COMPARISON OF PLETHYSMOGRAPHIC VARIABILITY INDEX (PVI)-BASED VERSUS STANDARD MONITORING BASED FLUID THERAPY IN SEVERE TRAUMATIC BRAIN INJURY PATIENTS UNDERGOING CRANIOTOMIES: A RANDOMISED CONTROLLED TRIAL

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LIST OF ABBREVIATIONS

ABG	Arterial Blood Gas
AC	Alternating Current
ASA	American Society of Anaesthesiology
BW	Body Weight
CPP	Cerebral Perfusion Pressure
CVP	Central Venous Pressure
DAI	Diffuse Axonal Injury
DC	Direct Current
DI	Diabetes Insipidus
ECG	Electrocardiogram
ERAS	Enhanced Recovery After Surgery
FFP	Fresh Frozen Plasma
Hb	Hemoglobin
HES	Hydroxyethy starch
HR	Heart rate
ICP	Intracranial Pressure
ICU	Intensive Care Unit
MAP	Mean Arterial Pressure
MOH	Ministry Of Health
Na^+	Sodium Ion
NIBP	Non Invasive Blood Pressure
NS	Normal Saline
PAOP	Pulmonary Artery Occlusion Pressure

pCO2	Partial Pressure of Carbon dioxide
PI	Perfusion Index
PHC	Pre hospital Care
PPV	Pulse pressure variability
PRBC	Packed Red Blood Cell
PVI	Plethysmographic Variability Index
RTA	Road Traffic Accidents
SBP	Systolic Blood Pressure
SVV	Stroke Volume Variability
TBI	Traumatic brain injury

ABSTRAK

Tajuk

Perbandingan Rawatan Cairan Berpandukan Indeks Variasi Plethysmografik (PVI) Dan Pemantauan Standard Untuk Pesakit Trauma Otak Parah Yang Menjalani Perbedahan Otak

Latar Belakang

Rawatan cairan bersasar adalah penting di kalangan pesakit trauma otak parah. Kekurangan cairan akan memburukkan kecederaan otak sekunder,manakala pemberian cairan intravena berlebihan boleh menyebabkan bengkak otak. Kajian ini bertujuan untuk menilai keberkesanan Indeks Variasi Plethysmografik (PVI) sebagai panduan rawatan cairan bersasar terhadap jumlah total cairan diberi, tahap ujian darah berkaitan (laktat, natrium, klorida , "blood gases" dan fungsi ginjal). PVI tidak invasif , and telah digunakan dalam kumpulan pesakit lain dengan berjaya. Ini adalah antara penyelidikan pertama untuk menilai keberkesanan PVI di kalangan pesakit dewasa dengan kecederaan trauma otak parah yang melalui pembedahan.

Kaedah

Ini adalah "single blinded randomised control trial". Semua pesakit 18-60 tahun dirujuk ke bahagian Kecemasan di HUSM, yang mengalami kecederaan trauma otak parah dan menjalani pembedahan otak direkrut ke dalam kajian ini. Sejumlah 68 pesakit direkrut dan diasingkan ke kumpulan PVI dan konvensional, masing- masing seramai 34 pesakit.

Setelah pesakit dibiuskan secara lazim dan disediakan untuk pembedahan, alat pemantauan standard seperti alat mengukur tekanan darah, nadi jantung dan kadar

oxigen darah dipasang. Alat tekanan darah invasif dan “central line” dipasangkan berdasarkan praktis lazim d institusi ini. PVI dipasangkan kepada pesakit dalam kumpulan PVI dari permulaan bius (0 jam) sehingga 24 jam di unit rawatan rapi.

Semua pesakit diberikan cairan berdasarkan Holliday-Segar. Di dalam kumpulan konvensional, jika tekanan darah (MAP) < 70 mmHg atau nadi ≥ 100 bpm , pesakit diberi cairan kristaloid (Natrium Klorida 0.9% atau cairan seimbang seperti Stereofundin) sehingga 20mls/kg, seterusnya 250mls gelafundin dan infusi noradrenaline atau sel darah merah jika haemoglobin (Hb) < 10g/dL. Di kalangan kumpulan PVI, jika PVI ≥ 13%, pesakit diberi 20mls/kg cairan kristaloid , diikuti dengan gelafundin 250mls sehingga PVI .< 13% dan sel darah merah jika Hb < 10g/dL. Jika PVI < 13% , dan MAP <70 mmHg atau nadi ≥ 100 bpm, infusi noradrenaline dimulakan . Protocol cairan di unit rawatan rapi juga menggunakan jumlah kencing sebagai parameter. Data hemodinamik, jumlah cairan, dan keputusan makmal (lactat, natrium, klorida, pH, BE, kreatinin) pada 0 jam dan 24 jam dicatat.

Data demografi di antara kumpulan di analisa menggunakan “chi-square test”. Data amaun and jenis cairan, serta keputusan makmal (tahap laktat, natrium, klorida, pH, BE dan kreatinin) antara kumpulan dianalisa menggunakan “independent t-test”.

