ST elevation mostly ˆnleads V2-V3)
5	Concave ST elevation
6	Spontaneously reperfused STEMI
7	Aneurysm/old myocardia infarcation
8	Pericarditis/myocarditis
9	Wolf-Parkinson-White syndrome (pre-excitation)
10	Brudgada pattern
11	Takotsubo (apical ballooning) syndrome
12	Takotsubo (apical ballooning) syndrome
13	Hyperkalemia
14	Hypercalcemia

After reviewing the serial electrocardiograms, the negative chest wall echocardiogram and biomarkers, the most plausible explanation of the STE consisted of either Brugada pattern or hyperkalemia. In patients with acutely elevated serum potassium levels, pseudomyocardial infarction pattern has been reported to appear as massive STEMI that develops secondary to derangement in myocyte repolarization.[10] The existence of a "Brugada Phenocopy" has been described to exist secondary to various reversible causes such as electrolyte abnormalities.[4,11] However, this seems unlikely given that the potassium never exceeded 6.5 and the typical pattern of peaked T waves, widening QRS, PR interval prolongation never appeared. A prolonged QT interval up to 610 milliseconds was noteworthy, but again this is not specific for hyperkalemia, and in fact is found more in toxic drug related malignant arrhythmias such as PRIS. Moreover, EKG changes persisted inspite of correcting the hyperkalemia which contradicts a sole diagnosis of hyperkalemia to explain the STE.

Type 1 Brugada pattern typically presents as STE with at least 2 mm down-sloping "coved-type" in the anterior precordial leads (V1-V3) followed by deep wide T wave inversions.[1,2,11,12] This pattern can occur spontaneously or after provocation with a sodium channel blocker[12]. The Brugada syndrome is linked to an increased risk of ventricular arrhythmia and sudden cardiac death.[1,2,12] Figure 1 compares the classic morphology in BS contrasted with the benign Early Repolarization (ER) phenomenon.[13] The Ratio of the J point (STJ) to the point 80 milliseconds after the J point (STJ80) is called STJ/STJ80. In BS, this ratio is characteristically greater than one. Less than one identifies an upward sloping ST segment as occurs in ER. An STJ/ST80 ratio <1 is a highly accurate parameter for differential diagnosis between ER and BS, with sensitivity of 97%, specificity of 100%, and diagnostic accuracy of 98.7%. In addition, multivariate analysis showed that the STJ/ST80 ratio is superior to other electrocardiographic parameters previously reported, such as QRS duration and degree of STE.[13]

ence of ECG with a Brugada-like pattern in a patient with documented history of ventricular fibrillation or polymorphic ventricular tachycardia, or a history of sudden cardiac death in family members that are younger than 45 years, comparable ECG configuration in relatives, unexplained syncope, ability to induce ventricular tachycardia with programmed electrical stimulation, or agonal respiration at night.[12] The EKGs in Figures 1B-1D clearly demonstrate classic morphology of Brugada pattern in the anterior precordial leads (V2-V3) when the metabolic derangements and repolarization abnormalities peaked. However, the initial and most pronounced STE pattern can be seen in the inferior leads (II, III, AVF) lending this case more to the phenotype variant Brugada pattern.[1] Given that this patient lacked a history of sudden cardiac arrest, syncope, or malignant arrhythmia on telemetry, electrophysiological specialists at our institution labeled this phenomenon a "drug-induced Brugada-like ECG pattern" consistent with a toxic metabolic derangement.

PRIS, a channelopathy, which has not been fully elucidated, frequently presents inconsistently. Elevated TAG, ARF, hyperkalemia, rhabdomyolysis, and lactic acidosis are classic findings.[3-5,14] It is unclear how many signs must exist to make the diagnosis and which patients are susceptible. Consistently, PRIS case reports implicate long durations of high dose propofol.[5] Vernooy et al. described 67 patients with head injury that received prolonged propofol infusions, seven had been identified as having propofol infusion syndrome. Six of the seven PRIS patients developed the Brugada-like EKG and died within hours. The other 60 patients did not develop ventricular arrhythmias, suggesting that the mechanism underlying the arrhythmogenesis in PRIS is similar to that responsible for ventricular arrhythmias in the BS.[2] Frequently, case fatalities are diagnosed too late. Similarly, cases of

survival are documented when propofol is discontinued early and perhaps at times go unreported because of favorable outcome defending the importance of this case report.[6]

Moreover, PRIS has been linked to BS in previous reports but no gene study to date has definitively linked the two syndromes.[4] Twenty percent of BS is linked to a genetic defect of the Na+ channel. Propofol has significant neurologic and myocardial sodium channel inhibitory effects presenting the possible overlap in the two syndromes at the gene level.[4] The Brugada SNP could be analyzed in PRIS patients and may have a reasonably high frequency meriting investigation. I believe future research is essential because both syndromes are potentially deadly and under-investigated. Perhaps in the past PRIS has gone underdiagnosed in adults since it was originally thought to be a childhood syndrome. However, in the past decade, the diagnosis has been established in adults, thus, there is an increased incidence as a result of heightened awareness of the syndrome.

This diagnosis of PRIS could be debated. Although the classic diagnosis of PRIS presents with elevated CPK and TAG in the thousands, I argue that elevated CPK is a late finding of the syndrome. Elevated CPK signifies cell death and should be considered ominous in this condition. Moreover, while elevated TAG demonstrates altered fat metabolism, patients receiving propofol without the PRIS phenotype often demonstrate elevated TAG, green urine, and pancreatitis. Elevated TAG therefore does not necessarily imply toxic effects to the organs, rather it simply means over-usage of Propofol and should warn against continued high dose. Indeed several cases of normal CPK and TAG levels have been reported in patients with PRIS.[15]

In conclusion, early recognition of PRIS is crucial to preventing bad outcomes.[2,6] This can be accomplished by ordering daily triglyceride levels, blood gases looking for lactic acidosis, and doing routine daily 12-lead EKG in the setting of a patient on high dose propofol for increased duration. The goal should be to make fewer autopsy diagnoses of PRIS by discontinuing the propofol early.[6]

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Decompressive Hemicraniectomy in Acute Neurological Diseases

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ABSTRACT

Increased intracranial pressure (ICP) secondary to severe brain injury is common. Increased ICP is commonly encountered in malignant middle cerebral artery ischemic stroke, traumatic brain injury, subarachnoid hemorrhage, and intracerebral hemorrhage. Multiple interventions – both medical and surgical – exist to manage increased ICP. Medical management is used as first-line therapy; however it is not always effective and is associated with significant risks. Decompressive hemicraniectomy is a surgical option to reduce ICP, increase cerebral compliance, and increase cerebral blood perfusion when medical management becomes insufficient. The purpose of this review is to provide an up-to-date summary of the use of decompressive hemicraniectomy for the management of refractory elevated ICP in malignant middle cerebral artery ischemic stroke, traumatic brain injury, subarachnoid hemorrhage, and intracerebral hemorrhage.

KEYWORDS

Decompressive Hemicraniectomy, Intracerebral Hemorrhage, Malignant MCA Stroke, Traumatic Brain Injury, Aneurysmal Subarachnoid Hemorrhage, Intracranial Pressure, Herniation

INTRODUCTION

Increased intracranial pressure (ICP) secondary to cerebral edema is common in acute neurological disorders. Severe edema can be seen in malignant middle cerebral artery (MCA) ischemic stroke, traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), and intracerebral hemorrhage (ICH). Increased ICP can lead to life-threatening herniation syndromes and is a common cause of death when left untreated.

Decompressive hemicraniectomy (DHC) is a surgical option to reduce ICP, increase cerebral compliance, and increase cerebral blood perfusion when medical management becomes insufficient. By removing the skull, the brain is allowed to expand, thereby normalizing ICP and reducing compression and/or midline shift. By reducing ICP, cerebral perfusion pressure and blood flow are restored.

This article will summarize current medical literature regarding DHC in intracerebral hemorrhages, subarachnoid hemorrhage, malignant MCA stroke and traumatic brain injury.

DHC IN THE SETTING OF INTRACEREBRAL HEMORRHAGE

Current guidelines for the management of spontaneous ICH developed from the American Heart Association and American Stroke Association (AHA/ASA) recommend initial medical therapy for elevated ICP (external ventricular drainage [EVD]).[1] The guidelines also address surgical management, but not for treatment of refractory elevated ICP.

There are currently no large randomized controlled trials regarding the use of DHC in ICH. There have only been a few case/control and case series regarding DHC for management of refractory ICP in ICH, and these studies are divided between DHC alone versus a hematoma evacuation alongside with DHC.[2-9] Table 1 provides a summary of the key studies that have been published thus far.

DHC WITHOUT HEMATOMA EVACUATION

We were able to find two relevant studies in which DHC was done without evacuation of the hematoma. The largest study conducted by Ramnarayan et al.[4] evaluated 23 patients with primary putaminal hemorrhage. Only seven patients had a Glasgow Comas Scale (GCS) less than 8, while more than half had a GCS of 9-12. Seven patients had an ICH volume of greater than 60 cc, while 13 had a volume between 30-60 cc. The majority of patients had surgery performed within 6 hours of presentation, but no details regarding exact timing were provided. Mortality rate was low in this case series (13%), but this finding may be partly explained by the low severity of illness with a relatively high GCS and small hematoma volumes. ICH score was not reported which would have allowed for better comparison with other studies.

Fung et al.[8] performed a case-control study of 12 patients. These patients had a larger median hematoma volume of 61 cc compared to Ramnarayan et al.[4] Median time to DHC was within 12 hours with a mortality rate of 25% in the DHC group while the controls had a 53% mortality rate. Mortality was higher in the control group with hemorrhages greater than 60cc as compared to the DHC group.

DHC WITH HEMATOMA EVACUATION

The oldest and largest reported series of patients with hematoma evacuation along with DHC is a 73 patient case-control series by Dierssen et al.[9] in 1983.

Figure 1.

Authors	Study Design	No. of Cases	Age (years)	Admission GCS	ICH Volume (cc)	Percentage with IVH	ICH Score	Time to DHC (hours)	Mortality	Good Outcome	Follow-up Duration
Decompressive Craniectomy WITH clot evacuation											
Dierssen et al, 1983	Case-Control	73	52 (mean)	43 stuporous to deep coma	unknown	33%	unknown	unknown	33%	45% (no deficit to minor deficit only	2 years
Murthy et al. 2005	Case Series	12	49.8 (mean)	7 (median)	71 (mean)	92%	3 (median)	10.7 (mean)	8%	55% (mRS 0-3)	17 months
Kim et al., 2009	Case Series	24	56.2 (mean)	19 with GCS < 8	unknown	unknown	unknown	8.3 (mean)	25%	50% (GOS 4-5)	6 months
Ma et al., 2010	Case-Control	38	43 (mean)	11.0 (mean)	58 (mean)	74%	3 (mean)	22 (mean)	32%	55% (GOS 3-5)	6 months
Takeuchi et al., 2013	Case Series	21	57.1 (mean)	6.9 (mean)	74 (mean)	52%	3 (median)	Within 24 hours	17%	25% (GOS 4-5)	135 days
Decompressive Craniectomy WITHOUT clot evacuation											
Ramnarayan et al., 2009	Case Series	23	31-68	7 with GCS 3-8	More than 60 in 7	26%	unknown	unknown	13%	56% (GOS 5)	1 month
Fung et al., 2012	Case-Control	12	48 (median)	8 (median)	61 (median)	unknown	unknown	12 (median)	25%	75% (mRS 0-4)	6 months

GCS was not directly reported on admission, but 43 (59%) patients presented with a neurological exam of stupor to deep coma. Despite having a poor initial presentation, the long-term functional outcome was good in nearly half of the survivors and a statistically significant improvement in mortality was found in the DHC group. Murthy et al.[5] published a 12 patient cases series in which the majority of the patients (92%) survived to follow-up at 17 months, and good functional outcome was achieved in 55% of patients (mRS 0-3). Good functional outcome would have increased to 67% if it was defined as a mRS of 0-4. One methodological weakness in this study is possible selection bias as 92% of the patients had right hemisphere pathology.

A larger case series was published by Kim et al.[7] including 24 patients, 19 (79%) of whom had a GCS less than 8. Good functional outcome was defined as a GOS of 4-5 and was present in half the patients at 6 months. Most of the patients had poor neurological exams, but the authors did not provide enough information to determine the utility of DHC. Also, indications for surgery in this study (GCS <8) may have caused delays for patients that would have benefited from earlier decompression.

Ma et al.[6] performed a case-control study of 38 patients. Controls were patients who received a hematoma evacuation alone. In unadjusted analysis, there was a 32% mortality rate in the DHC group compared to 43% in the control group (p=0.26). There were significantly more patients with herniation, patients with intraventricular hemorrhage (IVH), and patients with a higher ICH score in the DHC group than the control group. The patients' ICH score, hematoma volumes, and admission GCS may have played a role in the higher mortality rates than other studies in our review. When adjusted for these variables, the odds ratio for 30-day mortality was 0.12 (95% CI 0.02-0.64, p=0.01), and an adjusted odds ratio for good outcome (GOS 3-5) of 23.23 (95% CI 2.13-252.86, p=0.01).

The most recent study was conducted by Takeuchi et al.[2] The median ICH score was 3, and all patients were taken for surgery within 24 hours of presentation. Patients had lower GCS scores, higher ICH volumes, and longer delay prior to surgery in comparison to other studies reviewed, which may explain the worse outcomes.

CONCLUSIONS

Bearing in mind the differences in methodology between all 7 studies, there was an overall combined mortality of 26%. It is fair to conclude that DHC done alone or combined with hematoma evacuation appears to be safe. Patients in both populations demonstrated that this surgical technique may reduce mortality, as well as improve functional outcome, especially in those who have large hematoma volume, low GCS score, and high ICH score.

We recommend that patients with refractory ICP elevation in the setting of ICH

Figure 2.

Authors	Study Design	Total Study Population	Age (years)	Clinical Presentation	Fisher Grade	Endovascular Coiling
Dorfer et al, 2010	Retrospective case-series	66	53 (mean)	HH 4-5 (67%), HH 1-3 (34%)	4 (71%), 3 (24%), 2 (5%)	20%
Buschmann et al, 2006	Retrospective case-series	12	50.1 (mean)	HH 4-5 (82%), HH 1-3 (18%)	4 (79%), 3 (18%), 2 (3%)	0%
D'Ambrosio et al, 2005	Retrospective case-control	12	54.1 (mean)	HH 4-5 (100%)	NA	0%
Schirmer et al, 2007	Retrospective case-series	16	48.8 (median)	HH 4-5 (69%), HH 1-3 (31%)	4 (69%), 2 (25%), 1 (6%)	50%
Guresir et al, 2009	Prospective observational cohort	43	51.0 (mean)	WFNS 4-5 (83.7%)	3 (100%)	21%
Smith et al, 2002	Retrospective case-series	8	56.5 (mean)	HH 4-5 (100%)	NA	0

should undergo DHC with or without hematoma evacuation depending on individual characteristics. Patients that seem to benefit the most are those with poor neurological exams and large hematoma volumes. If a decision is made to proceed with DHC, it should be performed in a timely manner as delay is associated with diminishing benefit.

DHC IN THE SETTING OF ANEURYSMAL SUBARACHNOID HEMORRHAGE

DHC has been performed for the management of refractory elevated ICP in patients suffering from aneurysmal subarachnoid hemorrhage (SAH). The current literature consists of single institution case series and a single case control study. Table 2 provides a summary of the key studies that have been published thus far. The largest study done by Dorfer et al.[10] stratified patients into 4 different groups for their retrospective analysis. Group 1 consisted of patients undergoing aneurysm clipping and DHC during the initial procedure (i.e., primary DHC). Group 2 consisted of patients undergoing DHC who had endovascular treatment of their ruptured aneurysm and developed intractable intracranial hypertension immediately or in a delayed fashion. Group 3 consisted of patients who had DHC done after initial clipping of aneurysm but in a delayed fashion. Group 4 consisted of patients in group 1 who required repeat surgery to enlarge the primary DHC. The authors found no significant difference in neurological outcome based on the group the patient was assigned. Interestingly, the authors did not find that timing of DHC influenced functional outcome. The main finding of their study was that etiology of intractable ICP influenced functional outcome. Patients undergoing DHC due to intractable ICP elevation secondary to a hematoma had improved functional outcome ($p=0.038$) compared to patients undergoing DHC due to cerebral edema secondary to ischemic infarction. The weakness of the study is the lack of a comparison group and its retrospective design.

In contrast, Buschmann et al.[11] also grouped patients based on indication for DHC and showed that timing of DHC could potentially be a factor affecting long-term functional outcome. Patients in group 1 had primary DHC; group 2 were patients who developed intractable ICP (>20 mmHg) and space occupying epidural, subdural, or intracerebral hematoma after aneurysm surgery (secondary DHC due to hematoma); group 3 consisted of patients who developed cerebral edema and intractable ICP without infarctions (secondary DHC without infarctions); and group 4 had elevated ICP and infarctions (secondary DHC with infarctions). Notably the majority of the patients in their study were in group 1 (55%). Patients who recovered with good functional outcome (GOS 4 and 5) were treated earlier by secondary DHC (within 3.6 ± 1.6 days after SAH) than those who died or survived with severe or moderate disability (GOS 1-3) who were treated later (within 5.9 ± 5.5 days [$p=0.12$]). Also in this study, the outcome of the patients differed according to the indication for DHC with 83.3% of patients in group 3 (secondary DHC without infarctions) having a good functional outcome.