Keputusan

Kumpulan PVI dan konvensional hampir sama dari segi umur (purata 32 tahun), jantina (kebanyakkan lelaki), jenis pembedahan, GCS (“Glasgow Coma Scale”), “SAPS” , “Marshall” dan “Rotterdam CT Scoring”. Dari penilaian matlamat utama, kumpulan PVI tidak menunjukkan pengurangan dari jumlah kesuluruhan cairan yang digunakan berbanding konvensional. [6352.72(2134.82) berbanding 5917.50(2171.42); p 0.422]. Tiada perbezaan dari segi jenis cairan yang diberikan

kepada kedua kumpulan tersebut. Dari penilaian matlamat kedua, tiada perbezaan antara tahap laktat pada 0 jam antara kumpulan PVI dan konvensional [2.37(1.74-3.00) and 3.13(2.58- 3.67); p 0.069] and laktat 24 jam [1.42(1.16-1.68) and 1.75(1.39-2.11) ;p 0.135] . Tiada perbezaan tahap Natrium, Klorida, Kreatinin pada 0 and 24 jam antara kedua kumpulan tersebut. Tiada perbezaan pH and BE pada awal pembiusan antara kumpulan PVI dan konvensional. Ada perbezaan tahap pH pada 24 jam antara kumpulan PVI dan konvensional [7.38(7.35 – 7.40) and 7.41(7.39-7.42); p 0.030] dan BE 24 jam [-1.81 (-2.97 to -0.65) and 0.41(-0.71 to 1.54); p< 0.007], tetapi semua nilai ini merangkumi nilai normal pH and BE.

Kesimpulan

Pengunaan PVI tidak menunjukkan pengurangan dari segi jumlah dan jenis cairan. PVI tidak memberi sebarang kelebihan berbanding konvensional dari tahap laktat, natrium, klorida, pH, BE Dan kreatinin.

Kata kunci *Rawatan Cairan Bersasar, Kecederaan Trauma Otak Parah, PVI, konvensional, cairan, laktat,*

ABSTRACT

Title:

Comparison of Plethysmographic Variability Index (PVI) based and Standard Monitoring Based Fluid Therapy In Severe Traumatic Brain Injury Patients undergoing Emergency Craniotomies

Background:

Goal directed fluid therapy in imperative in the management of patients with traumatic brain injury. Inadequate resuscitation can worsen secondary brain injury wherelse excessive fluid may worsen cerebral oedema. This study aims to ascertain the use of Plethysmographic Variability Index (PVI), as a guide for targeted therapy based on total fluids used and blood tests, which include lactate, electrolytes, blood gases and renal function. PVI is a non invasive method of dynamic fluid status monitoring, which have been used to varying success in other patient population. This is the first study to assess the utility of PVI in severe traumatic brain injury patient undergoing emergency craniotomies and craniectomies.

Methods

This is a single blinded randomised control trial. All patients presenting or referred to the emergency department HUSM diagnosed with severe traumatic brain injury , and planned for craniotomies, aged between 18-60 years, were recruited to this study. A total of 68 patient were recruited. The patients were randomly assigned to PVI group and Standard monitoring (SM) group with 34 patients in each group.

The primary outcome of this study aims to assess if PVI-based goal directed fluid therapy show a reduction in amount of fluid used. The secondary outcomes

reduction in postoperative lactate, no significant increase in electrolyte (sodium and chloride) levels, reduction in serum creatinine and improvement of blood gases in term of pH and BE as compared to conventional fluid therapy.

After induction with standard anaesthesia procedure, all patients were monitored with the electrocardiogram (ECG), Non Invasive Blood Pressure (NIBP), Pulse oximetry (SpO_2) and invasively with the arterial line and central venous line as per stanadrard protocol for craniotomies in our institution Patients in the PVI group were given the Massimo Pulse Oximetry to measure PVI from induction (0 H) until 24 hours (24 H) in the ICU.

All patient were subjected to maintenance fluid regime according to Holliday-Segar . In conventional group, if the mean arterial pressure (MAP) < 70mmHg or heart rate (HR) ≥ 100 bpm , patient were given crystalloids (Sodium Chloride 0.9% or a balanced solution such as Stereofundin) up to 20mls/kg, subsequently 250mls of Gelafundin and Noradrenaline infusion or packed cell transfusion if Hb levels < 10g/dL. In the PVI group, PVI ≥ 13 indicates hypovolemia. These patient were given up to 20 mls/kg of crystalloids , followed by Gelafundin 250 mls and packed cell transfusion if Hb was < 10g/dL , until PVI .< 13% . A PVI of < 13% indicated adequate volume. However in these patient with a PVI of < 13% and MAP <70 mmHg or HR ≥ 100 bpm, Noradrenaline infusion was initiated . Fluid management protocols in the Intensive Care Unit included urine output, with recommended intervention at a urine output of less than 0.5-1cc/kg/hr. The hemodynamic data and total fluid administered, and laboratory parameters (serum lactate, sodium (Na), chloride (Cl), pH, base excess (BE), creatinine) at 0 H and 24 H was recorded.

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The demographic data in between groups were analysed using descriptive analysis chi square test. Independent t-test was used to analyze the amount of different types of fluids used, total amount of fluid used and blood loss. The difference in lactate, pH, BE, Na^+ and Cl^- and creatinine between groups was analysed using the Independent t-test.

Results

Demographic features of both the conventional and PVI group were similar in terms of age (mean age of 32 years) , sex (predominantly male) , types of surgery , GCS (Glasgow coma score), SAPS scores, Marshal and Rotterdam CT scoring. The primary outcome evaluation revealed that PVI group showed no significant difference in term of total fluid used as compared to the conventional group [6352.72(2134.82) vs 5917.50(2171.42); p 0.422]. In addition , there were no significant difference in individual fluid types and blood component administered between both groups. Analysis of the secondary outcomes showed that here was no significant difference in pre lactate levels PVI and conventional [2.37(1.74-3.00) and 3.13(2.58- 3.67); p 0.069] and 24 H lactate levels [1.42(1.16-1.68) and 1.75(1.39-2.11) ;p 0.135] .There were no significant differences in pre and post serum sodium, chloride and creatinine levels between PVI and conventional group. There were no significant differences in pH and BE levels at 0 H between PVI and conventional group. There was a significant difference in 24 H pH levels between PVI and conventional [7.38(7.35 – 7.40) and 7.41(7.39-7.42); p 0.030] and 24 H BE [-1.81 (-2.97 to -0.65) and 0.41(-0.71 to 1.54); p< 0.007], however in both groups remain within the normal safe range of pH and BE.

Conclusion

In summary, PVI guided fluid therapy is not associated with a significant reduction in amount and type of fluid used. PVI confers no clinically significant benefit to conventional therapy in terms of lactate, sodium, chloride, pH, BE and creatinine levels.

Keywords Keywords *Gold Directed Fluid Therapy, Traumatic Brain Injury, Plethymographic Variability Index, Standard monitoring, Fluid, Lactate*

CHAPTER 1: INTRODUCTION

1.1 General Introduction

In 2018, the Ministry of Transport reported 548598 Road Traffic Accidents (RTAs), leading to 6284 (1.15%) deaths and 2964 (0.54%) severe disabilities. (Transport, 2019). Traumatic brain injury is a common cause of death in road traffic accidents (RTA). It probably accounts for three quarter of the morbidity and mortality rates in RTA in the country. (Liew *et al.*, 2009)

According to the Malaysia Clinical Practical Guidelines for Early Management of Head Injury 2015, head injury was the fifth (7.86%) commonest cause of hospitalisation in MOH (Ministry of Health) hospitals. The younger age group between 15-34 years (56.6%) was at the highest risk of major trauma, with 75% of motorcyclists being most commonly injured. (Boon Seng *et al.*, 2015) In 2015, head injury was the third commonest cause for Intensive Care admission in MOH hospitals. (Tong *et al.*, 2015)

Based on the World Health Organization Global status report on road safety 2018, the global road traffic fatality rate was 18.2 per 100 000 population. Malaysia's road traffic fatality rate is 23 per 100 000 populations, whereas in Europe the fatality rate is 9.3 per 100,000 population. (World Health Organization, 2018)

Trauma patients provide a unique challenge for all health providers involved, as they present with multiple injuries. Head injury patients may present with facial and

spine injuries. Factor that increase likelihood of death including flail chest, open or depressed skull fracture, pelvic fracture, penetrating injury to the head, neck, torso and extremities and two or more proximal long-bone fractures. (Boon Seng *et al.*, 2015)

Many lives can be saved with good pre-hospital care (PHC) , quick transportation to hospitals, effective trauma services provided by secondary and tertiary hospitals in Malaysia.

There are many aspects to managing traumatic brain injury patients. Fluid management is an integral part of this process.

1.2 Background

Fluid management in imperative in resuscitation in patient with traumatic brain injury. Inadequate resuscitation can lead to hypotension, low cerebral perfusion pressure and worsen secondary brain injury. Excessive fluid can cause interstitial fluid accumulation may worsen cerebral oedema can cause pulmonary oedema, which will increase morbidity and mortality.

To date there are no specific guidelines to address this issue. The finding criteria to predict fluid responsiveness in the bedside has been challenging for years. For this purpose, static indicators such as central venous pressure, have significant limitations. Therefore, dynamic indices are preferred. Such an index is the PVI (Plethysmographic variability index). The PVI is a non invasive technique based on perfusion index (PI) variations during the respiratory cycle. PVI allows automated and continuous calculation of the respiratory variations in the pulse oximeter waveform amplitude.

Our study aims to look into the utility of PVI, which is a non invasive, continuous monitoring of intravascular volume and a guide to manage fluids in these subset of patients.

1.3 Literature Review

1.3.1 Anaesthetic Considerations In Emergency Craniotomy And Craniectomy

Traumatic brain injury can be classified by its pathophysiology into primary and secondary brain injury. Primary injury occurs during the trauma impact itself as there will be energy transfer to the brain tissue causing direct neuronal damages, causing irreversible damages to the neuronal structures. This can lead to focal contusions and hematomas, as well as shearing of white matter tracts (diffuse axonal injury [DAI]) along with cerebral oedema and swelling. Extra-axial hematomas are generally encountered when forces are distributed to the cranial vault and the most superficial cerebral layers. These include epidural, subdural, and subarachnoid haemorrhage. (Idris *et al.*, 2019)

Approximately one-third of patients with severe TBI develop a coagulopathy, which is associated with an increased risk of haemorrhage enlargement, poor neurologic outcomes, and death. While the coagulopathy may result from existing patient medications such as warfarin or antiplatelet agents, acute TBI is also thought to produce a coagulopathy through the systemic release of tissue factor and brain

phospholipids into the circulation, leading to inappropriate intravascular coagulation and a consumptive coagulopathy. (Wafaisade *et al.*, 2010)

Secondary brain injury involves a cascade of molecular injury mechanisms that are initiated at the time of initial trauma and continue for hours or days. Secondary injuries will be subsequently triggered by hypoxic-ischemic event, inflammatory cytokines, and free radicals, which are released by the injured neuronal cells. Secondary injuries play an important role in determining posttraumatic recovery. Secondary injuries will lead to breakdown of the cerebral blood brain barrier, leading to worsening cerebral oedema and thus forming a vicious cycle toward further neuronal damages. (Idris *et al.*, 2019)