	Outcome Assessment	Follow-up Duration	Timing of DHC after SAH	Good Outcome	Comments
	mRS	14.9-48.2 months	Varied according to indication	28% (mRS 0-3)	Subgroup of patients with DHC due to hematoma formation had improved outcome (P=0.038) compared to patients with DHC due to cerebral edema secondary to ischemic infarction
	GOS)	12 months	Varied according to indication	53% (GOS 4-5)	Subgroup of patients with DHC for treatment of cerebral edema without infarction had 83.3% good functional outcome
	mRS, GOS, EQ-5d	12 months	11.4 hours	33% (mRS 0-3)	Poor-grade aSAH patients with associated ICH and evidence of focal mass effect treated with DHC did not have improved quality of life compared to a similar group of patients treated conservatively.
	mRS	39-1175 days, median 450	2 days (median), 3.2 days (mean)	44% (mRS 0-3)	Early DHC was associated with better outcome: 6/8 patients (75%) had good mRS outcomes compared with 1/8 patients in whom the decompression was performed after 48 hours (p<0.01).
	mRS	6 months	7.7 hours (primary), 93.6 hours (secondary)	26% (mRS 0-3)	The outcome was comparable regardless of the underlying etiology leading to DHC being performed.
	mGOS	12 months	NA	62% (excellent/good)	Only included patients with MCA aneurysm associated with hematoma volume greater than 25 mL.

However, there were only 6 patients in this group. Overall, 53% of the patients had a good functional outcome (GOS 4-5) at 1 year which is impressive given that 82% of the patients presented with a Hunt and Hess grade IV-V SAH.

Nonetheless, the study by D'Ambrosio et al.[12] came to a different conclusion. In this study of poor-grade SAH patients presenting with focal ICH necessitating DHC, quality of life (QoL) was assessed in addition to functional outcome. Notably the patients all had Hunt and Hess grade IV-V SAH and clinical signs of brainstem compression. Patients who underwent DHC did not have improved QoL or functional outcome compared to a similar group of patients treated conservatively. A methodological weakness is that the control group used had smaller hematoma volume, less midline shift, and higher GCS. Furthermore, although the average time to hemicraniectomy for the group as a whole was only 11.4 ($\pm$4.3) hours, half the patients had DHC performed greater than 24 hours after onset of clinical signs of brainstem compression. However, the authors did not find a statistically significant difference comparing the early hemicraniectomy group to the control group. Given the small sample size, the subgroup analysis is not powered to detect a statistically significant difference. Despite the negative findings of this study, 33% of patients in the DHC group had a good functional outcome at one year.

A similar study was conducted by Smith et al.,[13] also in a population of poor-grade SAH patients presenting with a focal ICH (sylvian fissure hematoma greater than 25 mL ipsilateral to an MCA aneurysm). However, unlike the study done by D'Ambrosio et al.,[12] the patients in this study all had a prophylactic DHC which was planned from the outset of the aneurysm clipping operation. This earlier time frame for the performance of the DHC may explain the significantly different results which showed that 62% of the patients had good functional outcome at one year. Unfortunately the authors do not report on the actual timing of the DHC in relation to onset of SAH. In this study, DHC led to significant and sustained decrease in elevated ICP and the procedure added only 20-25 minutes to the original operation.

In contrast to the two previous studies, Schirmer et al.[14] evaluated patients presenting with SAH with small to no ICH. Notably, in this small study half of the patients had their aneurysm treated via endovascular coiling. This study also lends support to the idea that early DHC may be more beneficial than delayed DHC. The authors noted that DHC performed within the first 48 hours after SAH had a beneficial effect on outcome: 75% of the patients who underwent early DHC fared better at long-term follow-up (mRS 0-3) compared to 12.5% of patients in whom DHC was performed after 48 hours (p<0.01). The strength of this study is that herniated brain volume was assessed, however the authors do not describe in detail what is meant by maximal medical management which was an inclusion criteria.

Lastly, Guresir et al.[15] evaluated the outcome of patients undergoing primary or secondary DHC for management of refractory elevated ICH stratified according to the different underlying pathologies in order to determine predictors to help guide treatment. Patients were stratified as follows: group 1 (primary DHC) had

Figure 3. Decompressive Hemicraniectomy for Malignant Middle Cerebral Artery Infarct Randomized Controlled Trials

Authors	No. of Cases	Ages Represented	Hours to Surgery	Outcomes: Surgery versus Medical	
				Mortality	mRS
Vahedi, et al. 2007 DECIMAL	38	Criteria: <55 Range: 22-55 Mean: 43.4	Criteria: <24 Range: 7-43 Mean: 20.5	At 12 months: 25 vs. 78% ARR 52.8% in surgery arm **p<0.0001**	At 12 months: <3: 50 vs. 22% (p=0.10) <4: 75 vs 22% **(p=0.0029**)
Jüttler, et al. 2007 DESTINY	132	Criteria: 18-60 Range: 29-60 Mean: 44.6	Criteria: 12-36 Range and mean not reported	At 12 months: 18 vs. 53% **p=0.03**	At 12 months: <3: 47 vs. 27% (p=0.23) <4: 77 vs 33% **(p=0.01)**
Hofmiejer, et al. 2006 HAMLET	64	Criteria: 18-60 Range: 51-60 Mean: 48.7	Criteria: <96 Range: 29-50* Mean: 41*	At 12 months: 22 vs. 59% ARR 38% in surgery arm **p=0.002**	At 12 months: <3: groups equal (p=1.00) <4: 41 vs. 59% (p=0.13)
Zhao, et al. 2012	47	Criteria: 18-80 Range: 29-80 Median: 64	Criteria: <48 Range and mean not reported	At 12 months: 16.7 vs. 69.6% **p<0.001**	At 12 months: <3: 25 vs 8.7% (p=0.272) <4: 75 vs 13% **(p<0.001)**
Jüttler, et al. 20 DESTINY II	112	Criteria: >60 Range: 61-82 Median: 70	Criteria: <48 Range: 16-50 Median: 28	At 12 months: 43 vs 76% **p<0.001**	At 6 months: <4: 38 vs 18% **(p=0.04)**

*This was time to randomization; time to surgery is not reported.

craniectomy enlarged after aneurysm clipping in the presence of massive brain swelling, group 2 had craniectomy enlarged after aneurysm clipping in the presence of massive brain swelling with additional ICH, group 3 had intractable ICP without radiological signs of rebleeding or infarction, group 4 had intractable ICP with signs of infarction, and group 5 had intractable ICP with rebleeding. They found that the outcome was comparable regardless of the underlying etiology leading to DHC. The weakness of the study is the small number of patients in groups 1, 3, and 5.

One of the challenges particular to the management of patients with SAH is the development of delayed cerebral ischemia. In a patient afflicted by ICH associated with SAH, the timing of peak perihematomal edema formation coincides with the beginning of the development of vasospasm. Therefore a dilemma may occur in which deterioration in a patient's neurological exam is difficult to distinguish whether it is due to delayed cerebral ischemia, elevated ICP, or both. It is clear that DHC leads to effective and sustained ICP control thus helping to address this clinical dilemma. If a patient has significant improvement after DHC is performed, it can be inferred that the underlying pathophysiology was elevated ICP and not delayed cerebral ischemia. More importantly perhaps is that the treatment of elevated ICP and vasospasm use conflicting strategies. The use of hyperventilation and hyperosmolar therapy, for instance, could lead to increased vasoconstriction and dehydration respectively, both potentially worsening vasospasm. DHC in SAH patients allows the clinician to treat vasospasm effectively without concern for exacerbating elevated ICP from induced hypertension or hypervolemia.

Furthermore, patients with SAH may have various underlying etiologies leading to elevated ICP including ICH, infarction, rebleeding, and cerebral edema. Several studies[10,11,13] suggest that the underlying etiology leading to elevated ICP could play a role in determining the effectiveness of DHC. These studies suggest that performing DHC for intractable ICP in the setting of an ICH associated with SAH is beneficial. However, Guresir et al. [15] came to a different conclusion, that the underlying etiology is not relevant in determining the usefulness of DHC. Regardless of the etiology leading to intractable ICP, there is a final common pathway of decreased cerebral perfusion which can lead to ischemia and further cerebral edema. This vicious cycle can perhaps be halted by the timely performance of DHC. Therefore, these conflicting findings could possibly be accounted for by the differences in the timing of DHC depending on the indication and underlying pathology. Early DHC versus delayed DHC was associated with improved functional outcome in several of these studies.[11,13,14]

All of the studies reviewed found that DHC can be done safely in a population of poor-grade SAH patients. Most of the studies suffer from the weaknesses inherent to a retrospective observational study and a very small sample size. Clearly, there is a need for prospective studies with standardized treatment protocols and clear indications for DHC in SAH.

DHC IN THE SETTING OF MALIGNANT MIDDLE CEREBRAL ARTERY INFARCT

Malignant middle cerebral artery (MCA) infarct is described as a total or near total infarction of the MCA territory.[16] Due to the large area of ischemia, this injury is followed by massive amounts of cerebral edema,[17] peaking between days two and five.[18] This progressive edema leads to herniation, resulting in death in approximately 80% of patients, even with the use of maximum medical therapy.[16,19] Patients that survive are typically left severely disabled.

The guidelines by the American Heart Association acknowledge the lack of evidence for conservative medical management in the treatment of patients with elevated ICP following stroke.[18] There is poor evidence for the benefit of hyperventilation, corticosteroids, or osmotic diuretics in improving functional outcome. It is currently a Class I recommendation that patients should be monitored closely for increased ICP. Currently American Heart and American Stroke Associations' guidelines state osmotic therapy for patients with deterioration concerning for swelling is reasonable, but do not recommend hypothermia, barbiturates, or steroids given insufficient data. They also state a Class I recommendation for DHC in patients under the age of 60 within 48 hours.[20] The Neurocritical Care Society (NCS) has similar recommendations against steroids and barbiturates, but states hypothermia may be considered in patients who are not eligible for surgery. They share the recommendation for osmotic therapy. In regards to surgery, the NCS also recommends DHC within 24-48 hours, regardless of age. However, an additional recommendation is made that families of patients over 60 should consider the higher likelihood of severe disability.[21] Though these guidelines acknowledge the use of DHC to acutely decrease ICP and reduce secondary injury as potentially lifesaving, the resulting functional outcome remains unclear.

In recent years, there have been a number of randomized controlled trials comparing mortality and functional outcome between patients undergoing DHC and patients managed with maximum medical therapy. These studies have attempted to prove not just a mortality benefit of decompression, but also improvement in functional outcome. Table 3 provides a summary of the key studies that have been published thus far.

HAMLET, DECIMAL, and DESTINY are three European trials that were published within two years of each other, and represented the first set of randomized controlled trials to compare DHC with standard medical therapy.

Jüttler et al.[22] (DESTINY) published a trial evaluating 32 patients ranging in ages from 18 to 60 with symptom onset less than 36 hours prior to randomization and used a primary outcome of a modified Rankin Scale (mRS) score 0 to 3 versus 4 to 6. The study was based on a sequential design, first evaluating 30-day mortality, and the study discontinued enrollment after 32 patients had undergone randomization and the mortality endpoint was reached. The conservative therapy group had a higher median National Institutes of Heath Stroke Scale (NIHSS) of 24 when compared to the DHC group whose median NIHSS was 21. Survival was significantly higher in the surgical group compared to the conservative therapy group at 12 months. DESTINY was limited by its small patient size, in part because the trial was terminated early given the immense survival benefit of the procedure, and in light of the simultaneously conducted trials that will be discussed below. Though the article failed to reach its primary outcome, survival benefit was decisively shown.

Vahedi et al.[23] (DECIMAL) studied 38 patients aged 18-55 years who were randomized within 24 hours of symptom onset. Patients randomized to DCH were required to undergo the procedure within 6 hours of randomization, at most 30 hours after symptom onset. Similar to DESTINY, the primary outcome was a favorable functional outcome (mRS $\leq$3) at 6 months. Under the guidance of the data safety monitoring committee, enrollment was suspended early at 38 patients (18 medical, 20 surgical) due to slow patient enrollment and the intention of DECIMAL, DESTINY, and HAMLET to pool data and publish together. Again, the primary outcome of mRS $\leq$3 did not reach statistical significance.

The third European randomized controlled trial (HAMLET) was conducted by Hofmeijer et al.[24] This study reported on 64 patients randomized equally between surgical and medical management. One notable difference about HAMLET is that this study randomized patients up to 4 days after initial symptom onset. The primary outcome was mRS at 1 year, with a good outcome defined as 0-3 and poor outcome of 4-6. Recruitment was stopped under the advisement of the data monitoring committee after 64 patients were enrolled because it was thought to be very unlikely that the primary outcome measure would produce a statistically significant difference. Like DECIMAL and DESTINY, HAMLET did not show a statistically significant difference between an mRS of 0 to 3 versus 4 to 6. HAMLET, unlike DESTINY and DECIMAL did not show a significant difference when outcome was dichotomized for mRS $\leq$ 4 (p=0.13).

With DESTINY, DECIMAL, and HAMLET recruiting patients simultaneously, authors from each of these studies contributed data to an article by Vahedi et al.[25] This article pooled the data of the first three European trials to include patients randomized within 48 hours of symptoms onset. The article reported the data of 93 patients 18 to 60 years old. All of the patients from DESTINY and DECIMAL were included; 23 HAMLET patients were included. Overall, 51 patients received decompressive surgery, while 42 received conservative therapy. Like each of the individual studies, there was a significant benefit for mRS >4 cutoff and mortality at 1 year. Additionally, with the pooled data, there was a statistically significant difference between the groups for an mRS >3 at 12 months (medical patients 79%, surgical patients 57%, p=0.014). This study also reported that the likelihood of ending up with an mRS of 4 was 10 times greater after surgery than after standard medical therapy, but the risk of ending up with an mRS of 5 was not increased.

Studies then began to consider the benefits of this procedure in an older population. Zhao et al.[26] had a similar study design to the European trials, but allowed patients to enroll up to 80 years of age. In patients older than 60, risk of death was also significantly lower at 1 year. There was no statistical difference between the groups for an mRS >3. However, in the older subgroup, there was still a statistically significant difference when dichotomizing the groups to an mRS >4, similar to the results with a younger patient population.

The DESTINY group conducted a second randomized controlled trial further evaluating the effect of DCH on older patients.[27,28] Unlike the pooled analysis of the European trials, the older patient

population was not able to achieve statistical significance when the data was dichotomized to an mRS of 0 to 3 versus 4 to 6. DESTINY II showed a survival benefit and functional benefit with data dichotomized to an mRS of ≤ 4, though the treatment effect was diminished in the older population.

Frank et al. published HEADDFIRST,[29] which randomized 26 patients within 96 hours after symptom onset. At 6 months, the DHC group had a mortality rate of 36% and 40% in the medical group which was not consistent with the previous trials. However, the randomization for HeADDFIRST required more mass effect and allowed greater delay to randomization, which the authors speculated could have led to worse outcomes. Small enrollment numbers were another methodological limitation in this study.

This discussion focuses on the major randomized controlled trials evaluating DHC in the management of malignant MCA infarction. Mortality benefit is significant in all studies but HeADDFIRST. However, the question of benefit in terms of functional outcome is less clear. Though the pooled European trials were able to show a benefit of surgery with an mRS of 0-3 compared to 4-6, it also showed the increased risk of having an mRS of 4. Whether this represents an acceptable outcome is a matter of debate and must be individualized for the patient. Even physicians have not come to a consensus as to the definition of an acceptable outcome (Neugebauer et al.), though Kiphuth et al. did find that most patients or their families would still retrospectively consent following decompression.[30,31] These benefits were not reproducible using an older population, though mortality benefit and benefit with data dichotomized with an mRS ≤ 4 remained significant. More data regarding quality of life and depression following DHC for malignant MCA stroke would be helpful in determining the utility of this life-saving procedure.

DHC IN THE SETTING OF TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is an extremely prevalent problem in the United States. Approximately 2 million people each year sustain TBI, many of whom can be treated and released from emergency departments. However, for the nearly 300,000 patients hospitalized each year, those with severe disease can have devastating outcomes, leading to thousands of deaths and patients with permanent disability.[32] The reported overall mortality with medical management varies widely throughout the literature, but ranges approximately 30-40%.[33]

Evaluation of hemicraniectomy in nonpenetrating diffuse TBI represents a more difficult analysis than surgery following malignant MCA infarct. The initial injury prompting evaluation for surgery has more variability. The decompressions themselves can be pursued for different purposes, aiming to treat primary damage caused by lesions causing mass effect or secondary damage caused by elevated intracranial pressure.[34,35]

Additionally, the preferred surgical approach and timing[35] of the surgery is still unclear. The pivotal study DECRA used a bifrontal approach to their craniectomy.[36,37] Other studies used a bilateral hemicraniectomy approach.[38] Both of these approaches fall outside of the scope of this review. The literature available is therefore limited due to the variability of the initial injury as well as the surgical approach employed.

To our knowledge, there have only been two published randomized controlled trials evaluating decompressive craniectomy in traumatic brain injury compared to maximum medical management: DECRA evaluated a bifrontal approach and yielded disappointing results,[36] and a small study evaluating decompression in children showed a possible benefit.[39] A third randomized controlled trial, RescueICP, has yet to be published and will evaluate bifrontal and unilateral hemicraniectomies.[40] With so few randomized controlled trials, the optimal surgical approach remains controversial for TBI.