The prevention and treatment of secondary brain injury decreases mortality and improve outcomes. Specifically, treatment should address not only cerebral protection but also prevention of injury to other organ systems. Examples include avoiding hypotension and hypoxia (which decrease substrate delivery of oxygen and glucose to injured brain), ameliorating fever and seizures (which may further increase metabolic demand), avoiding hyperglycaemia, hypernatremia, hyponatremia and acidosis (which may exacerbate ongoing injury mechanisms)

The Brain Trauma Foundation guideline for severe TBI recommend target CPP value for survival and favourable outcomes is between 60 and 70 mm Hg. In practice, a CPP of 50- 70 mmHg is used. Based on the formula CPP= MAP – ICP. We need a target Avoiding aggressive attempts to maintain CPP .70 mm Hg with fluids

and pressors may be considered because of the risk of adult respiratory failure. (Carney *et al.*, 2017)

1.3.2 Perioperative And Critical Care Fluid Management And Vasopressors

It is prudent to maintain euvolemia in TBI patients as both hypovolemia and hypervolemia can have deleterious result. Maintenance fluids are given as per the Holliday Segar formula. The first 10 kgs is 4ml/kg/hour, the second 10kgs is 2ml/kg/hour , and every subsequent weight is 1ml/kg/hour.

Fluid resuscitation in the trauma patient is challenging as they may have presented with haemorrhagic shock. It is important to remember that isolated traumatic brain injury does not cause shock till terminal stage. Common causes of shock in trauma patients include external bleeding, or trauma to the chest, abdomen, pelvis and retroperitoneum and long bones, which need to be ruled out. (Tandon & Kior, 2016)

Primary studies on fluid therapy in traumatic brain injury patients are scarce (Alvis-Miranda, Castellar-Leones & Moscote-Salazar, 2014). Many studies and recommendation in neurosurgery and neurocritical care are targeted at patients diagnosed with Subarachnoid Haemorrhage (SAH). (van der Jagt, 2016). The Brain Trauma Foundation 2016 have no recommendations for fluid management in TBI patients. (Carney *et al.*, 2017)

The end goal of fluid therapy is in traumatic brain injury patients, is to maintain adequacy of cerebral perfusion and oxygenation. A review article in 2014

recommends maintenance of normovolemia and colloid osmotic pressure, with a neutral to a slightly negative fluid balance for severe TBI. Injury. (Alvis-Miranda, Castellar-Leones & Moscote-Salazar, 2014).

In TBI, destruction of the normally tightly intact endothelium of the blood brain barrier allows uncontrolled movement of fluid and serum proteins into the brain parenchyma leading to vasogenic cerebral edema and increased ICP. This is compounded by administration of colloids such as albumin. Knowledge of various IV fluids, and pathophysiology of endothelial, parenchymal and endocrine alterations emerging in TBI should guide IV fluid administration which favors better neurological, morbidity and mortality outcomes.(Alvis-Miranda, Castellar-Leones & Moscote-Salazar, 2014).

The resuscitation fluid of choice is Normal Saline 0.9% (NS). However, some of the disadvantages include the need for larger volume of NS to maintain the target MAP causing undesirable expansion of peripheral compartment, dilutional coagulopathy and non-ionic gap hyperchloremic acidosis. Hypotonic crystalloids such as compounded sodium lactate (Ringer's lactate or Hartmann's solution) should be avoided. As a general principle, glucose-containing solutions are not recommended. (Myburgh & Saxena, 2014)

Colloids have the benefit that they remain in the vascular compartment for a longer period and not only restore but expand the blood volume, the volume required to replace the blood loss is much less than crystalloids, thus reducing the cellular oedema. The role of colloid in traumatic brain injury is still debated. The use of

albumin is associated with increased mortality in traumatic brain injury, as demonstrated in the SAFE trial 2004. (Finfer *et al.*, 2004) . Starches (HES) are avoided as well due to the high incidence of nephrotoxicity. Gelatins have lower incidence of dilutional coagulopathy, and no dose limitation as compared to starches and gelatins, however are associated with hypersensitivity reaction. (Ramesh, Uma & Farhath, 2019)

Hypertonic saline has been studied as an alternative for crystalloid therapy for fluid resuscitation in patients with traumatic brain injury. The confer the advantage of better restoration of intravascular volume than crystalloid , and reduction in cerebral oedema due to the higher tonicity. A metanalysis in 2019, showed no significant difference in improving the clinical outcome and reducing mortality in hypertonic solutions as compared to crystalloid in patients with TBI. (Schwimmbeck *et al.*, 2019)

In our settings, mannitol which is the recommended hyperosmolar therapy by the Brain Trauma Foundation is generally used in the prehospital and emergency department. Hypertonic Saline is generally used to manage raised intracranial pressure post operatively in the ICU. Hypertonic saline cause less hypovolemia, less rebound hypertension, and less renal toxicity than mannitol. (Fatima *et al.*, 2020) However, hypertonic saline is also associated with hypernatremia, and hyperchloremic acidosis.

Blood and blood products form a part of balanced resuscitation where limited volumes of crystalloids are infused in the initial period till blood is available for transfusion. However, transfusion of only RBCs does not suffice as there is dilution of coagulation factors because of crystalloid infusions and platelet deficiency. (Klein *et*

al., 2016) Administration of PRBC and FFP in a ratio of 1:1 should be used to replace fluid volume . Consider the administration of cryoprecipitate (two pools) and platelets(one adult therapeutic dose) until test results are available and bleeding is controlled (Tandon & Kior, 2016)

Vasoactive therapy such as epinephrine, norepinephrine or dopamine can be used to augment mean arterial pressure to attain an adequate cerebral perfusion pressure. Norepinephrine is currently regarded as the initial agent of choice for patients with traumatic brain injury. (Myburgh & Saxena, 2014)

1.3.3 Volume Status Monitoring

When these patient with severe TBI present for operation, it is pertinent to note that they have resuscitated in the field and primary care, and emergency department. It is important to take note of the patients premorbid, coexisting injuries, preoperative volume and duration of resuscitation , and current assessment of volume status and fluid responsiveness.

The Frank Startling curve illustrates the relationship between the ventricular preload and stroke volume. The response to volume infusion is more likely to occur when the cardiac preload is low than when it is high. However static markers of preload such as CVP and PAOP (pulmonary artery occlusion pressure) cannot provides a perfect measure of preload and the curve itself is different for patients, and affected by ventricular contractile function. (Guerin, Monnet & Teboul, 2013)

Conventional monitoring include static indices such as blood pressure, pulse rate, central venous pressure, and urine output. It has been shown that static parameter correlate poorly with fluid responsiveness and have disadvantages. Blood pressure is valuable to ensure adequate organ perfusion by maintaining mean arterial pressure. However, blood pressures are not predictable in individual patients. Heart rate is also affected by medication usage such as beta blockers. Elevation in central venous pressure (CVP; i.e. >10 mmHg) reflects right ventricular pressure overload, although this gives no information on the precise aetiology involved, and can be affected by multiple factors such as lung pathologies, and mechanical ventilation. (Pinsky & Payen, 2005; Guerin, Monnet & Teboul, 2013) Oliguria, urine output < 0.5cc/kg/hour in patients undergoing anaesthesia and surgery, is not a sufficient indication for fluid administration. Inhalation anaesthetics, as well as surgical stress, may reduce urine output.

Dynamic indices have been studied extensively intraoperatively and the critical care. They have shown to be valuable in predicting fluid responsiveness. This alternative method for predicting volume responsiveness is simply to challenge the Frank–Starling relationship. The principle of this dynamic method is to induce a change in cardiac preload and to observe the resulting effects on stroke volume, or cardiac output or any surrogates that are available at the bedside. Non invasive methods such as stroke volume variation (SVV), pulse pressure variation (PPV) and PVI (plethymographic variability index) and more invasive methods involving CO measurement such as PiCCO and transoesophageal doppler can be used. (Guerin, Monnet & Teboul, 2013)

1.3.4 PVI (Plethysmographic Variability Index)

PVI is a dynamic index of fluid responsiveness and an invaluable tool in goal directed fluid therapy. The Massimo ® pulse oximeter (Massimo Corp., Irvine, CA, USA) adds a module for monitoring of respiratory changes in the pulse oximetry plethysmographic waveform, derived from the perfusion index (PI). (Liu *et al.*, 2020) PVI automatically and continuously calculates the respiratory variations in the photoplethysmogram from data collected noninvasively via a pulse oximeter sensor. PI reflects the amplitude of the pulse oximeter waveform and is calculated as the pulsatile infrared signal (AC or variable component) , indexed against non pulsatile infrared signal (DC or constant component)

PI (%) = (AC/DC) x 100

Using PI, PVI is calculated PVI= $(PI_{max}-PI_{min}/PI_{max})$x 100%

Many studies have been conducted to ascertain the reliability in PVI for predicting fluid responsiveness. Most studies have been done in patient undergoing abdominal surgery, as part of the goal directed fluid therapy in ERAS (enhanced recovery after surgery) and in the critical care. Most studies in patiet undergoing abdominal surgery show a significant reduction in total amount of fluid used . (Forget, Lois & Kock, 2010; Yu, Dong & Xu, 2014; Demirel *et al.*, 2017; Cesur *et al.*, 2018)

A study involving low risk patients undergoing colorectal surgery, showed no difference in using oesophageal Doppler and the less invasive plethysmographic variability index to guide intraoperative fluid therapy. (Warnakulasuriya *et al.*, 2016)

A systematic review in 2016 involving patients in the OT and ICU showed PVI has a reasonable ability to predict fluid responsiveness. (Chu *et al.*, 2016)

A systematic review and meta-analysis in 2019 examined the reliability of PVI in predicting preload responsiveness of mechanically ventilated patients under various conditions. They concluded that the PVI can plays an important role in bedside monitoring for mechanically ventilated patients who are not undergoing surgery, such as patients after cardiac surgery and ICU patients. For different individuals, the optimal PVI cut-off value must be further determined. PVI has disadvantages in condition that affect perfusion situation of the monitored site (such as peripheral vascular disease, severe heart failure, application of vasoactive drugs, and damage of the monitored site). (Liu *et al.*, 2020)

The are very little studies to ascertain the role of PVI in trauma neurosurgery. A small study involving children undergoing neurosurgery showed that PVI can be used to predict volume responsiveness in children. (Byon *et al.*, 2013) A study in HUSM in 2016 examined the use of PVI in elective neurosurgery patient showed a significant reduction in total amount of fluids used and serum lactate levels. (Tat, 2016)

1.3.5 Lactate, Acid Base Status And Electrolytes

Lactate is a metabolic end-product of anaerobic glycolysis and is produced by the reduction of pyruvate in a reaction catalysed by lactate dehydrogenase (LDH). Normal lactate levels are less than 2 mmol/L. Lactate levels are usually raised in shock

due to hypoperfusion and tissue hypoxia , leading to lactic acidosis. Lactic acidosis is defined as the combination of a blood lactate concentration greater than 5 mmol/L and an arterial blood pH of less than 7.35, and is associated with a high mortality rate in critically ill . Surgical ICU patients had a 67% mortality when the time to normalise lactate levels was greater than 48 hours , with a 100% mortality when lactate levels failed to normalise.((Myburgh & Saxena, 2014)