Current guidelines for controlling ICP in TBI remain focused on conservative management as first line therapies: elevation of the head of the bed, pain control, sedation, ventriculostomy. When this fails to acutely manage ICP, barbiturate, hypothermia and hyperosmolar therapies have been used.[41] Outcomes of patients with severe TBI managed with maximum medical therapy vary in the literature, but frequently show a mortality rate of around 40%, and rates of good outcome (Glasgow Outcome Score 4-5) of 40%.[42] DHC is considered when these therapies fail and ICP remains elevated. DHC can rapidly decrease ICP, however, the clinical significance and outcome benefit remains unclear.[41]

Wen et al.[35] compared early versus late DHC, defining early DHC as within 24 hours of injury in 44 TBI patients. Both groups had a 6 month mortality rate of approximately 20%. However, 52% in the early DHC group achieved a GOS of 4-5, compared to 63% in the late group, which did not reach statistical significance. Though the groups were similar, the early group had more significant midline shift. It is possible that the treatment effect is too small to be detected with such a small sample size.

Aside from the study of early versus late DHC in patients with TBI, there is controversy regarding whether decompression with or without evacuation of a mass lesion is more efficacious. Yuan et al.[43] studied this question by examining 164 patients, 93 of whom underwent decompression with evacuation of a mass lesion at least 25mL and 71 who were decompressed without evacuation of a mass lesion. About 15% more patients from the mass lesion group underwent surgery within 24 hours (72% mass lesion, 58% diffuse edema). The mortality rate was 22% at 60 days and favored the mass lesion group (14% mass lesion, 32% diffuse edema, p=0.014). Overall rate of good outcome was about 42% without a statistically significance difference between the two groups.

Aarabi et al.[44] performed a similar retrospective cohort study to evaluate 50 patients with severe closed TBI, but excluded patients who had DHC with evacuation of a mass lesion. Ten patients went to surgery within the first 24 hours (9 immediately, 1 secondary to clinical worsening). The remaining 40 patients underwent DHC after 24 hours. Overall mortality was 28%, and 51% of the patients had a good outcome with GOS 4-5 at 30 days. The remaining patients were left vegetative or severely disabled.

Qiu et al.[45] evaluated 74 patients with brain swelling after severe TBI and randomized patients to undergo a traditional DHC (bone window diameter 15cm) compared to the control group which underwent a unilateral temporoparietal craniectomy (bone window diameter 8cm). Thirty-seven patients underwent a DHC, and 57% of these patients had a GOS of 4-5 at 6 months. Additionally, 27% of the patients died, and the remaining were vegetative or severely disabled. The control group had a 57% mortality rate with only 33% achieving a good outcome. Jiang et al.[46] conducted a similar study which included 486 patients. The results were similar favoring the group who underwent a traditional DHC versus a subtotal DHC.

Some of the most relevant data is from Chibbaro et al.[47] This prospective study of 147 patients evaluated DHC following TBI. Of these patients, 67% had a GOS 4-5 at a mean follow up of 26 months. GOS was 2-3 in 19% of patients, and mortality rate was just 14%. Subgroup analysis was performed to determine factors associated with improved outcome. Good outcomes were significantly associated with age less than 50 ($p<0.0001$) and operation within 9 hours of trauma ($p<0.03$).

Throughout the literature, good outcome rates vary from 30-50% in the DHC group, with a mortality rate approximately 20%.[48,49] DHC remains a controversial option in the management of patients following TBI. The surgery may decrease mortality, and it appears, similar to other studies evaluating DHC for other indications, that timing plays a significant role. However, studies in the form of randomized controlled trials comparing DHC to maximal medical management are needed. Unfortunately, there remain a number of barriers to studies of this kind. The heterogeneity of TBI patients will be a constant challenge. Mechanism of injury, the presence or absence of a mass lesion, and the possible presence of other injury remain challenges for patient randomization and data interpretation. Additionally, researchers continue to disagree about the surgery's timing (early versus late), use for mass lesions versus diffuse edema, and even the preferred surgical approach.

CONCLUSIONS

In this review, we describe the current evidence regarding the utility of DHC for the management of elevated ICP due to malignant MCA stroke, ICH, TBI, and SAH. All of these disease processes share a common pathophysiologic endpoint of elevated ICP that can be refractory to maximal medical therapy and lead to herniation syndromes. It appears that DHC can be safely performed with minimal risk in these critically ill patients. Furthermore, it appears that the earlier DHC is performed the greater the potential benefit. While DHC may be a life-saving procedure, the patients are nevertheless often left significantly impaired. Therefore, it is imperative to discuss the potential outcomes that are possible with the patient or surrogate decision maker. The issue of prognostication of outcome in severe brain injury is beyond the scope of this paper, but it is clear that in all of the disease processes reviewed that a potential exists for a good functional recovery. Therefore, DHC should be part of the armamentarium in the management of elevated ICP in the conditions discussed. Ultimately, the decision to pursue DHC should be individualized taking into consideration the patient's values and goals of care.

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Early Ambulation in Patients with External Ventricular Drains: Results of a Quality Improvement Project

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Key Words

External ventricular drain, EVD, ambulation, mobilization, early ambulation

Introduction

Prolonged immobility in ICU patients can lead to muscle wasting and weakness, longer hospital stays, increased number of days in restraints and hospital acquired infections. Increasing evidence demonstrates the safety and feasibility of early mobilization in the ICU. However, there is a lack of evidence in the safety and feasibility of mobilizing patients with external ventricular drains (EVD). The purpose of this study was to determine the safety and feasibility of early mobility in this patient population.

Methods

We conducted a prospective, observational study. All patients in the study were managed with standard protocols and procedures practiced in our ICU including early mobility. Patients with an EVD that received early mobilization were awake and following commands, had a Lindegaard ratio <3.0 or middle cerebral artery (MCA) mean flow velocity<120 cm/sec, a MAP>80 mm Hg, and an ICP consistently <20 mm Hg. Data was collected by physical therapists at the time of encounter.

Results

90 patients with a total of 185 patient encounters were recorded over a 12-month period. The average time between EVD placement and PT session was 8.3±5.5 days. In 149 encounters (81%), patients were at least standing or better. Patients were walking with assistance or better in 99 encounters (54%). There were four adverse events recorded (2.2%) during the entire study.

Conclusion

This observational study suggests that PT is feasible in patients with EVDs and can be safely tolerated. Further research in a larger patient population conducted prospectively is warranted to assess the potential benefit of early mobility in this patient population.

INTRODUCTION

Prolonged immobility in the intensive care unit (ICU) patients can lead to a myriad of complications. From loss of muscle mass and strength[1] which may contribute to ICU-acquired weakness[2, 3] to a quality of life that remains lower than that of the general population after long-term follow-up,[4] ICU survivors suffer the consequences of physical inactivity during their stay. Increasing evidence demonstrates the safety and feasibility of early mobilization in the ICU.[5] Specifically in the neurointensive care unit (NICU), these positive outcomes included decreased length of stay, number of patient days in restraints, number of hospital-acquired infections, and a clinically significant reduction in unit catheter-related urinary tract infection (UTI) rate.[6]

Increasing evidence however supports not only the benefits but also the safety of early mobilization in the NICU.[6,7] Moreover, it has been shown that mechanically ventilated patients[7] and patients with femoral catheters[8] can be safely mobilized. There was no set protocol in place for moving these patients, nor any parameters to monitor. Upon review of the literature within physical medicine and rehabilitation, neurocritical care, and physical therapy, we found very few dedicated studies investigating mobility in patients with EVDs. Interestingly, amongst Canadian physiotherapists, those with relatively less experience were more reluctant to mobilize patients with external ventricular drains (EVD) compared to those with over 10 years of experience[9]. This increased reluctance has been attributed to less experienced physiotherapists being more likely to consult existing literature and rely on external sources of information such as the Guide to Physical Therapist Practice.[9, 10] At our institution, all patients who would be able to tolerate physical therapy are routinely evaluated and mobilized if possible, including those with EVDs. These patients are consistently mobilized by therapists with only a few years' experience, questioning the above mentioned study. Given the lack of published literature and our routine practice of mobilizing this patient population, we wanted to implement a formal protocol as a measure of a quality improvement study.

METHODS

We conducted a prospective, case series study as part of a quality improvement project. The study was approved by the Institutional Review Board of Thomas Jefferson University Hospital (IRB# 14D.424). From June 1, 2014 until July 31, 2015, a total of 90 patients with 185 patient encounters that had EVDs occurred. All patients in the study were

Figure 1. Safety Checklist and Data Collection Form

Thomas Jefferson University Hospital

Safety and Feasibility of Early Ambulation in Patients with External Ventricular Drains: An Observational Study

Safety Checklist: Please ask nursing staff prior to initialization of PT

1. Is the EVD closed?
2. Have the ICPs been well controlled?
3. Is the EVD secure enough for the patient to be mobilized?

MRN	DOB	Date of Admit/ Date of EVD Placement	Diagnosis	Date of Activity	Activity Code	Adverse Event?	Years of Primary Experience

Activity Code:

0: nothing (lying in bed)
1: Transferring bed to chair without standing
2: Sitting in bed/exercises in bed
3: Tilt table/tilt bed
4: Sitting at edge of bed
5: Standing
6: Transferring bed to chair with standing
7: Marching in place
8: Walking with assistance of 2 or more people
9: Walking with assistance of 1 person
10: Walking with gait aid and no assistance
11: Walking without gait aid and no assistance

managed with standard protocols and procedures practiced in our NICU. EVDs are placed by neurological surgery residents using standard freehand pass technique with surface landmarks. It is then tunneled through the skin through a separate incision and secured by sutures. At our institution, we follow guideline based therapies for acute ischemic stroke (AIS), intracerebral hemorrhage (ICH) and subarachnoid patients (SAH).[11-13] All patients are initially on bedrest on admission day, and then evaluated for physical therapy the next day. To be evaluated for physical therapy, the patient had to be able to ambulate. Our protocol for SAH patients who were deemed eligible for physical therapy were similar to a recently published study by Olkowski et al.[14] Patients with SAH were deemed eligible for early mobilization if they were awake and following commands, had a Lindegaard ratio <3.0 or middle cerebral artery(MCA) mean flow velocity <120 cm/sec, a MAP>80 mm Hg, and an intracranial pressure (ICP) consistently <20 mm Hg. For patients with ICH, a

Table 1. Age, admitting diagnosis and types of therapies tolerated. SD – Standard Deviation.

		Percent of Total
Age, X (SD)	56 (14)	
Female	49	54
Male	42	46
Admitting GCS, median (IQR)	11 (8-15)	
GCS on Ambulation, median (IQR)	15 (14-15)	
Admitting Diagnoses		
Subarachnoid Hemorrhage	45	50
Hunt Hess Grade, median (IQR)	3 (3-4)	
Modified Fisher, median (IQR)	4 (3-4)	
Intracerebral Hemorrhage	23	26
ICH Score, median (IQR)	2 (1-2)	
Tumor	12	13
Ischemic Strokes	3	3
NIHSS on Admission, median (IQR)	12 (9-21)	
Chronic Hydrocephalus	6	7
Trauma	1	1
Total Patients	**90**	
Type of Therapy Tolerated		
Walking without any Assistance	10	5.4
Walking with Gait Aid and No Assistance	5	2.7
Walking with Assistance of 1 Person	65	35.1
Walking with Assistance of 2 People	19	10.3
Marching in Place	7	3.8
Transferring Bed to Chair with Standing	31	16.8
Standing	12	6.5
Sitting at Edge of Bed	18	9.8
Sitting in Bed/Exercise in Bed	5	2.7
Transferring Bed to Chair	6	3.2
Passive Range of Motion in bed	7	3.8
Total Encounters	**185**	

follow-up computed tomography (CT) scan is obtained 24 hours after the initial bleed at our institution. This is done to determine stability of the hemorrhage in order to begin subcutaneous heparin for deep vein thrombosis prophylaxis. If the repeat CT scan was stable and ICPs were consistently <20 mm Hg, the patient was also then deemed eligible for early mobilization. Patients with AIS, traumatic brain injury, tumors or chronic hydrocephalus were deemed appropriate if the ICPs were consistently <20 mm Hg. All patients that met these criteria were then entered in our study. Patients were excluded if they were delirious using the CAM-ICU score. Intubated patients were also excluded as our patient population is exclusively neurologically injured patients. Patients in our unit who are mechanically ventilated, for the most part have a poor Glasgow Coma Scale (GCS) rather than have a primary lung injury. For this study, we thought it prudent to evaluate patients who were not mechanically ventilated first and then add this patient population to further projects.

The protocol implemented included an initial assessment by the physician on service to determine readiness to participate in physical therapy. If deemed appropriate, physical therapy (PT) and occupational therapy (OT) consult were requested. Therapy was then initiated after the nurse clamped the EVD and if the ICPs were less than 20 mm Hg for greater than 30 min.

Physical therapists completed a sheet as they performed their assessments. The date of admission and EVD placement, type of activity, years of experience of the primary therapist, and the number of people mobilized in a day were recorded. Activity codes utilized were based on forms obtained from Dale Needham at Johns Hopkins University with his permission. Physical therapists were also instructed to record changes in vital signs, arrhythmia, changes in ICPs, and/or dislodging lines. All adverse events were recorded. If an adverse event occurred during a therapy session, the session was immediately stopped and the attending physician was notified.

A preplanned interim analysis was conducted to review adverse events after a 6-month data collection period. Investigators discussed the adverse events that occurred and then created a questionnaire to be filled out by the therapy team before each mobilization session in order to prevent further adverse events. The patients must have an EVD that was clamped, ICPs that are well controlled and an EVD that is well secured. Protocol was adjusted so that the physical therapists would have to answer yes to all questions before any initiation of therapy. The resulting questionnaire is shown in Figure 1.

RESULTS

Ninety patients with a total of 185 patient encounters were recorded over a 12-month period. Table 1 summarizes the admitting diagnoses and types of therapy tolerated by the patients. The mean age was 56±14 years old. The average time between EVD placement and PT session for patients with SAH was 7.7±4.5 days. ICH and tumor patients were seen on day 6.6±3.1 days and 8.1±5.8 days. Subarachnoid hemorrhage patients had a median Hunt Hess Grade of 3 and a modified Fisher grading scale of 4. Intracerebral hemorrhage patients had an ICH score of 2.

A priori, we determined adverse events to be any event that caused an abrupt termination of therapy. Four adverse events were recorded (2.2%) during the entire study. Prior to the interim analysis, there were two adverse events in 132 patient encounters. The first event was an increase in ICP after patient went from supine to sitting position. The second event was dislodgement of the EVD while walking the patient. At the interim analysis both cases were reviewed in detail and an adjustment to the protocol was made as discussed above. Post interim analysis, there were two events. The first event was patient emesis after rolling the patient in bed. The second event was an increase in ICP. No changes in neurological exam were recorded during any of the four adverse events. Although not directly part of this study, we did not see any secondary complications of SAH such as vasospasm or DCI as a consequence of mobilizing this patient population.

To determine the feasibility of mobilizing these patients, we determined what type of therapy was tolerated by the patients. In 149 encounters (81%), patients were at least standing or better. Patients were walking with assistance or better in 99 encounters (54%). Only 3.8% of patients had passive range of motion in the bed.

DISCUSSION

After implementation of the new safety checklist, there were no further EVD dislodgements. We attribute this to the question in the checklist that questions whether the EVD is secure enough to have the patient manipulated. As with any drain or line, the longer it stays in the patient the greater the chance for dislodgement. During the preplanned interim analysis, it was discovered that the dislodged EVD was in fact not securely in place before the PT session.

We routinely drain EVDs when ICPs are greater than 20 mm Hg. Both ICP events were increases in ICP no higher than 22 mm Hg. After prompt cerebrospinal fluid (CSF) drainage, the ICPs returned to normal. Although the checklist does ask whether the ICPs have been controlled, ICPs in general can fluctuate at any given time. Moreover, our patients only have limited mobility until they are seen by the physical therapy team. This encounter may be the first instance in which the patient's ICP compliance is truly tested.

Our average day until PT initiation was longer than what was recently reported by Olkowski, 2.3 days versus 7.7 for SAH patients.[14] We attribute this to our patient population having higher grade SAH. Also all of our patients have EVD placed, while Olkowski included patients without EVD as well. Patients that require EVD placement require longer time for their mental status to improve.

Increasing evidence supports not only the benefits but also the safety of early mobilization in the NICU. In a study investigating early mobilization in aneurysmal subarachnoid hemorrhage patients, 32% of patients had external ventricular drains placed. In this group, only 5.9% of early mobilization program sessions had an adverse event and such a program was concluded to be safe and feasible[14]. Adverse events were a MAP <70 mm Hg or >120 mm Hg, or heart rate >130 bpm. Very early mobilization of stroke patients within 24 hours of stroke onset resulted in patients returning to independent walking sooner and remaining more independent in motor function at 12 months[15]. Bimmouille et al. demonstrated that patients with normal and elevated ICP could perform most exercises with physical therapy without changes in ICP, with the exclusion of hip flexion[16]. Titsworth et al[6] reported there was no significant difference in the total number of falls, fall rate per 1000 patient days, or critical line pull rate before and after a comprehensive mobility initiative.

While clear recommendations cannot be inferred from this study, our study does show that early mobilization in patients with EVDs can be safely performed. Only 2.2% of encounters had significant events and none of these events caused significant harm to the patient. Although a dislodgement of an EVD may cause immediate harm, our patient was able to tolerate the removal without any change in neurological exam.