In traumatic brain injury patients, a study in 2012 involving 60 patients, showed that initial blood lactate level can used as an outcome predictor in TBI patients. however that the 2 24-hour lactate clearance did not affect patient's outcome. (Djoko *et al.*, 2012) A retrospective study in 2019, showed that elevated admission lactate in children with moderate to severe TBI is associated with death, reduced ventilator-free, ICU-free, and hospital-free days. (Fu, Bai & Liu, 2019) A 2019 study involving trauma patients showed that less than 50% reduction from the initial lactate to the 24-hour lactate increased the risk of dying by 2.8 times more than in those who achieved this clearance. (Morales, Ascuntar & María, 2019)

Sodium disorders are the most common electrolyte disturbances encountered in neuroanaesthesia and critical care, and are associated with a high mortality. Hypernatremia has a complex relationship with traumatic brain injury. In the brain, hypernatremia leads to increased cellular dehydration and decreased cerebral oedema, which is often the therapeutic goal in TBI. However, this altered homeostatic state can lead to myelin damage and even neuronal death. Hypernatremia can impair other organ functions as well such as decreased left ventricular contractility, impaired glucose utilization, gluconeogenesis, and renal dysfunction. Hypernatremia (≥ 150 mEq/L) is

seen in 30%– 40% of patients with TBI. The causes of hypernatremia in TBI may be multifactorial; it may be due to hypovolemia, insensible free water losses; or high sodium load in intravenous fluids, feeds, or medications and DI (Diabetes Insipidus). It is important to note that mild hypernatremia (Na 145-155mmol/L) is often targeted in treating cerebral oedema. Therefore close monitoring of sodium levels is important to monitor and prevent rapid rise in sodium levels, and they should be treated accordingly. (Vedantam, Robertson & Gopinath, 2017).

Hyponatremia is defined as a Sodium levels < 135mmol/L. Hyponatremia in the settings of traumatic brain injury occurs due cerebral salt wasting and SIADH (Syndrome of Inappropriate Diuretic Hormone). If it is not corrected promptly, it may cause serious complications such as malignant brain oedema leading to brainstem herniation, and eventually to death. (Ahmad *et al.*, 2017)

Maintenance of normal pH is prudent in prevention of secondary brain injury. pH is defined as the decimal logarithm of the reciprocal of the hydrogen ion activity in a solution. Normal blood pH is 7.35-7.45. Metabolic acidosis, metabolic alkalosis, respiratory acidosis and respiratory alkalosis can occur in TBI patients. In one study, the most common arterial blood gas imbalance upon admission was metabolic acidosis and followed by respiratory alkalosis. These changes were significantly associated with bad outcome. (Taha & Ammar, 2015)

Metabolic acidosis in traumatic brain injury can be due to hypovolemia, hypoperfusion, lactic acidosis, seizures and hyperchloremic metabolic acidosis from iatrogenic fluid administration. Respiratory alkalosis will also lead to hypocarbia.

Prolonged prophylactic hyperventilation with PaCO2 of 25 mm Hg is not recommended. Hyperventilation is recommended as a temporizing measure for the reduction of elevated ICP. (Carney *et al.*, 2017)

Base excess and Base Deficit are measures of acid-base abnormality, described as the amount of acid or base required to bring 1 L of whole blood to a pH of 7.4, given that arterial partial pressure of CO_2 at 40mmHg and temperature at 37degress. In trauma patients, BE has been long established as an important marker of tissue perfusion and hypoxia. It also has a notable role in predicting outcomes, risk of complications, and mortality and is an important addition to prognostic scores such as Revised Injury Severity Classification (RISC) and RISC II. (Shallwani *et al.*, 2015). However, the relationship of pH and Base excess in traumatic brain injury patients, still requires further evaluation.

Creatinine levels are used as a marker to assess kidney function. In patients with TBI, acute kidney injury (AKI) develops as a result of brain insult or as a consequence of secondary inflammatory reactions. Using drugs with nephrotoxic side effects, such as mannitol and rhabdomyolysis secondary to trauma might play a considerable role in kidney injury as well.

In 2016, one study showed the significant rates of mortality and multiorgan failure among patients with severe traumatic brain injury and AKI, necessitates consideration of renoprotective measures from the early days of hospital admission. (Ramtinfar *et al.*, 2016)

1.4 Study Objectives

1.4.1 General Objectives

Comparison of conventional fluid management with Plethysmographic Variability Index (PVI)-based goal directed fluid management in severe traumatic brain injury patients undergoing craniotomies or craniectomies

1.4.2 Specific Objectives

1) To compare the total amount and types of fluids (crystalloid, colloid and blood) used between PVI and SM group at induction of anaesthesia until at the end of 24 hours
2) To compare the mean difference in blood lactate levels between PVI and SM group at induction and at the end of 24 hours
3) To compare serum electrolytes (sodium and chloride) levels between PVI and SM group at induction and at the end of 24 hours
4) To compare pH and base excess between PVI and SM group at induction and at the end of 24 hours
5) To compare serum creatinine between PVI and SM group at induction and at the end of 24 hours

1.5 Study Hypothesis

Hypothesis

PVI-based goal directed fluid therapy improves patient outcome in terms of reduced amount and type of fluid used, lower postoperative lactate levels, lesser increment in sodium and chloride levels, improvement of blood gases in term of pH and BE, and reduction in serum creatinine as compared to conventional fluid therapy.

Null hypothesis:

1) There is no difference in terms of the total amount and types of fluids (crystalloid, colloid and blood) between PVI and SM group at induction of anaesthesia until at the end of 24 hours
2) There is no difference of mean difference in blood lactate levels between PVI and SM group at induction and at the end of 24 hours
3) There is no difference in serum electrolytes (sodium and chloride) levels between PVI and SM group at induction and at the end of 24 hours
4) There is no difference in pH and base excess between PVI and SM group at induction and at the end of 24 hours
5) There is no difference in serum creatinine between PVI and SM group at induction and at the end of 24 hours

CHAPTER 2: MANUSCRIPT

2.1 Title Page

Article title:

Comparison of Standard Monitoring and Plethysmographic Variability Index-Guided Fluid Therapy In Severe Traumatic Brain Injury Patients Scheduled for Emergency Craniotomies: A Randomised Control Trial

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Potential Conflict of Interest None

2.2 Abstract

Background

Fluid management in traumatic brain injury (TBI) patients is crucial. Both excessive and inadequate fluid worsen secondary brain injury. Previous studies showed Plethysmographic Variability Index (PVI) to be beneficial in guiding fluid therapy. We aim to investigate the merit of PVI-guided fluid therapy for severe TBI patients scheduled for emergency craniotomies.

Methods

64 patients were equally assigned to standard monitoring (SM), which includes MAP, HR, urine output and PVI group. In the SM group, patient were given fluids if MAP < 70mmHg or HR > 100 bpm. In the PVI group , if PVI ≥13%, patients were given fluids. Blood products were given if haemoglobin <10 g/dL in both groups. Primary outcomes were total volume and types of fluid administered. Secondary outcome was laboratory parameters (serum lactate, sodium, chloride, pH, base excess, creatinine) at 0 and 24 hours (H) postoperatively. Independent t-test was used to analyse the amount of fluids used, and the difference in laboratory parameters at 0 and 24 H.

Results

There were no significant differences in term of the mean amount of fluid administered [6352.72(2134.82) and 5917.50(2171.42); p 0.422] and types of fluid administered

between the two groups within 24 hours.The changes of lactate, sodium, chloride, pH, base excess and creatinine between 0 and 24 H for both groups were comparable and within clinical range.

Conclusion

PVI guided fluid therapy showed no difference in amount and type of fluids given to patient with severe TBI when compared to standard monitoring.

Keywords *Guided Fluid Therapy, Traumatic Brain Injury, Plethysmographic Variability Index, Standard monitoring, Fluid, Lactate*

2.3 Introduction

Goal directed fluid management is imperative in the management of patients with traumatic brain injury. Inadequate resuscitation can worsen secondary brain injury wherelse excessive fluid may worsen cerebral oedema (1). Treatment should address not only cerebral protection but also ensuring adequate perfusion to vital organs.

Standard monitoring includes static indices such as blood pressure, pulse rate, central venous pressure, and urine output. It has been shown that these static parameters correlate poorly with fluid responsiveness (2). Dynamic indices work by inducing a change in cardiac preload and to observe the resulting effects on stroke volume, or cardiac output or any surrogates that are available at the bedside. Non invasive methods such as stroke volume variation (SVV), pulse pressure variation (PPV) require the use of specific equipment. More invasive methods involving cardiac

output measurement such as PiCCO and transesophageal doppler can be used, but require specialised equipment and training to be used (3).

PVI is a non invasive method of dynamic fluid status monitoring, which have been used to varying success in other patient population and other types of surgery. It is portable, easy to use, beneficial in emergency surgeries and places with limited resources for invasive cardiac output monitoring. Many studies have been done in abdominal surgery patients to assess the benefit of PVI, and have had a favourable outcome; reduced fluid administration (4–7). A study in elective neurosurgery in 2016 , showed a significant reduction in amount of fluid used and lactate levels in the PVI group (8). Another study in children undergoing neurosurgery showed that PVI can be used to predict volume responsiveness in children. (9)

PVI role in neurosurgery is an area that has much potential for research. Furthermore, protocols pertaining to fluid management in traumatic brain injury patients are scarce. This is the first study to ascertain the use of PVI in adults with traumatic brain injury undergoing emergency craniotomies. In this study, we aims to ascertain the merit of Plethysmographic Variability Index (PVI)- guided fluid therapy for severe TBI patients scheduled for emergency craniotomies.

2.4 Methods

Trial Design

This is a single centre, with equal randomisation, single blind, parallel group study conducted in Hospital Universiti Sains Malaysia. The physician allocated to the standard monitoring or PVI group were aware of the allocated arm, wherelse the next of kin were blinded to the allocated arm. This study was approved by The Human

Research Ethics Committee of USM (USM/JEPeM/19010085). It was registered at the US National Institutes of Health (ClinicalTrials.gov) retrospectively, and complied with good clinical practice.

Study Population

This study took place in Hospital Universiti Sains Malaysia , Kubang Kerian , Kelantan from July 2019 Until October 2020. Patient who presented to emergency department HUSM diagnosed with severe traumatic brain injury based on a GCS (Glasgow Coma Scale ≤ 8), Brain CT Scan finding (based on Marshall and Rotterdam scoring), and the SAPS (simplified acute physical injury) score and planned for craniotomies were assessed for eligibility. Patients who were between 18-60 years old and ASA (American Society of Anaesthesiology) Class I and II were included. Patients with serious cardiac arrhythmias, peripheral artery disease, presence of renal or liver dysfunction, presence of concurrent thoracic injury requiring higher ventilator settings with tidal volume > 10 ml/kg or PEEP > 10 cmH_2O, extracranial major vascular injury (upper limb, lower limb, intrathoracic or intrabdominal , and patients with no valid consent from next of kin or caretaker were excluded.