Our study has several limitations. This is a not a randomized trial and thus we can only report association and not causation. Secondly, there is bias to our data collection as we only included patients that had PT orders placed in our electronic medical record system. There may have been potential participants who were missed. Moreover, patients in whom the primary team decided not to order PT consult due to these patients being deemed unable to tolerate PT, need to be considered. Lastly, this study is done at a single center institution that has access to a team of physical therapists, occupational therapists and physiatrists which may not be feasible for all hospitals.

The results of this quality improvement study allowed us to implement a protocol for early mobilization in patients with EVDs and make adjustments to the protocol as needed. With the institution of a standard protocol for mobilizing these patients, along with a safety checklist, we had few adverse events. With this preliminary data, a randomized controlled trial that examines the safety and feasibility is warranted in this patient population. A larger randomized controlled trial would also be better to evaluate if early ambulation decreases delirium, length of stay, or improves outcomes in patients with EVDs.

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Management of Severe TBI – A Review of Recent Literature

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INTRODUCTION

Traumatic Brain Injury (TBI) is the result of sudden trauma causing damage to the brain. TBI can occur when the head strongly and abruptly changes direction or contacts an object, or when an object penetrates the skull and brain tissue. (Figure 1 – TBI). CDC estimated that in 2010, TBI, alone and in conjunction with other injuries, accounted for approximately 2.5 million ED visits, hospitalizations, and deaths in the United States. Children aged 0–4 years, adolescents aged 15–19 years, and, most significantly, adults aged 75 years and older are the most likely to sustain a TBI and seek medical care[1]. The leading cause of non-fatal TBI in the U.S. is falls and the leading cause of TBI-related fatalities is motor vehicle accidents[2].

As a heterogeneous condition, TBI is conventionally categorized as mild, moderate, or severe. The most useful classification system is the Glasgow Coma Scale (GCS) which is based on level of consciousness as assessed by eye, motor, and verbal performance. A GCS score of 13 to 15 classifies a mild TBI, 9 to 12 a moderate TBI, and a score of 3 to 8 defines a severe TBI (sTBI). Each year, the direct and indirect medical cost of TBI is nearly $76.5 billion, with 90% directed at severe TBI[3].

Although little can be done to reverse the initial, or primary, brain injury caused by trauma, care is directed at stabilizing the patient and preventing further, or secondary, brain injury. Concerns of delayed non-mechanical damage include swelling, inadequate oxygenation, lack of autoregulation, and metabolic dysfunction. Elevated intracranial pressure (ICP), often the result of increasing mass effect from hematomas and contusions, diffuse cerebral edema, or hydrocephalus, is an important promoter of secondary brain injury and is associated with worse neurological outcomes in patients after TBI. Consequently, medical and surgical efforts attempt to normalize ICP in order to maintain cerebral blood flow and prevent parenchymal death. (Figure 2 and 3– ICPmonitor1 and 2). In the past 5 years, three landmark trials have explored the beneficence of three individual techniques for mitigating secondary brain injury associated with intracranial hypertension. Although the following investigations do not isolate and then evaluate ICP treatment, they do smear the guidelines of practice for approach and management of sTBI.

DISCUSSION

BEST TRIP: A call for greater investigation into the efficacy of ICP Monitoring

For decades, ICP monitoring has been considered the gold standard for steering treatment in patients with sTBI. Despite guidelines, there is a great deal of variation in its use and patients may undergo ICP modification without the use of a monitor. (Figure 4 – ICP monitor 3). Only recently has the efficacy of direct monitoring on outcome improvement been explored by more than observational and nonrandomized studies. The Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST TRIP) trial was a multicenter, prospective RCT that enrolled 324 sTBI patients 13 years of age or older from four ICU's in Bolivia and Ecuador. Participants were randomized to one of two management strategies determined either by ICP monitoring maintaining ≤20mmHg or by clinical examination and serial computed tomography (CT) imaging[4]. The overall composite outcome was calculated as the average of percentiles from 21 measures, including survival time, duration and level of impaired consciousness, functional status at 3 and 6 months, and cognitive status at 6 months, with lower percentiles representing worse outcome. This five-year investigation demonstrated no statistical difference in overall outcome between the two groups (56% composite for pressure monitoring group vs. 53% composite for imaging-clinical exam group; p = 0.49). Six-month mortality, median length of stay in the ICU, and distribution of serious adverse events were also not significantly different.[5] These results suggest that clinical findings and imaging are sufficient for practitioners to determine a treatment regimen.

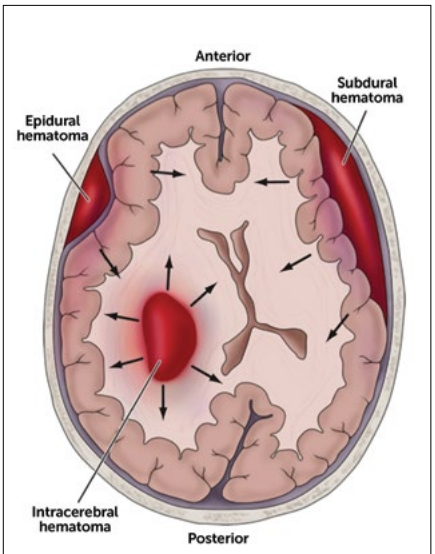

Figure 1.
TBI

However, the ability to generalize these findings and extend them to practice in developed countries is questionable. BEST TRIP was conducted in Bolivia and Ecuador; prehospital care is not as advanced as in higher income countries and rehabilitation is essentially non-existent. Severely injured patients in the sampled nations do not survive long enough to reach a care facility; consequently, sTBI cases represented in this trial are likely less severe than those seen in the U.S.[6] ICP monitoring may in fact assist in approaching treatment of more severe patients and this study could not include that population. Elderly patients, the largest contributors to sTBI care in the U.S., were also missed. Accurate information on prehospital interventions or early secondary insults such as hypothermia and hypoxia were not recorded or assessed in both transfer patients and trauma patients[7].

It is important to note that the BEST TRIP study did not intend to question the value of knowing the ICP and actively managing brain edema. What this trial did reveal was that our understanding of ICP manipulation is oversimplified and does not produce improved recovery in a general sTBI population[8]. For instance, a universal threshold of 20mmHg was used as recommended; in light of the study's findings, monitoring may be productive if this number could be personalized beyond the current standardized value. Overall, the strongest clinical implication stemming from the BEST TRIP trail is the need to refine the role of ICP monitoring in sTBI management, determining when it is efficacious and how to guide therapy based on its findings.

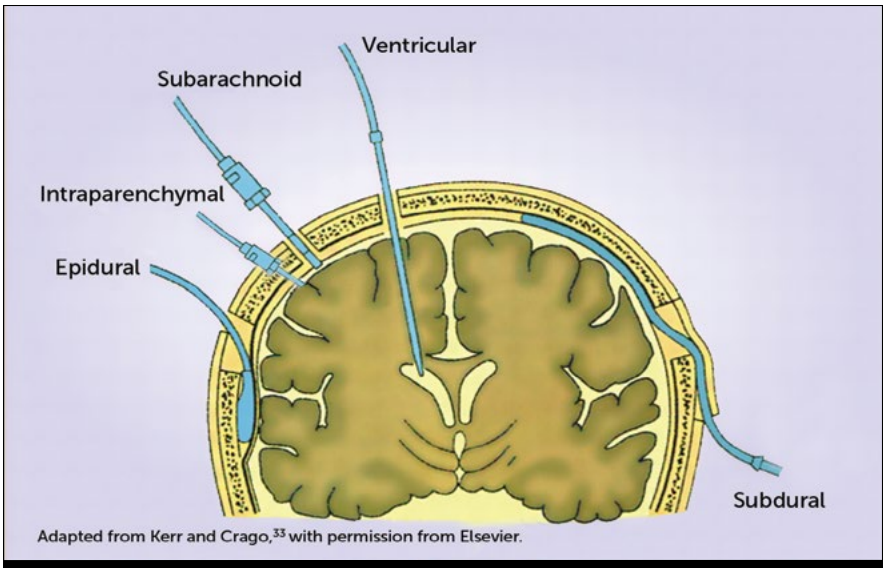

Figure 2.
ICP monitor 1

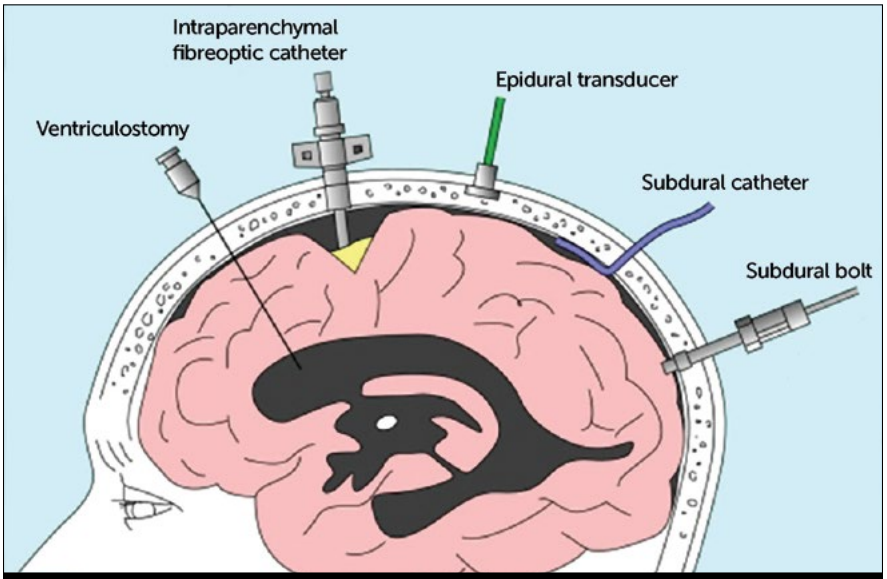

Figure 3.
ICP monitor 2

DECRA: Questioning the putative benefits of decompressive craniectomy

When patients with severe head injury have raised ICP that is refractory to first-tier therapies such as hyperosmolar infusions, surgical decompressive craniectomy (DC) is recommended. This procedure has been increasingly performed in the last 15 years and only recently has a randomized control trial taken place to explore its efficacy. The Decompressive Craniectomy (DECRA) Trial was conducted over eight years in fifteen ICUs in Australia, New Zealand, and Saudi Arabia to evaluate the impact of this optional approach on clinical outcome. Investigators assigned 155 adults between 15 and 59 years of age with severe diffuse TBI and refractory intracranial hypertension to receive either bifrontotemporoparietal decompressive craniotomy with standard care or standard care alone. The clinical outcomes were measured 6 months after injury using the Extended Glasgow Outcome Scale (GOS-E). Although the surgical group did demonstrate a significant decrease in ICP, fewer interventions,

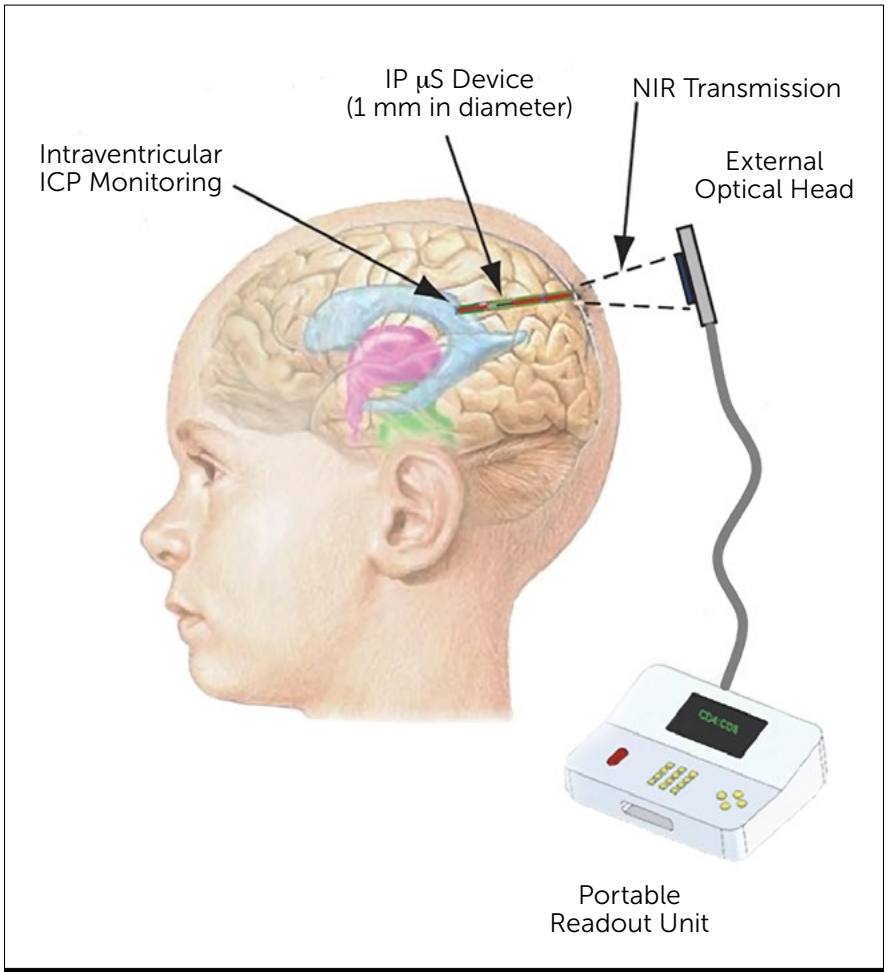

Figure 4.
ICP monitor

and a reduced length of stay, clinical outcomes were worse in the surgical group versus the standard-care group (70% versus 51%; p=0.02)[9]. The authors speculate axonal stretch, alterations in cerebral blood flow and metabolism, or complications of a bilateral approach as potentially relevant to these unexpected findings.

There are once again concerns of applicability raised by this study. Investigators enrolled only 155 patients despite the screening of 3478 patients, suggesting that the results are limited to a specific subpopulation. Further, the aggressive approach of a DC is typically not considered in patients with the guideline-based, standardized parameters used in this trial: ICP above 20mmHg for over 15 minutes despite medical therapy. Decompressive craniectomy is used as a last resort and DECRA may have included patients that are not typical candidates. There were also two exclusion criteria that may serve as points of contention: patients needing a unilateral DC and patients with previous evacuation of a mass lesion; in a multicenter study of 729 patients, it was found that about one third of patients receiving removal of an intracranial hematoma also required a typically unilateral decompressive craniectomy[10]. An important patient type was neglected from this evaluation.

Regardless of potential limitations, the DECRA study offered convincing support that early neuro-protective bifrontal DC is not superior to medical management for patients with severe diffuse TBI. Two more trials are currently underway – RESCUE-ASDH – and RESCUEicp – evaluating the efficacy of primary and secondary DC, respectively, and the parameters outlined seem more accurate and applicable[11]. In light of the currently available findings and the potential complications associated with DC, use of DC for patients with severe diffuse TBI should continue to remain highly selective.

Eurotherm3235: An unexpected response to therapeutic hypothermia

Elevated body temperature following brain trauma is associated with increased cytokine release and worsening of outcome. Given this as well as the neuro-protective effect of induced hypothermia after global brain ischemia caused by cardiac arrest, neonatal asphyxia, or drowning in cold water, hypothermia has become routinely used in some ICUs to treat elevated ICP in patients with TBI. However, its effect on outcome in this context has limited evaluation. The European Study of Therapeutic Hypothermia (32–35°C) for Intracranial Pressure Reduction after Traumatic Brain Injury (Eurotherm3235) randomized 387 patients at 47 centers in 18 countries to receive standard care or standard care plus therapeutic hypothermia. Temperature was adjusted to maintain ICP at or below 20mmHg, and treatment continued for at least 48 hours as needed. The primary outcome measure was the score on the Extended Glasgow Outcome Scale (GOS-E) at 6 months after injury. GOS-E score of 5 to 8, indicating moderate disability or good recovery, occurred less often in the hypothermia group than in the control group (25.7% vs. 36.5%; P=0.03)[12]. The occurrence of serious adverse events and mortality also favored the control group. Importantly, hypothermia-induced reduction of ICP had a similar efficacy as standard medical protocols.

The study's findings are implying a contraindication of active hypothermia in ICP management. However, there are important considerations raised by study critics. The Eurotherm3235 trial was terminated early due to safety concerns. Additionally, a lack of blinding

to the intervention, problematic in any trial involving therapeutic hypothermia, may have introduced bias[13]. Participants receiving hypothermia treatment may have more often reported serious adverse events, while control group participants expected these results. In regards to study design, investigators used an intracranial pressure of 20 mm Hg as a treatment threshold, but many protocols also measure cerebral perfusion pressure; intracranial pressures of up to 25 mm Hg may be safe provided that cerebral perfusion pressure is maintained.

Although it would be difficult to appreciate an effect of hypothermia alone on outcome, Eurotherm3235 demonstrated a lack of evidence supporting the benefit of therapeutic hypothermia in decreasing ICP and improving patient outcome 6 months after treatment. Interestingly, hypothermia resulted in a largely decreased need for pentobarbital-induced coma[14]. This may suggest that barbiturates provide similar or better metabolic suppression and neuroprotection as compared with hypothermia.

CONCLUSION

The overall goal of medical and surgical treatment for severe TBI is to prevent secondary injury by maintaining blood flow and oxygen delivery to the brain and minimizing swelling and pressure. The trials assessed in this review were not concerned with the challenge of isolating the effect of a single treatment, nor could they establish if successful treatment of intracranial hypertension improved outcomes. The collective effect of these investigations is to increase awareness of the lack of evidence supporting commonly used approaches for the management of patients with sTBI. It has become unclear how beneficial ICP monitoring, decompressive craniectomy, and therapeutic hypothermia are when compared to other standard treatment regimens. The unpredictable nature of the pathophysiology of traumatic brain injury demands guidelines for a pressure-focused approach to be more firmly established in order to effectively tailor treatment to the individual.