Study Interventions

Patients were randomly assigned to SM group and PVI group , with 34 patients in each group. All patient were mechanically ventilated. All patients were monitored with the electrocardiogram (ECG), Non Invasive Blood Pressure (NIBP), Pulse oximetry (SpO_2) and arterial line . A central venous line was inserted. All patient were subjected to maintenance fluid regime according to Holliday-Segar (4ml/kg/hr for the 1^{st} 10kg BW, 2ml/kg/hr for 2^{nd} 10kg BW and 1ml/kg/hr for the remainder BW).

In the SM group, if the mean arterial pressure (MAP) < 70mmHg or HR ≥ 100 bpm , patient were given crystalloid boluses up to 20mls/kg. If the MAP remained < 70mmHg or HR ≥ 100 bpm, a gelafundin bolus of 250mls was given and IVI noradrenaline was initiated at 0.05-1.5 mcg/kg/min. If Hb was < 10g/dL, packed cell transfusion was initiated. Once in the ICU, a urine output of < 0.5cc- 1cc/kg/hr, would necessitate a fluid bolus same as mentioned above.

In the PVI group, a pulse oximetry probe was connected to the fourth finger of the hand that did not have an arterial cannulation. The pulse oximeter was connected to a monitor The Massimo ® pulse oximeter (Massimo Corp., Irvine, CA, USA), which has a module for PVI measurements.

PVI automatically and continuously calculates the respiratory variations in the photoplethysmogram from data collected noninvasively via a pulse oximeter sensor. PI reflects the amplitude of the pulse oximeter waveform and is calculated as the pulsatile infrared signal (AC or variable component) , indexed against non pulsatile infrared signal (DC or constant component) (PI (%) = (AC/DC) x 100). Using PI, PVI is calculated PVI= $(PI_{max}-PI_{min}/PI_{max})$x 100%.

If value of PVI ≥13% was obtained, crystalloid boluses up to 20mls/kg were given. If PVI ≥13%, a gelafundin bolus of 250mls were given until PVI .< 13%. If Hb was < 10g/dL, packed cell transfusion was initiated until PVI < 13%. If the PVI value of < 13% and the MAP <70 mmHg or HR ≥ 100 bpm, IVI noradrenaline infusion was initiated at 0.05-1.5 mcg/kg/min. In the ICU if PVI ≥ 13, urine output < 0.5cc/kg/hour, fluid boluses were given as above.The protocols were meant to be a guide with no restrictions to type of fluids (NS 0.9%, Stereofundin,,colloids) used, and no guideline for initiation of blood product transfusion in both groups.

Randomisation

Randomisation sequence was created using the online randomisation application. (www.randomizer.org), with a 1:1 allocation by the primary investigator. Once a patient with severe traumatic brain injury has been posted for an emergency craniotomy, a white envelope was given to the anaesthetic medical officer, If the patient fulfils the eligibility criteria, and the next of kin have consented for recruitment to this study, a second sealed white envelope will be given to the anaesthetic medical officer in charge, which contains data collection sheets and protocols. The envelope given was sequentially numbered and sealed , with the patients name, identity card, and date of enrolment written on it by the physician. These sealed white envelopes, with the PVI machine was kept in a locked cupboard in the Anaesthesia department in Hospital Universiti Sains Malaysia, only accessible to the primary investigator.

Study Outcomes

Primary outcomes were to compare the total amount and type of fluids (crystalloids, colloids and blood products) administered in both groups at 0 hours (at induction) until 24 hours post operatively in the ICU. Secondary Outcomes were to measure the mean difference in blood lactate levels, serum electrolytes (sodium and chloride) , pH and base excess and serum creatinine of both groups at induction (0 H) and at the end of 24 H.

Sample Size and Statistical Analyses

The sample size calculation was performed using Power and Sample Size Calculations System, . From the study by Tat in 2016, the standard deviation for amount of fluid

used was 2637.45, with a mean difference of 1361.31. The α value is set at 0.05 and power of study at 80%. The sample size is calculated using t test. Adding a drop out rate of 10%, the number in each arm will be 34. All statistical analysis was performed using Statistical Package for the Social Science (SPSS) version 26. Results were presented as frequency (percentages) for descriptive data, mean (standard deviation) for total fluids as well as mean (confidence interval) for laboratory parameters. A total of 64 patient were deemed eligible. The demographic data in between groups were analyzed using descriptive analysis chi square test. Independent t-test was used to analyze the total volume and different types of fluid used. The difference in lactate, pH, BE, Na^+ and Cl^- and Creatinine between groups was analysed using the Independent t-test.

2.5 Results

68 samples were recruited for this study from July 2019 till October 2020. 34 patients were randomly assigned to SM group and PVI group 2 each. The drop out rate in this study was 5.9%, with a total of 4 patients. In the PVI group, one patient developed anaphylactoid reaction secondary to Gelafundin and another patient developed cranial diabetic insipidus. One patient in the control group was excluded , as the patient required an emergency decompressive craniectomy less than 24 hours after the first craniotomy, and another loss to follow up due to transfer back to the referral hospital post operation.

Analysis of the descriptive variables (Table 2.1) showed that there were no significant difference in group demographic. There was no significant difference in