A recently completed study, BOOST 2 – Brain Tissue Oxygen Monitoring in Traumatic Brain Injury, is a multi-center randomized control phase 2 trial which uses a newly approved device to maintain continuous monitoring of the partial pressure of oxygen in brain tissue (pBrO2). 182 patients requiring ICP monitoring received both an ICP monitor and a pBrO2 monitor; patients in the control group had pBrO2 monitors masked by opaque tape in order to manage treatment based on ICP alone. Patients in the treatment group were managed based on results from both. Level of recovery was assessed 6 months after injury using GOS-E.[15] As the results of this trial are awaited, it can be noted that the treatment group incorporated two modalities to direct care for patients with sTBI. Although there is contention to the efficacy of some of these techniques individually, there may be a benefit in determining care based on evaluating and balancing more than one parameter. A multi-modal monitoring approach is a likely direction for future research into the management of patients with severe TBI.

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COMMENTARY:
Tele-ICU Development and Application

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BACKGROUND

The demand for intensivist care aimed at the critically ill in ICUs is ever-growing as life expectancy increases, creating a tension in supply and demand.[1] With the aging population rapidly expanding and there being a lack of new board-certified critical care specialists, it is predicted that there will be a shortage of staff in the intensive care unit.[2,3] Part of this scarcity can be attributed to the aging nurse population as the number of RNs under the age of 30 has seen a major regression.[4] Also, lack of physicians in rural areas has caused a decline in the quality of health care offered to patients who reside in these areas. It is estimated that 20% of US citizens live in rural areas and only 9% of its physicians practice there.[5] To counter this decline in specialists and lack of access to those who live in rural areas, the industry has turned to alternative forms of care, much of the substitute being technology based; also known as telemedicine.[6]

APPLICATION

Telemedicine is defined as the exchange of medical information from one site to another through electronic communications, to improve a patient's clinical health status.[7] This new technology allows organizations to transcend past the boundaries of geographic space and time to offer their services.[8] There are a variety of applications as telemedicine is a general term, such applications include: two-way video, email, smartphones, remote monitoring, and robotic presence.[7,9]

The idea of telemedicine can be traced back to as early as the 1800s when electronics such as the telegraph became available for public use.[10] When the telephone was invented in the early 1900's, it became a quick way for physicians to communicate and is still one of the primary forms of communication in the medical world.[11] Modern telemedicine systems, in particular remote-monitoring, can be linked to the National Aeronautic and Space Administration (NASA). The respiratory and circulatory function of the human body when in space was questioned during the early times of manned flight. This prompted the development of the Integrated Medical and Behavioral Laboratories and Measurement Systems (IMBLMS) program in 1964. The IMBLMS expanded upon the measurements system that allowed the biometrics of the astronauts to be monitored during critical times.[12] The updated technology aided in the case of emergencies when return to earth wasn't possible. Not only would biometric data be transmitted to the base, but also guided medical treatment by non-physicians when made available. In medical emergencies mid-flight, only the crewmembers were there to help.[13]

Around the time of the development of remote-monitoring, the development of two-way video communication emerged. A clinical trial for two-way video took place at the University of Nebraska in the early 1960's when neurological examinations were transmitted across campus to medical students. Next, group consultation was tested and a telemedicine link was set up between the University and Norfolk State Hospital. Speech therapy, neurological-examinations, diagnoses and consultations were successfully provided.[14,15]

ROBOTIC TELEPRESENCE

Within recent years the use of robotic telepresence has seen major growth. Robotic telepresence is the incorporation of video conferencing equipment onto mobile robotic devices, which is then controlled from a remote location, including mobile devices like iPad and smart phones.[16] This new technology allows for more timely responses from specialists, which has been seen in other tele-ICU applications. The primary headquarters for the robotics is InTouch Health located in California, which is integrated with Global Care Quest. A study done at UCLA from 2005-2006 set out to test the effectiveness of telerobotics in the ICU. Observations were made during nighttime rounds where physicians and attendants would determine if any patients seemed unstable. Physicians, via the robotic presence, then monitored these patients determined to be unstable. From a remote location the physician could control the movement of the robot to examine patients as well as speak to them, asking them to perform certain tasks as part of the neurological examination. The results showed that the length of stay for patients admitted into the ICU was reduced which in turn also cut costs for the ICU by $1.1 million during the year the trial took place.[17]

TELEMEDICINE IN THE ICU

A clinical trial conducted by Grundy et. al.[16] published in 1977 reveals the success telemedicine has on patients in critical care who have limited access to specialists. The project set up took place between a large university hospital and a small inner-city hospital. An intensivist provided consultation from the remote hospital via a two-way audiovisual link and camera. The results showed that telemedicine could provide a valuable link between smaller and larger hospitals to deliver better quality care. The

program was however shut down due to funding costs. A similar study conducted by Breslow et. al.[17] yielded positive results as well. From the years 1999-2001, 2,140 patients in two adult ICUs of a large tertiary care hospital were provided with a supplemental remote care program. It was concluded that the additional supplement improved clinical outcomes and hospital financial performance. It was then concluded that telemedicine may be an alternative to provide quality care with fewer intensivists needed on-site.

TELENEURO-ICU/ TELESTROKE

The development of teleneuro and telestroke ICU is still fairly new. The idea behind teleneuro-ICU is to optimize the diagnosis and treatment of neurological emergencies. Most neurological emergencies such as acute ischemic strokes are extremely time sensitive and require specialist diagnosis.[18] Ischemic stroke in particular is a major problem that has low treatment rates. The conflict between distribution of specialists and incidence of stroke presentation greatly affects the accessibility to timely and appropriate care.[19] In a study done in Burgundy, France the safety and effectiveness of telemedicine for acute ischemic stroke was evaluated. The outcomes measured at 3 months by a modified Ranking scale score and case fatality concluded that the use of regional telemedicine was effective in the treatment and management of acute ischemic stroke. It was then determined that the percentage of patients who benefit from thrombolysis will increase.[20]

THE FUTURE OF TELEMEDICINE IN NEURO ICUS

The future for teleneuro and telestroke is promising as the application and promises of telemedicine in the neurocritical-ICU increase as a whole. Telestroke has the potential to enhance stroke education through patient and health-care professional interaction. Not only is education enhanced from this aspect, but also through the ability to use telecommunication-links to provide classes on interactive stroke care and prevention to locations that are limited otherwise.[21]

Economically, telestroke has been shown to be cost-effective from both societal and hospital perspective. The drawbacks to telestroke use come from the need for state licensing and credentialing of physicians. Also from a technical aspect, telestroke and telemedicine in general require a minimum network bandwidth; some regions don't have access to this yet. These issues can however be mitigated as technology expands to the more rural regions and licensing becomes easier to acquire as the application of telemedicine and telestroke continues to expand.[22]

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Utility of Biomarkers in the Evaluation of Fever in the Intensive Care Unit After Brain Injury

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ABSTRACT

Fever is frequent in patients with neurologic injury. Differentiating infectious fever from central fever can be challenging. It is important to diagnose the cause of fever in the neurological intensive care unit because of the detrimental effects of fever on brain injured patients. This is a comprehensive review of the role of the two commonly available biomarkers, C-reactive protein and procalcitonin in differentiating the central fever from infectious fever.

Key words

Proclacitonin, C reactive protein, Subarachnoid hemorrhage, Intracerebral hemorrhage.

INTRODUCTION AND BACKGROUND

Fever is frequently seen in the neurologic intensive care unit (NICU). Incidence rates of up to 70% have been reported in various studies.[1-5] Fever can help host defenses by local activation of the coagulation cascade, cytokine-mediated T-cell activation, as well as neutrophil and macrophage recruitment to injured tissues. In brain injured patients, after the initial insult, secondary neuronal injury is speculated to be caused by several processes including mitochondrial dysfunction, inflammatory response, free radical generation, and excitatory neurotransmitter release. Fever has been shown to exacerbate secondary neuronal injury and physiologic dysfunction after traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), and major neurosurgery.[6]

CAUSES OF FEVER IN NEUROLOGICALLY INJURED PATIENTS

Infections are the most common cause of fever in the NICU population, accounting for at least half of the febrile episodes.[2,4-7] A significant percentage of patients in the NICU have central fevers. Central fever results from loss of physiological regulation of body temperature by the hypothalamus.[7] The diagnosis of central fever is challenging as there is no clear definition or diagnostic criteria. In addition, the prevalence of systemic inflammatory response syndrome (SIRS) and leukocytosis may be similar in patients with both central and infectious fevers.[8] When there is clinical suspicion of infection, it is common practice to initiate broad spectrum antibiotics after obtaining appropriate culture specimens in ICU patients. This practice results in another challenge for neurointensivists as many patients with brain injury have central fever and antibiotics may be continued unnecessarily in these patients. This may result in the emergence of antibiotic resistant organisms, increase side effects of antibiotics as well as healthcare costs. A better understanding of predictors of central fever is important as it will help in antibiotic stewardship and may also allow for earlier discontinuation of antibiotics in patients with central fever.[2] Rabinstein et al identified a number of variables that are predictive of central fever in the neurocritical care population. Their study showed that in patients with onset of fever within 72 hours of admission, patients with persistent fevers, negative cultures and lack of infiltrates on chest X-ray were more likely to have central fever. This was especially true if their primary diagnosis was SAH, tumor or they had intraventricular hemorrhage.[8]

In addition to these variables, a biomarker predictive of sepsis can be helpful in differentiating infectious from central fever and can also aid in antibiotic stewardship.

Overview of Biomarkers

Ideally, in order to guide antibiotic use, clinicians need a valid, reliable and readily available test that would correlate well with their clinical suspicion and also help them in differentiating between central and infectious fever. A number of biomarkers have been studied in patients with sepsis, some of which have also been evaluated in brain injured patients. One of the more promising ones is procalcitonin (PCT). Other biomarkers include C reactive protein (CRP) and Interleukin-6 (IL-6). These biomarkers and their validity, efficacy and availability in intensive care unit are discussed under.

Procalcitonin

Procalcitonin (PCT) is a glycopeptide consisting of 116 amino acids produced under normal conditions in the C cells of the thyroid gland as the precursor molecule of calcitonin. Several studies have demonstrated that PCT levels are raised in severe invasive bacterial infections and decrease rapidly after appropriate antibiotic therapy.[9-14] In contrast, PCT levels are normal or only slightly increased in localized bacterial infections, viral infections, and inflammatory reactions of noninfectious origin.[9,15-17] There is recent evidence suggesting that PCT can distinguish sepsis from non-infectious SIRS in general critical care patients, allowing clinicians to make better diagnostic and therapeutic decisions.[18-21]

Procalcitonin vs. Other Biomarkers

A number of studies have evaluated the role of PCT in comparison with CRP and IL-6 as a diagnostic and prognostic

biomarker. In a prospective cohort study Ville Pettilä et al evaluated the predictive value of PCT and IL-6 in patients with suspected sepsis. PCT and IL-6 values on day 2 of suspected sepsis were independently predictive of hospital mortality.[22]

Simon et al conducted a systemic review and meta-analysis. They studied the relation between serum PCT and CRP levels as a marker of inflammation. PCT had higher accuracy than CRP for discriminating bacterial infections from non-infectious causes of inflammation. In addition PCT was also significantly better than CRP in differentiating bacterial from viral infections.[23]

Choi et al conducted a prospective study to evaluate the predictive performance of serum PCT as a differentiating marker between postoperative bacterial meningitis (PBM) and postoperative aseptic meningitis (PAM). For the diagnosis of PBM, PCT level ≥ 0.15 ng/mL had a specificity of 80.0% and sensitivity of 50%. The combined criteria of a CRP level ≥2.5 mg/dL, WBC count ≥ 9,500/mm3, and PCT level ≥ 0.15 ng/mL had the highest specificity of 92.6% and higher sensitivity of 85.7%. They concluded that PCT alone has a limited performance for the diagnosis of PBM, but has improved diagnostic value when used as an adjunct test with other inflammatory markers.[24]

Procalcitonin as a biomarker for diagnosis of sepsis in brain injured patients

Fever is common in brain injured patients. As stated earlier, a significant proportion of these patients have central fever and differentiating central from infectious fever is challenging. In a prospective observational study, Festic et al showed that PCT may be a useful tool when managing SIRS in a patient with aneurysmal subarachnoid hemorrhage (aSAH). They found that in these patients, serum PCT values have high specificity, high negative predictive value and good overall predictive utility for infections, particularly for major infections. Patients with infection were > 25 times more likely to have an elevated PCT values compared to those with no infection. For patients with a major infection, the odds ratio was even higher (>33).[25]

Early diagnosis of bacterial or viral meningitis is important so that antibiotic treatment can be started without delay. For immediate diagnosis of bacterial meningitis, the sensitivity of direct cerebrospinal fluid (CSF) examination or the detection of bacterial antigens in CSF is low.[26-29]

Viallon et al conducted a prospective study to determine the ability of inflammatory biomarkers commonly used for the diagnosis of acute meningitis to differentiate between bacterial and viral meningitis, in adult patients with a negative CSF examination. Out of 254 patients with meningitis with a negative direct CSF examination, 35 had bacterial meningitis and 181 had viral meningitis. Serum PCT was a highly discriminative biomarker and had a sensitivity of 95%, a specificity of 100%, a negative predictive value of 100%, and a positive predictive value of 97% at a diagnostic cut-off level of 0.28 ng/ml .[30]

In another prospective study, Berger et al measured daily PCT levels in patients requiring temporary external ventricular drains (EVD). They showed that PCT levels were significantly higher (4.7 vs 0.2 ng/ml) in patients with proven cerebral ventriculitits. CSF cell count could not differentiate bacterial infections from abacterial reactions.[31]

Martinez et al measured serum PCT in 15 consecutive patients with ventriculitis in which an EVD had been inserted and compared the data with ten patients who had bacterial meningitis. Four out of fifteen patients had microbiologically proven bacterial ventriculitis with positive bacterial cultures. PCT value of 1.0 ng/ml showed a specificity of 77% and sensitivity of 68% in patients with ventriculitis with positive CSF bacterial cultures.[32]

In a prospective case series Schwarz et al compared serum PCT levels in patients with bacterial meningitis to those with abacterial meningitis. At admission, PCT levels were significantly higher in patients with bacterial meningitis as compared with those with abacterial meningitis ($p < .001$). The specificity of PCT was 100% for bacterial infections, but there were false-negative findings in five patients with bacterial meningitis (a sensitivity of 69%). Persistently elevated or increasing PCT levels after 2 days were associated with an unfavorable clinical course.[33]

In a case series comparing 7 patients with Neuro-Behcet disease to 3 patients with bacterial meningitis, Suzuki et al showed that serum PCT levels were increased in patients with bacterial meningitis, but not in those with Neuro-Behcet disease. Therefore, serum PCT may be a useful marker for discrimination between Neuro-Behcet disease and septic meningitis, especially in cases of the meningeal form of Neuro-Behcet disease.[34]

Figure 1. Studies describing the role of Procalcitonin as a differentiating marker.

Study	PCT Cut off	No. of Patients	Specificity	Sensitivity	PPV	NPV
Festic et al. (25)	0.2	40	97.7	37.5	85.7	80.8
Viallon et al. (29)	0.28	254	100	95	97	100
Berger et al. (31)	>1	34	100	100	100	100
Schwarz et al. (33)	>0.5	30	100	69	100	74
Martinez et al. (32)	1	15	77	68	NA	NA

PCT: Procalcitonin. PPV: Positive Predictive Value. NPV: Negative Predictive Value.
PCT Cut of value is ng/ml for all studies.

Results of these studies show that PCT can serve as a valuable tool in differentiating central fever from infectious fever, as well as discriminating primary bacterial CNS infections from non-bacterial CNS inflammatory processes.

C-Reactive Protein as a biomarker in Neurologically Injured Patients:

CRP is a major acute-phase plasma protein which is rapidly released in response to infection or tissue injury. We will discuss the role of CRP as a differentiating marker in CNS infections and other CNS inflammatory conditions. In a retrospective analysis of 35 patients with brain abscess requiring surgical drainage, Neidert et al found that preoperative mean CRP levels were significantly higher in the group requiring repeated surgical drainage. They concluded that patients with higher CRP level at baseline should be monitored closely to determine the need for repeat surgical drainage.[35]

Cerebral vasospasm is a common and potentially devastating complication of aneurysmal subarachnoid hemorrhage (aSAH). An inflammatory mechanism is implicated in the development of vasospasm. In a prospective study of 61 adult patients with aSAH, Hwang et al measured Serum CRP levels on days 1, 3, 5, 7, 9, 11 and 13 after aneurysm rupture. They found that Serum CRP levels peaked on the 3rd postoperative day and there were significant differences between the vasospasm group and the non-vasospasm group on the days 1, 3 and 5. They suggested that these patients may require closer observation to monitor for the development of vasospasm.[36]

In a prospective study of 100 adult patients with aneurysmal SAH, Romero et al showed that higher serum CRP levels are associated with worse clinical outcome and the occurrence of delayed ischemic neurological deficits.[37] In a prospective study, Napoli et al evaluated whether elevation of white blood cell count (WBC), C-reactive protein (CRP), and blood glucose (BG) concentration at presentation were prognostic of poor outcome in spontaneous Intracerebral Hemorrhage (sICH) patients. Higher WBC, CRP, and BG were associated with increased mortality in univariate analysis. However, only CRP elevation remained associated with mortality in the multivariate model, after adjusting for multiple confounders.[38]

The review of the studies related to CRP show that it is raised universally in all kinds of inflammatory responses, whether infectious or noninfectious. It may be useful in addition to PCT, but it cannot be solely used to differentiate between infectious and noninfectious fever. As a result its utility for antibiotic stewardship in NICU is limited.

CONCLUSIONS AND FUTURE APPROACHES:

The development of fever in critically ill patient needs immediate attention and action to rule out infection. This situation is more challenging in the NICU patient population due to the high rate of noninfectious fever. On one hand there is high morbidity and mortality associated with sepsis, but on the other hand use of broad spectrum antibiotics in patients who do not have infection results in high rates of antibiotic resistance, infections, and adverse drug reactions. In order to help diagnosis, a test is definitely needed that can differentiate between infectious and noninfectious fever. If a test helps us rule out infection and diagnose central fever correctly, then in spite of unnecessary use of antibiotics, we can use novel techniques such as surface or intravascular cooling measures like artic sun to treat hyperthermia in brain injured patients.

We conclude from the above review of literature that PCT may be a more sensitive and specific test that can help us differentiate between infectious and central fever. In addition it can also be a useful test to differentiate between primary bacterial CNS infections vs other types of CNS infections or non-infectious CNS inflammatory processes. However, data is very limited in neurocritical and neurosurgical patient populations. More clinical studies and clinical trials are needed that can validate the use of PCT as a diagnostic test to differentiate between infectious and noninfectious fever. In addition, the diagnostic cut-off levels of PCT also need to be validated.

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Declaring Brain Death on ECMO

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Key Words

ECMO, brain death, apnea test, ancillary test, organ donation

This abstract was presented at American Transplant Conference, Philadelphia, PA, on May 2, 2015

ABSTRACT

Purpose: Accumulating evidence suggests that organs from ECMO patients can be safely transplanted after a declaration of cardiac or brain death. However, making a diagnosis of brain death while a patient is on ECMO poses unique challenges and limited literature exists. We sought to describe the practice variations involved with declaring patients brain dead on ECMO by reviewing charts from our local organ procurement organization.

Methods: After institutional review board approval, a retrospective chart review from our local organ procurement organization was performed to identify patients declared brain dead on ECMO who became organ donors. Between 1995 and 2014, we identified 26 patients on ECMO who donated organs after being diagnosed with brain death. Demographics, causes of death, clinical and ancillary studies used to pronounce brain death were recorded from charts.

Results: All patients underwent one to two clinical exams as the initial step in the declaration of brain death. In addition to clinical examination, 15 (58%) of the patients underwent apnea testing, and of those, seven (47%) also had at least one ancillary test performed. Apnea testing was not utilized in 11 (42%) of the patients, and of those, nine (82%) had one or more ancillary tests performed to confirm brain death. Two (18%) patients underwent clinical examination only. Seventy-five percent of patients from 1995 - 2008 underwent apnea testing compared with only 50% of patients from 2009 to 2014.

Conclusions: This study demonstrated the variability of practice patterns in the declaration of brain death for patients on ECMO over time and the lack of understanding of the CO2 physiology on ECMO. Additional studies are needed to devise a national standardized protocol to declare brain death on ECMO.

INTRODUCTION

ECMO is becoming a widely used therapy for the supportive care of patients with acute cardiac and respiratory failure. From 2006 to 2011, the utilization of ECMO in adults in the United States has increased by 433%.[1] According to the Extracorporeal Life Support Organization Registry,[2] pediatric respiratory ECMO has also grown from approximately 200 cases per year from 1993 to 2004 to 331-448 cases per year from 2008 to 2012. This increase may be due to an enhanced understanding of the physiology of ECMO, as well as improvement in technology that occurred in the late 2000's.[3,4] As technology has improved, the survival rate of patients supported by ECMO has increased.[5]

As with many life-saving therapies, complications can arise. Neurological injuries can result on ECMO, although often times these injuries occur from other causes, such as hypoxic brain injury before the initiation of ECMO. The incidence of reported neurological complications in patients on ECMO varies from 13 to 37%.[6-10] When a neurological injury does occur in the patient on ECMO, it often results in poor outcomes, and sometimes brain death.[9,11,12] Patients who have been pronounced brain dead on ECMO have gone on to become viable organ donors, which is an important advantage in the setting of rapidly growing transplant lists.[13,14]

One component in the diagnosis of brain death, the apnea test, is technically challenging in the setting of ECMO. Limited literature describes apnea testing and declaration of brain death in adult and pediatric ECMO patients.[15-19] Several case reports have only been published in the past three to four years, but prior to that, no literature was available regarding how to pronounce brain death on ECMO. The purpose of this paper is to describe the clinical practice variations, ancillary testing and trends with declaring patients brain dead on ECMO and to highlight the need for the development of consensus guidelines to assist clinicians with the accurate diagnosis of brain death in this specific patient population.

METHODS

After obtaining institutional review board approval (#11D617), our local organ procurement organization (OPO) database was retrospectively analyzed to identify patients who had been declared brain dead on ECMO and went on to become organ donors. Our OPO partners with 130 acute care hospitals in the Delaware Valley region, which includes

Table 1. Modalities for Determining Brain Death on ECMO

Patient	Year	Clinical Exam (#)	Apnea test	EEG	CBF	TCD	Other
1	1995	xx	x	x			
2	1997	x		x			
3	2001	xx	x				
4	2006	xx	x				
5	2007	xx	x				
6	2007	x	x		x		
7	2008	xx	x	x			
8	2008	xx					
9	2009	xx		x		x	
10	2009	xx	x	x			
11	2010	xx	x				
12	2011	xx	x		x		
13	2012	xx	x				
14	2012	xx					x
15	2012	xx	x				
16	2013	xx	x				
17	2013	xx					
18	2013	xx		x			
19	2013	xx			x		
20	2013	x			x		
21	2013	xx	x		x		
22	2014	xx	x	x		x	
23	2014	x			x		
24	2014	xx			x	x	
25	2014	xx	x				
26	2014	xx					x

CBF: Cerebral blood flow nuclear study; EEG: Electro-encephalography; TCD: Trans-cranial Doppler. Other studies include CT scan and CT angiography.

Pennsylvania, Delaware, and New Jersey, and is the largest OPO in the United States.[20] The patients included in this study were from various hospitals within the region. Patients were excluded from the study if they were on another form of mechanical circulatory support or if they were not on ECMO at the time of brain death diagnosis. Only patients on ECMO who had been diagnosed with brain death were included in the study, therefore patients with a diagnosis of cardiac death were excluded. Once patients were identified, we reviewed the medical records from the OPO, focusing on the methods used to diagnosis brain death. The original hospital records for each patient were not available.

RESULTS

Twenty-six patients were retrospectively identified that donated organs after brain death was determined while on ECMO between October 1995 and July 2014. This cohort consisted of 13 male and 13 female, with a mean age of 27 +/- 22 years. The median length of days on ECMO before being pronounced brain dead was 3 days. Twenty-two (85%) of the patients underwent clinical examination by two separate clinicians at two separate times as the initial step in the declaration of brain death, whereas 4 (15%) patients only had one clinical examination. In addition to clinical examination, 15 (58%) of the patients underwent apnea testing. Among those patients, 7 (47%) also had at least one ancillary test performed to confirm the diagnoses of brain death. Of the 15-apnea tests that were performed, only 7 (47%) of them would actually be considered confirmatory based on American Academy of Neurology guidelines.[21] The apnea tests that were not confirmatory were due to the carbon dioxide levels not rising appropriately;[3] patients becoming hypoxic or unstable to continue the test;[3] due to the discretion of the neurologist who did not feel that an apnea test performed with a patient on ECMO was reliable.[2] Ancillary testing was performed in 75% (6/8) of the patients with non-confirmatory or undetermined apnea test. Apnea testing was not utilized in 11 (42%) of the patients, and of those patients, nine (82%) had at least one ancillary test performed to confirm the diagnosis of brain death (Figure 1). Two (18%) patients underwent clinical examination only. Seventy-five percent of patients from 1995 through 2008 underwent apnea testing compared with only 50% of patients from 2009 to 2014 (Figure 2).

In addition to apnea testing, multiple ancillary tests were used to assist with the diagnosis of brain death. These ancillary tests included electroencephalography (EEG), cerebral blood flow nuclear study (CBF), and trans-cranial Doppler (TCD). Two patients underwent CT angiogram of the head or CT of the head to ensure the diagnosis of brain death.

When apnea testing was not utilized in the determination of brain death or when ancillary studies were performed in addition to apnea testing, documented rationales were: "neurology's request",[1] "patient instability" (2), "drug intoxication",[1] and "ECMO".[7] All cases in which ECMO was documented as the reason for not performing an apnea test occurred after 2008.

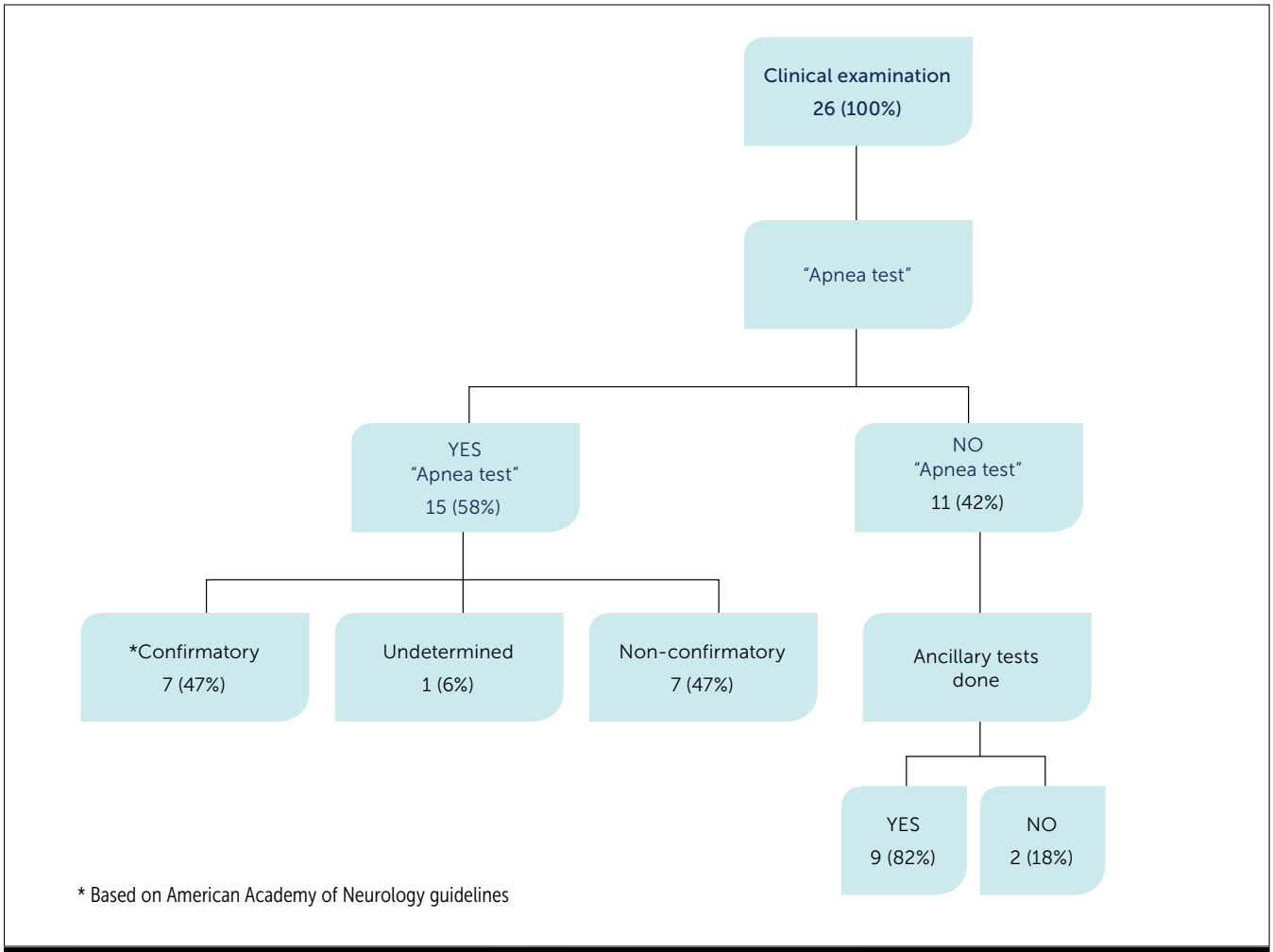

Figure 1. Determination of Brain Death on ECMO

DISCUSSION

This study represents the largest reported cohort of patients who were declared brain dead on ECMO and the clinical steps taken to confirm the diagnosis of brain death. This data not only confirmed the variations in clinical practices and use of ancillary testing, it highlighted uncertainties regarding how to confirm brain death in this specific patient population. Seven of the cases in this study documented ECMO as either the reason for not performing an apnea test or reason for performing confirmatory ancillary testing in addition to the apnea test. In five other cases, an apnea test was not performed without clear documentation as to why the apnea test was not done. It appears that many clinicians in these scenarios recognized the challenges and limitations of apnea testing in ECMO patients. Review of the data also revealed that the results of three apnea tests may have been reported incorrectly by the performing institution, further highlighting evidence of how difficult it can be to perform and interpret the apnea test in these patients.

Although apnea testing to confirm brain death in ECMO patients has been reported, the literature is limited to very few case reports and those case reports all suggest different processes for performing an apnea test on a patient on ECMO.[15-19] Similarly in this study, five charts did provide documentation as to how the apnea test was performed and all tests were performed differently. For example, our research showed one apnea test was performed with the sweep (ventilation control on ECMO) off, while another was performed with the sweep at minimum. In addition to the various procedures taken with regard to the sweep, the apnea tests also varied in regards to whether or not the patient remained on the ventilator with pressure support settings or was taken off the ventilator completely, what the ECMO flow rate was placed at, and the times in which the ECMO settings were

adjusted before making a decision about whether the test was positive or negative. Muralidharan et al,[22] suggested a procedure for performing an apnea test on ECMO, but made note of three cases in which patients on ECMO were found to have lost all brainstem reflexes, but apnea testing was not performed because it was deemed "difficult."

According to the guidelines from the American Academy of Neurology,[21] after meeting all of the prerequisites to proceed with brain death testing, a clinical examination should be performed, and if that examination is consistent with brain death, then apnea testing should occur. The procedure for the apnea test is as follows:[21] 1) Adjust vasopressors to a systolic blood pressure >/= 100mm Hg, 2) Pre-oxygenate for at least 10 minutes with 100% oxygen to a PaO_2 > 200mm Hg, 3) Reduce ventilation frequency to 10 breaths per minute to eucapnia, 4) Reduce positive end-expiratory pressure to 5cm H_2O, 5) If pulse oximetry oxygen saturation remains >95%, obtain a baseline blood gas, 6) Disconnect the patient from the ventilator, 7) Preserve oxygenation by placing an insufflation catheter through the endotracheal tube and close to the level of the carina and delivery 100% oxygen at 6L/min, 8) Look closely for respiratory movements for 8-10 minutes, 9) Abort if systolic blood pressure decreases to <90mm Hg or if oxygen saturation measured by pulse oximetry is < 85% for > 30 seconds, 10) If no respiratory drive is observed, repeat blood gas after approximately 8 minutes, 11) If respiratory movements are absent and arterial PCO_2 is >/= 60mm Hg or 20mm Hg over a baseline normal arterial PCO_2, the apnea test result is positive, and 12) If the test is inconclusive but the patient is hemodynamically stable during the procedure, it may be repeated for a longer period of time (10-15 minutes) after the patient is again adequately pre-oxygenated.

This apnea test presented multiple procedural challenges for the patient on ECMO. A PaO_2 of > 200 may not be obtainable in patients on ECMO by placing the ECMO FiO_2 to 100%, since the majority of patients are in acute respiratory distress syndrome or pulmonary edema. Secondly, patients on veno-arterial ECMO often have minimal pulsatility; therefore, they do not have a systolic blood pressure, only a mean arterial pressure. Furthermore, it has been demonstrated that even at a minimum gas sweep flow (less than 1L), a fraction of inspired oxygen of 100%, and minimum ECMO flow, carbon dioxide can still be effectively cleared by the oxygenator. The Maquet Quadrox oxygenator is very efficient at CO_2 removal and any sweep gas will effectively lower the CO_2. Therefore, in order to demonstrate a rise in CO_2 from an apneic patient, the sweep must be turned significantly down or off, and doing this will stop the oxygenation of the blood through the ECMO oxygenator.

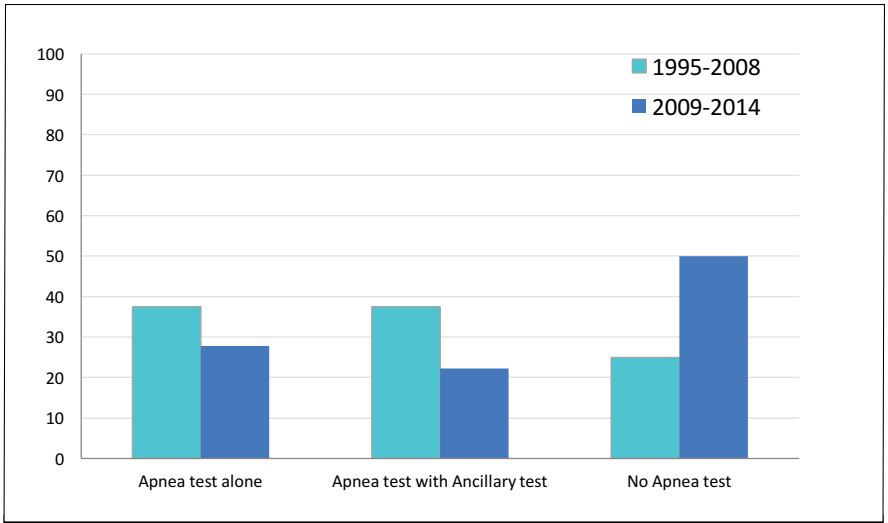

Figure 2. Trends in modalities determining Brain Death on ECMO

According to the American Academy of Neurology[21] guidelines, if an apnea test is aborted or inconclusive, ancillary testing should be performed. Beginning in 2009, we noted a trend in which apnea tests were less often utilized in the diagnosis of brain death for patients on ECMO (Figure 2). This was approximately the same time in which newer generations of ECMO circuits were being used. Ancillary tests are generally well supported in the literature to confirm a diagnosis of brain death in the general population; they have not been extensively studied or reported in the ECMO population. The alterations in blood flow patterns, oxygenation, and ventilation that are created by ECMO affect the usefulness of ancillary tests used for the diagnosis of brain death on ECMO.

This study demonstrates variations in practices in brain death declaration, especially in regards to apnea testing, in patients on ECMO. Standardization is urgently needed to assure consistent, accurate brain death pronouncement in order to facilitate organ procurement when appropriate. We hope future brain death guidelines incorporate the ECMO population.

This study was limited to the data from a single local OPO, although this OPO is the largest in the United States. Additional limitations include that the data on the studied patients were limited by what the OPO collected from various hospitals, and because we did not have access to the full medical records, information such as patient history (primary cardiac failure vs. primary respiratory failure), the type of ECMO (veno-arterial vs. veno-venous), and details of the apnea test and clinical examination was missing, incomplete, or difficult to interpret. The primary medical record review was not performed due to strict HIPAA violations. Also this study was limited to patients who were evaluated for organ donation and went on to become organ donors. Individuals who were evaluated for donation but were rejected were also unable to be included in this study.

CONCLUSION

Due to the substantial and continued increase in the utilization of ECMO for cardiac and respiratory support, the ethical and legal implications involved in the pronunciation of brain death, the growing number of patients on the organ waiting list, and the recent evidence that organs from ECMO donors have similar outcomes as other organs from other donors, it is imperative that consensus guidelines are developed to guide clinicians in the accurate diagnosis of brain death in patients receiving ECMO. Future research should focus on the best way to perform an apnea test with specific recommendations on ECMO settings, as well as the reliability of ancillary testing, such as CBF, TCD or EEG, when an appropriate apnea test cannot be performed.

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Disclosure

None of the listed authors have conflict of interest regarding this paper.

Paroxysmal Sympathetic Hyperactivity

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It is not uncommon for physicians who treat patients with traumatic brain injuries to see wide fluctuations in the heart rate, respiratory rate and blood pressure. For decades, these fluctuations were thought to be seizures, caused by pressure on the thalamus. They were originally termed Diencephalic Autonomic Seizures by Dr. Wilder Penfield in 1929. He described episodes of lacrimation, hypertension, diaphoresis and agitation. Dr. Penfield's "seizures" were later shown to have no electrographic correlate. Since that time, many names have been used to describe similar episodes: Dysautonomia, Sympathetic Storming, Brainstem Attacks, Autonomic Dysregulation, Paroxsymal Autonomic Instability with Dystonia and Paroxysmal Sympathetic Hyperactivity to name only a few.

Paroxysmal Sympathetic Hyperactivity (PSH) occurs in acquired brain injury and features simultaneous, paroxysmal transient increases in sympathetic and motor activity.[1] It is most commonly associated with traumatic brain injury. However, it has been documented in many neurologic conditions (Table 1) and an episode can be precipitated by a variety of triggers.[2] (Table 2).

One of the difficulties in recognizing PSH is that many of the symptoms are found in other clinical syndromes. It is a diagnosis of exclusion and the proper workup must be completed before beginning treatment.[3] The clinical features of PSH include tachycardia, tachypnea, hypertension, fever, diaphoresis and dystonic posturing during the episodes. Table 3 highlights many of the conditions which share similar features to PSH.

Table 1. Neurologic Conditions associated with Paroxysmal Sympathetic Hyperactivity

Traumatic Brain Injury
Anoxic Brain Injury
Ischemic Stroke
Intracranial Hemorrhage
Aneurysmal Subarachnoid Hemorrhage
Brain Tumor
Encephalitis

Table 2. Triggers Precipitating PSH Attack

Suctioning
Turning
Bathing
Physical Exam

PSH has been described as occurring in three phases.[4] The first phase occurs immediately after the injury. At this early point in the disease process, there

Table 3.

	Mental Status	T	HR	RR	BP	Pupil Size	Sweating	Agitation	Posturing	CPK
Paroxysmal Sympathetic Hyperactivity	↓	↑	↑	↑	↑	↑	+	+	↑	?
Malignant Hyperthermia	↓	↑	↑	↑	±↑	NA	NA	NA	+>-	↑
NMS	↓	↑	↑	↑	↑/↓	NA	+	NA	+	↑
Increased ICP	↓		↓	↓	↑	±↑	NA	NA	±	NA
Central Fever	±↓	↑	↑	↑	NA	NA	NA	NA	NA	NA
Infection	±↓	↑	↑	↑	↑/↓		±	NA	NA	NA
Nonconvulsive seizures/epilepsy	NA	NA	NA	NA	NA	±↑	NA	±	NA	NA
Narcotic Withdrawal	±↓	NA	↑	↑	NA	↑	+	NA	NA	NA
Autonomic dysreflexia	NA	↑	↑	↑	↑	NA	+	NA	NA	NA

Abbreviations: NMS, neuroleptic malignant syndrome; T, temperature; HR, heart rate; RR, respiratory rate; BP, blood pressure; CPK, creatine phosphokinase; up arrow, increased; down arrow, decreased. Adapted from Blackman et al Archives of Neurology 2004;61:321-328

Table 4. Severity of Clinical Features Assessment Tool

Paroxysmal Sympathetic Hyperactivity – Assessment Measure Clinical Features Scale					
	0	**1**	**2**	**3**	**Score**
Heart Rate	<100	100-119	120-139	≥140	
Respiratory Rate	<18	18-23	24-29	≥30	
Systolic Blood Pressure	<240	140-159	160-179	≥180	
Temperature	<37	37-37.9	38-38.9	≥39	
Sweating	None	Mild	Moderate	Severe	
Posturing during episodes	None	Mild	Moderate	Severe	
				CSF Total	

Severity of Clinical Features	CFS Total
None	0
Mild	1-6
Moderate	7-12
Severe	≥13

Table 5. Diagnosis Likelihood Tool (DLT)

Score 1 point for each feature present	
Clinical features occur simultaneously	
Episodes are paroxysmal in nature	
Sympathetic over-reactivity to normally non-painful stimuli	
Features persist ≥3 consecutive days	
Features persist ≥ 2 weeks post-brain injury	
Features persist despite treatment of alternative differential diagnoses	
Medication administered to decrease sympathetic features	
≥ 2 episodes daily	
Absence of parasympathetic features during episodes	
Absence of other presumed cause of features	
Antecedent acquired brain injury	
DLT total	

	Combined Total Points	
	Clinical Severity Features + Diagnostic Likelihood Tool	
PSH Diagnostic Likelihood	Unlikely < 8	
	Possible 8-16	
	Probable > 17	

(Adapted from Baguley I. et al. Journal of Neurotrauma 2014;31:1515-1520)

are no specific signs that distinguish a patient who will go on to develop PSH from those who don't. Phase two begins after the withdrawal of sedation and or paralytics. It is at this point that patients distinguish themselves and either develop typical PSH features (hypertension, hyperthermia, rigidity etc.) or don't. The PSH episodes are sporadic and intense at times and have variable responses to medical management. The duration of this phase is unpredictable. It can last from weeks to months. The third phase was called PSH "burnt out." The patient no longer exhibits all the clinical features and can be left in a spastic or dystonic position with varying degrees of recovery.

In 2014, the *Journal of Neurotrauma* published a consensus statement aimed at formalizing the nomenclature, including definition and diagnostic criteria. Tables 4 and 5 detail the diagnostic criteria.

PAROXYSMAL SYMPATHETIC HYPERACTIVITY – ASSESSMENT MEASURE

Management of PSH involves both non-pharmacologic and pharmacologic treatment. Non-pharmacologic management includes decreasing external stimuli, limiting visitation, minimizing exams or noxious stimuli, or grouping activities (turning, suctioning, bathing). Pharmacologic management is aimed at dampening sympathetic outflow or activating parasympathetic system. Most commonly used are benzodiazepines, beta-blockers and opiates. Most medical treatment involved depressing the CNS systems and causes increased sedation.[5] (Table 6).

Managing the symptoms is important in preventing secondary brain injury. Patients who are not treated are at risk for cerebral edema, intracranial bleeding from malignant hypertension. There is a risk of ischemia due to decreased cerebral oxygenation and neuronal loss due to prolonged sympathetic activation. There are other non-brain injury risks that occur due to prolonged untreated PSH. These include electrolyte abnormalities, dehydration and kidney injury from excessive diaphoresis. Cardiac injury can occur from repetitive significant tachycardia and muscle wasting. Weight loss and malnutrition can occur from increased metabolic demands.

Lastly, it is critical that physicians discuss PSH with the families, as these episodes can be very upsetting and distressful to witness. Explaining what is happening to the patient and how it is being managed can help alleviate this stress. It is also a way to involve the family in monitoring for triggers and timing of episodes. Developing a bedside chart which details triggers, timing, duration of episodes, medications administered and response to treatment is useful in the long-term management.

Table 6.

	Symptom	Receptor Agonist or Antagonist	Medication	Additional
First Line	Tachycardia	β2-Adrenergic blocker	Propranolol	– Dampens sympathetic activity; decreases serum catecholamines, reduces cardiac workload – Dosing limited by HR and BP – Caution in asthmatics
First Line	Hyperthermia	COX-2 inhibitor	Acetaminophen (Po 650-975mg q6hr) (IV 1gm q6h)	– Dosing max 4gm/daily
First Line	Diaphoresis & hyperthermia	Dopamine agonist	Bromocriptine (2.5-5mg q8hr)	– Acts at the hypothalamic level. – Can increase up to 30-40mg/day
First Line	Tachypnea	GABA-A Antagonist	Diazepam (po 5mg q8 hr and titrate up)	– No max dose – Dosing limited based on sedation
First Line	Pain	Opiate Agonist	Morphine Sulfate Fentanyl Oxycodone	– Start low and titrate to effect – Dosing varies by agent – High abuse potential long term
Second Line	Hyperthermia	Dopamine D2 Antagonist	Chlorpromazine	– Acts along the hypothalamus – Good for recurrent hyperthemia – Should not be used long term – Risk of extra-pyramidal effects & liver failure
Second line	Dystonia	GABA-B agonist	Baclofen	– Low potential for abuse – Long term use requires slow wean to avoid withdrawal/ seizures
Second Line	Dystonia	Post-synaptic muscle relaxant, Inhibits Ca+ release intracellularly	Dantrolene	– Caution if other Ca+ Channel Blockers on board can cause hyperkalemia and – Caution if liver disease
Second Line	Tachycardia	α2 Agonist	Clonidine	– Lowers levels of norepinephrine
Second Line	Tachyacrdia	β1, β2, α1 antagonist	Labetalol	– Dosing limited by HR and BP

Onset time	Trigger	HR	BP	Diaphoresis Y/N	ICP (mmHg)	Dystonia Y/N	Medications given	Duration of episode

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Incidence and Prevalence of Deep Vein Thrombosis Among Neurocritical Intensive Care Unit Patients

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Background: Deep venous thrombosis (DVT) of the lower extremities is a common cause of morbidity and mortality among neurologically injured patients. The data on incidence and prevalence rates of DVT among high risk neurologic populations is scarce. The available literature focuses largely on patients admitted to a medical or surgical intensive care unit with very limited information on patients in neuro-intensive care units (NICU). The aim of the present study is to assess the incidence and prevalence of deep vein thrombosis among patients admitted with acute neurologic injury.

Methods: We conducted a retrospective review of ultrasound records of 2,644 patients admitted to NICU, stroke or INICU at a university hospital over a 13-month period. We included all patients who underwent routine lower extremity ultrasound on admission and weekly. Data was abstracted and analyzed to assess the prevalence of DVT in this period. We excluded patients presenting with superficial vein thrombosis, hematoma and chronic venous scarring.

Results: Among the 2,644 patients studied, 161 were diagnosed with DVT. The overall prevalence of DVT was 6.1%. Of the 161 cases of DVT; 87 (54%) were diagnosed with DVT at the time of admission. In our sample, the rate of DVT present on admission was 3.3%. There were 74 cases of hospital-acquired DVT, yielding an incidence of 2.8%. Patients with DVT at the time of admission were largely Caucasian males with mean age 72 and mean SAPS II score of 34.2, ranging between 13 and 71.

Conclusions: Patients admitted to a neuro ICU are at high risk for having DVT present on admission and for acquiring DVT during their hospitalization. Further research is needed to understand the risk profile of patients with acute neurological injury. Asymptomatic screening of high risk patients on admission to a neurologic ICU, stroke unit, or intermediate care unit will identify a significant number of cases of DVT present of admission that might otherwise be misidentified as hospital acquired cases.

Table 1. Prevalence and Incidence of DVT among acute neuroscience patients

N	**2644**
Prevalence	161 (6.1%)
Incidence	74 (2.9%)
N	**161**
DVT present on admission	87 (54.0%)
DVT developed in hospital	74 (45.9%)

Table 2. Characteristics of patients with DVT at the time of admission

	N	**87**
Age (yrs)	Mean ± SD	72±12.0
	Range	29-94
Sex	Males	52.7%
	Females	47.3%
Race	Caucasian	72.9%
	African-American	12.2%
	Others	1.5%
SAPS II score	Mean ± SD	34.2±14.8
	Range	13-71

INTRODUCTION

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a significant health complication for critically ill hospitalized patients. DVT is a preventable health problem associated with several adverse outcomes including death. Among neurosurgical patients, the risk of DVT without prophylaxis is 22-35%, while spinal cord injury patients who do not receive prophylaxis have rates ranging from 50-85%.[1] It is tempting to assume that previously healthy, acutely injured neuroscience patients who are diagnosed with DVT represent hospital-acquired disease; these patients generally do not have identifiable risk factors for DVT prior to the onset of acute illness. However, there is no data to support these assumptions.

Intensive care unit patients represent a heterogeneous population. The available literature describes the prevalence, incidence and risk factors associated with the development of DVT among patients admitted to medical and surgical intensive care units and following trauma, neurosurgery, or spinal cord injury.[1-7] An estimated 10-30% of medical and surgical intensive care unit patients are known to develop DVT within the first week of admission. However, there is limited to no data about the DVT risk profile of patients admitted to a neuro-intensive care unit (NICU). The aim of the present study is to assess the incidence and prevalence of deep vein thrombosis among patients admitted with acute neurologic injury.

METHODS

In this retrospective study, data on all patients admitted to Neuro ICU, stroke or INICU of a tertiary care teaching hospital between December 2013 and January 2014 were included. Patients presenting with superficial vein thrombosis, hematoma and chronic venous scarring were excluded from the analysis. Our institution routinely conducts ultrasound screening within 24 hours of admission and weekly thereafter in high risk neurologically injured patients.

A retrospective review of ultrasound records was conducted to identify patients with DVT.

To estimate the prevalence of DVT; number of patients presenting with DVT, identified through ultrasound screening within 24 hours of admission; patients with a history of chronic DVT and patients who developed DVT during their stay in the hospital identified through weekly ultrasound screening were computed. We estimated the overall prevalence of DVT by calculating the rate of DVT in our study population. We also describe the rate of DVT present on admission and the incidence of hospital-acquired DVT.

Various demographic characteristics, such as patient's age, sex, race were abstracted and health evaluation (SAPS II) score was calculated to describe the population presenting with DVT at the time of admission. Continuous data are expressed as mean with standard deviation and range. Categorical data are summarized to present counts and percentages.

RESULTS

A total of 2,644 ultrasound records were reviewed. Over a period of one year; the prevalence of DVT among neuro ICU patients was found to be 6.1%, a total of 161 cases. Of the 161 patients diagnosed with DVT, 87 (54.0%) presented with DVT at the time of admission. Patients developed DVT during their stay in the hospital in 74/161 (46%) of all the cases diagnosed with DVT.

The study found that 3.3% of the 2,644 patients admitted to our acute neuroscience units between 2013-2014 presented with DVT at the time of admission. After excluding patients with a known case of DVT on admission, the population at risk of developing DVT in our sample comprised of 2,556 cases. The number of cases that developed DVT during their stay in the intensive care unit was 74 of 2,556 patients, resulting in an incidence rate of 2.9% among neuro ICU patients. (Table 1)

Analysis of various demographic characteristics revealed that majority of patients who presented with DVT on admission were Caucasian males with a mean age 72. The mean SAPS II score for these cases was found to be 34.2. (Table 2)

CONCLUSION

There are several studies assessing the incidence and prevalence of DVT among critically ill surgical and medical ICU patients. Our study is among the few describing the prevalence of DVT among patients with acute neurologic injury. The prevalence of DVT among patients admitted to a neuro ICU is relatively high. Slightly over half of the cases diagnosed with DVT presented with this problem at the time of admission to the intensive care unit. Without timely admission screening, these cases will be incorrectly identified as hospital-acquired cases. Current best-practices such as early mobilization, mechanical compression devices, and chemoprophylaxis, remain important. These data suggest, however, that many patients acquire DVT within hours of their acute neurologic injury. Inpatient DVT risk prevention strategies are unlikely to impact the diagnosis of DVT for these patients. These patients may benefit from ultra-early, pre-hospital or emergency department-based interventions. In addition to the findings reported herein, further research is needed to understand the risk factors for ultra-early DVT and hospital acquired DVT within the high-risk population of patients with acute neurological injury.

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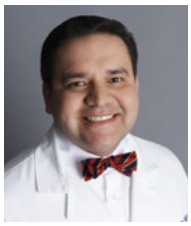

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Andres Fernandez, MD

Assistant Professor
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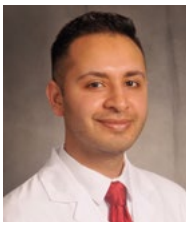
and Neurocritical Care



Omar Shah, MD, MBA

Assistant Professor
Department of Neurology
and Neurological Surgery
Division of Neurotrauma
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Recent Publications

- Shah, SO, Kraft J, Ankam N, Bu P, Stout K, Melnyk S, Rincon F, Athar MK. Ambulation in Patients with External Ventricular Drains: Results of a Quality Improvement Project. J Intensive Care Med. 2016. *Publication Pending*.

- Olkowski, B, Shah SO. Early Mobilization in the Neuro-ICU: How Far Can We Go? Neurocrit Care. 2016. *Publication Pending*

- Crudele A, Shah SO, Bar B. Decompressive Hemicraniectomy in Acute Neurological Diseases. J Intensive Care Med. 2015 Aug 31. pii: 0885066615601607.

- Shah SO, Rincon F and Bar B. Outcomes of Decompressive Hemicraniectomy for Spontaneous Intracerebral Hemorrhage: A Case-Control Study. Austin Neurol & Neurosci. 2016; 1(1): 1003.

- Dobak SD, Athar MK. A Survey of Current Practice Regarding Fasting Times in the Intubated, Neurocritically Ill Patient. Support Line. Feb 2016; 38(1): 14-17.

- Vespa P, Hanley D, Betz J, Hoffer A, Engh J, Carter BS, Nakaji P, Ogilvy C, Jallo J, Selman W, Bistran-Hall A, Lane K, McBee N, Saver J, Thompson R, Martin N. Intraoperative Computer Guided Endoscopic Surgery for Brain Hemorrhage (ICES): A Multicenter Randomized Controlled Trial. Approved Stroke AHA Journal 2016.

- Grieff AN, Ghobrial GM, Jallo J. Use of liposomal bupivacaine in the postoperative management of posterior spinal decompression. J Neurosurg Spine. 2016 Mar 4:1-6.

- Chalouhi C, Okabe T, Starke R, Daou B, Dalyai R, Bovenzy C, Anderson EC, Jabbour P, Tjoumakaris S, Rosenwasser R, Kraft W, Rincon F. Risk of VTE in Patients with Large Hemispheric Infarction Undergoing Decompressive Hemicraniectomy. Neurocrit Care 2016. (PMID: 26896092).

- Dobak S and, Rincon F. "Cool" Topic: Feeding during Induced Hypothermia after Intracranial Hemorrhage. Accepted JPEN 2016. (PIMD: PMID: 27323775)

- Kirk A, McDaniel C, Szarlej D, and Rincon F. Assessment of Anti-Shivering Medication Requirements During Therapeutic Normothermia: Effect of Cooling Methods. Accepted Therapeutic Hypothermia and Temperature Management 2016. (PMID: 26990844).

- Kon A, Shepard EK, Sederstrom N, Swoboda SM, Marshall MF, Birriel B, and Rincon F. Defining Potentially Inappropriate Treatment: A Policy Statement from the SCCM Ethics Committee. Accepted: Crit Care Med 2016.

- Sánchez S, Rincon F. Status Epilepticus: Epidemiology and Public Health Needs. J Clin Med. 2016 Aug 16;5(8).

- Kon AA, Shepard EK, Sederstrom NO, Swoboda SM, Marshall MF, Birriel B, Rincon F. Defining Futile and Potentially Inappropriate Interventions: A Policy Statement From the Society of Critical Care Medicine Ethics Committee. Crit Care Med. 2016 Sep;44(9):1769-74.

- Chalouhi N, Daou B, Okabe T, Starke RM, Dalyai R, Bovenzi CD, Anderson EC, Barros G, Reese A, Jabbour P, Tjoumakaris S, Rosenwasser R, Kraft WK, Rincon F. Beta-blocker therapy and impact on outcome after aneurysmal subarachnoid hemorrhage: a cohort study. J Neurosurg. 2016 Sep;125(3):730-6.

- Kraft J, Karpenko A, Rincon F. Intraoperative Targeted Temperature Management in Acute Brain and Spinal Cord Injury. Curr Neurol Neurosci Rep. 2016 Feb;16(2):18.

- Vespa P, Hanley D, Betz J, Hoffer A, Engh J, Carter R, Nakaji P, Ogilvy C, Jallo J, Selman W, Bistran-Hall A, Lane K, McBee N, Saver J, Thompson RE, Martin N; ICES Investigators. ICES (Intraoperative Stereotactic Computed Tomography-Guided Endoscopic Surgery) for Brain Hemorrhage: A Multicenter Randomized Controlled Trial. Stroke. 2016 Oct 6. pii: STROKEAHA.116.013837

- Haider HA, Esteller R, Hahn CD, Westover MB, Halford JJ, Lee JW, Shafi MM, Gaspard N, Herman ST, Gerard EE, Hirsch LJ, Ehrenberg JA, LaRoche SM; Critical Care EEG Monitoring Research Consortium. Sensitivity of quantitative EEG for seizure identification in the intensive care unit. Neurology. 2016 Aug 30;87(9):935-44.

- Matz PG, Meagher RJ, Lamer T, Tontz WL, Annaswamy TM, Cassidy RC, Cho CH, Dougherty P, Easa JE, Enix DE, Gunnoe BA. Guideline summary review: an evidence-based clinical guideline for the diagnosis and treatment of degenerative lumbar spondylolisthesis. The Spine Journal. 2016 Mar 31;16(3):439-48.

- Abdelmalik PA, Boorman DW, Tracy J, Jallo J, Rincon F. Acute Traumatic Coagulopathy Accompanying Isolated Traumatic Brain Injury is Associated with Worse Long-Term Functional and Cognitive Outcomes. Neurocritical care. 2016 Jun:1-0.

- Hart T, Novack TA, Temkin N, Barber J, Dikmen SS, Diaz-Arrastia R, Ricker J, Hesdorffer DC, Jallo J, Hsu NH, Zafonte R. Duration of Posttraumatic Amnesia Predicts Neuropsychological and Global Outcome in Complicated Mild Traumatic Brain Injury. The Journal of head trauma rehabilitation. 2015 Jan.

Support Groups

Brain Aneurysm and AVM Support Group at Jefferson

The Brain Aneurysm and AVM (arteriovenous malformation) Support Group provides support for individuals, family members and friends who have been affected by cerebral aneurysms, subarachnoid hemorrhage and AVMs. The purpose of the group is to gain and share knowledge and understanding of these vascular anomalies and the consequences of these disease processes. The group provides mutual support to its members by creating an atmosphere that engenders active listening and sincere and thoughtful speech within a caring environment.

When Third Wednesday of every month (September through June)

Time 6:30-8:30 p.m.

Place 900 Walnut Street, 3rd Floor, Conference Room
Philadelphia, PA 19107

Moderator/ Secretary Jill Galvao

Parking Complimentary parking is provided in the parking garage located in the JHN Building (Jefferson Hospital for Neuroscience) on 9th Street (between Locust & Walnut)

Information For additional information please call: 215-503-1714

The Brain Tumor Support Group at Jefferson

The Delaware Valley Brain Tumor Support Group at Jefferson provides an opportunity for patients and their families to gain support in obtaining their optimum level of well-being while coping with, and adjusting to the diagnosis of brain tumor. Members are encouraged to share their support strategies so members can confront the challenges that this disease process has imposed on their lives. The strength gained from group can be a source of comfort and hope for whatever lies ahead.

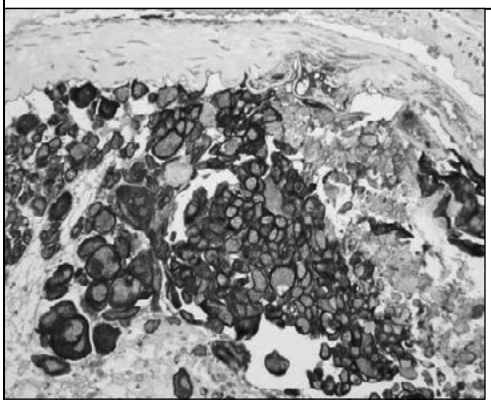
When Second Thursday of every month

Time 7-8:30 p.m.

Place Jefferson Hospital for Neuroscience,
3rd Floor conference room
900 Walnut Street Philadelphia, PA 19107

Facilitator Joseph McBride, BSN, RN and Katelyn Salvatore, BSN, RN.
215-955-4429 or katlyn.salvatore@jefferson.edu

Light refreshments and snacks will be served. Free parking is available at the Jefferson Hospital for Neuroscience parking lot.



Neurosurgical Emergency Hotline

Jefferson Hospital for Neuroscience

Aneurysms • AVMs • Intracranial Bleeds

7 day • 24 hour coverage

1-866-200-4854

Patient Profile of Anna Poszmik

BY ANNALISE DE JESUS

In May of 2015 at her home in Mount Laurel, NJ, Anna Poszmik, just 23 at the time, suffered from a severe asthma attack that led to cardiac arrest. Anna was pursuing her degree in neuroscience at Columbia University. She had been diagnosed with asthma at the age of 22 and began suffering from major attacks that often landed her in the hospital during the early months of 2015.

She had decided to come home for the weekend before she was due to take her last final exam when she suffered another attack that left her barely able to breathe or speak. Before the ambulance could arrive, Anna's breathing had stopped and she went into a cardiac arrest. Her mother, Annamaria Fulep, frantically tried to resuscitate her but there was little she could do.

"It was the worst hour of my life and the worst moment having my child down on the floor blue, and not having any idea what to do," said Fulep.

When the paramedics arrived, they successfully resuscitated her and took her to a local hospital. She was then placed on a therapeutic hypothermia protocol

> Her condition was complicated by long-lasting, uncontrollable seizures and doctors initially thought Poszmik's condition may be terminal.

for neuroprotection. Five days later, she was transferred to Thomas Jefferson University Hospital's ICU for tertiary care. Her condition was complicated by long-lasting, uncontrollable seizures and doctors initially thought that Poszmik might never regain meaningful consciousness. "I'll never forget being told that the part of my daughter's brain that makes us human is dead," said Fulep.

Devastated by the poor prognosis at the time, Fulep tried to remain patient as more testing was performed. Over the course of the next two weeks, the results came back and a meeting was set up with the attending physician of neurological ICU at the time, Rodney Bell, MD, Lynne and Harold Honickman Professor of Neurology & Neurosurgery, and other members of the department to discuss Anna's prognosis.

"I remember driving there after cancelling class. It was so stressful not knowing what would happen," said Fulep. After a thorough discussion, the neuro-ICU team decided to pursue aggressive care. Life support was continued and her seizures were aggressively managed.

Anna stayed in the ICU for seven weeks and showed gradual improvement in her level of consciousness. She also began to undergo initial physical therapy. After noticeable improvement, Anna was sent to an acute rehabilitation facility to join a six-week program.

Anna is now alert with a remarkable improvement in her neurological status. She has no apparent speech difficulty and is able to walk with assistance. After a drastic recovery, Anna has been able to finish her last exam and complete her degree at Columbia University.

UPCOMING JEFFERSON NEUROSURGERY CME PROGRAMS

As a part of the Vickie and Jack Farber Institute for Neuroscience at Jefferson, the Department of Neurological Surgery is one of the busiest academic neurosurgical programs in the country, offering state-of-the-art treatment to patients with neurological diseases affecting the brain and spine, such as brain tumors, spinal disease, vascular brain diseases, epilepsy, pain, Parkinson's disease and many other neurological disorders (**Jefferson.edu/Neurosurgery**).

As part of a larger educational initiative from the Jefferson Department of Neurological Surgery, the Sidney Kimmel Medical College Office of Continuing Medical Education is offering the following continuing professional educational opportunities for 2016 - 2017:

- **6th International Hypothermia and Temperature Management Symposium**
  September 12-14, 2016
  Jefferson Alumni Hall
  Campus of Thomas Jefferson University
- **6th Annual Brain Tumor Symposium**
  October 28, 2016
  DoubleTree by Hilton Philadelphia Center City
- **28th Annual Pan Philadelphia Neurosurgery Conference**
  December 2, 2016
  The Union League of Philadelphia
- **6th Annual Neurocritical Care Symposium: A Practical Approach**
  February 3-4, 2017
  Jefferson Alumni Hall
  Campus of Thomas Jefferson University
- **16th Annual Cerebrovascular Update**
  March 16-17, 2017
  Hyatt at the Bellevue, Philadelphia
- **Fundamental Critical Care Support Course**
  April 2017
  On the Campus of Thomas Jefferson University
- **3rd Annual Philadelphia Spine Summit**
  May 19-20, 2017
  Campuses of Thomas Jefferson University and University of Pennsylvania

For additional information regarding these and other Jefferson CME programs, please visit our website at CME.Jefferson.edu or call the Office of CME at 888-JEFF-CME (888-533-3263).

Sidney Kimmel Medical College at Thomas Jefferson University is accredited by the ACCME to provide continuing medical education for physicians.

Vickie and Jack Farber Institute for Neuroscience™ at Jefferson

Follow us on Twitter at @JeffCME for updates and new information

6TH ANNUAL
Neurocritical Care Symposium: A Practical Approach

*Featuring *Case-Based Practical Workshop at Thomas Jefferson University*

Friday, February 3, 2017 and *Saturday, February 4, 2017

Featuring Guest Speakers

Daniel F. Hanley, Jr, MD
Johns Hopkins University School of Medicine • Baltimore, MD

David Gaieski, MD
Sidney Kimmel Medical College Philadelphia, PA

Stephen K. Klasko, MD, MBA
Thomas Jefferson University & Jefferson Health • Philadelphia, PA

Course Co-Directors

M. Kamran Athar, MD

Jack Jallo, MD, PhD

Stroke Credit Available!

The content for this educational activity meets The Joint Commission standard for Primary Stroke Centers and Comprehensive Stroke Centers for staff who care for stroke patients.

For more information, or to register*, visit CME.Jefferson.edu.

**Registration fees apply. See website for details*

Follow us on Twitter @JeffCME and use #NCCS17 to join the conversation!

The 5th Annual Neurocritical Care Symposium focuses on practical issues facing the healthcare professional caring for the critically-ill neurological patient. Through case presentations carefully selected to illustrate the difficulties of diagnosing and managing these patients, participants will learn how recent advances in the field can be applied in their practices.

Why you should attend:

- Critique and discuss treatment approach in the neuro-ICU with expert interdisciplinary faculty.
- Earn additional credit for participating in a pre & post test, and web-based audio review of each correct response.
- ***Back by popular demand*** Engage in critical care scenarios through immersive simulations during Saturday optional workshops.
- Network with expert faculty and colleagues in the field throughout the conference.

NEW THIS YEAR – continuing education credit for pharmacists!

Accreditation and Certification Statements:

PHYSICIANS: Sidney Kimmel Medical College at Thomas Jefferson University is accredited by the ACCME to provide medical education for physicians.

Sidney Kimmel Medical College at Thomas Jefferson University designates this live activity for a maximum of ***12 AMA PRA Category 1 Credits™***. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

NURSES: Thomas Jefferson University Hospital is an approved provider of Continuing Nursing Education (CNE) by the Pennsylvania State Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation. A maximum of **12 nursing contact hours** will be awarded for this program.

To obtain the maximum 12 credit hours, physicians and nurses must complete the pre-test, attend the live conference, complete the post-test, listen to audio explanation of correct answers and attend the Saturday simulation workshop.

PHARMACISTS: This activity is eligible for ACPE credit; see final CPE activity announcement for specific details.

Friday, February 3, 2017

Jefferson Alumni Hall

7:50 am to 4:15 pm

Topics Include:

- *Management of Status Epilepticus*
- *Intracerebral Hemorrhage Management: Status of New Treatments*
- *Applying the ABCDEF Bundle in the Neuro-ICU*
- *Neuro-Critical Care on demand: Reinventing ICU Medicine in South Jersey*
- *Perioperative Management in the Neuro-ICU*
- *Infections in the Neuro-ICU*

Saturday, February 4, 2017

Case-based Practical Workshop at Jefferson's Rector Clinical Skills & Simulation Center

8:00 am to 12 noon

Case-Based Practical Workshop

*Case 1: Intracranial Pressure Crisis**

*Case 2: Status Epilepticus**

*Case 3: Malignant MCA Stroke**

Case 4: Brain Death - Didactic Cases

** Includes simulation. Space is limited for the simulation workshops.*

Vickie and Jack Farber Institute for Neuroscience™ at Jefferson

ENDORSED BY Neurocritical Care Society www.neurocriticalcare.org

Friday, February 3, 2017
Jefferson Alumni Hall

Saturday, February 4, 2017
Rector Clinical Skills & Simulation Center