COMPARISON OF INTRAOPERATIVE GOAL-DIRECTED FLUID THERAPY BETWEEN PLETHYSMOGRAPHIC VARIABILITY INDEX (PVI) - GUIDED AND STANDARD INVASIVE MONITORING - GUIDED(SIM) DURING ELECTIVE NEUROSURGERY

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LIST OF ABBREVIATIONS

ABG	Arterial blood gas
ASA	American Society of Anaesthesiologists
BP	Blood pressure
BUSE	Blood Urea and serum electrolytes
CBF	Cerebral blood flow
CI	Cardiac index
CMR	Cerebral metabolic rate
CPP	Cerebral perfusion pressure
CVP	Central venous pressure
DBP	Diastolic blood pressure
DI	Diabetes insipidus
ECF	Extracellular fluid
ECG	Electrocardiogram
EDM	Esophageal doppler monitor
GDFT	Goal directed fluid therapy
HR	Heart rate
ICF	Intracellular fluid
ICP	Intracranial pressure
ICU	Intensive care unit
K^+	Potassium ion
MAP	Mean Arterial Pressure

Na^+	Sodium ion
PAC	Pulmonary artery catheter
PaCO2	Arterial partial pressure of carbon dioxide
PaO2	Arterial partial pressure of oxygen
PI	Perfusion index
PPV	Pulse pressure variability
PVI	Plethysmographic variability index
SAH	Subarachnoichaemorrhage
SPV	Systolic pressure variability
SVV	Stroke volume variability
TBI	Traumatic brain injury
TBW	Total body water
TCI	Targeted controlled infusion

ABSTRACT

Tajuk: Perbandingan Intraoperatif Cecair Berpandukan Matlamat Antara Plethysmographic Variability Index Dan Pemerhatian Berpandukan Invasif Semasa Pembedahan Elektif Neurosurgeri.

Latar Belakang :

Pemberian cecair secara berhati – hati adalah penting untuk mencegah komplikasi perioperative. Matlamat utama kajian ini adalah untuk mengetahui samada penggunaan plethysmographic variability index (PVI) akan membimbing penggunaan cecair dan meningkatkan perfusi darah sebagai mana ditentukan melalui tahap lactate dalam darah.

Metodologi :

Lapan puluh empat pesakit yang berumur antara 18 hingga 65 tahun yang menjalani pembedahan elektif neurosurgery telah dipilih secara rawak ke dalam kumpulan yang menggunakan PVI (PVI, n =42) atau Pemerhatian Berpandukan Invasif (SIM, n =42). Di dalam kumpulan PVI, preload cecair Normal Saline 0.9% sebanyak 500ml diberikan sebelum induksi pembiusan penuh. Keperluan cecair mereka ditentukann melalui formula Holliday Segar. Seandainya nilai PVI > 14%, pesakit akan diberikan cecair atau darah, berdasarkan protocol yang telah dijadualkan. Di dalam kumpulan SIM, preload sebanyak 500ml Normal Saline 0.9% diberikan sebelum induksi pembiusan. Keperluan cecair mereka ditentukann melalui formula Holliday

Segar. Normal Saline 0.9% sebanyak 250ml akan diberikan secara bolus untuk mencapai keseimbangan hemodinamik yang stabil seperti mana ditunjukkan daripada mean arterial pressure (MAP) yang kurang daripada 70mmHg dan nadi (HR) yang lebih daripada 100 kali per minute. Cecair koloid dan darah tambahan diberikan mengikut perubahan nilai pemantauan dan kadar kehilangan darah daripada badan. Infusi noradrenaline telah diberikan untuk mencapai MAP lebih daripada 70mmHg di dalam kedua – dua kumpulan jika MAP masih rendah daripada 70mmHg setelah diberikan cecair yang mencukupi. Tahap darah nilai laktat dan elektrolit, data hemodinamik dan jumlah cecair yang diberikan semasa intraoperative telah direkodkan untuk kedua – dua kumpulan pesakit tersebut.

Keputusan :

Kumpulan PVI menerima jumlah amaun normal saline dan jumlah Cecair yang lebih rendah daripada kumpulan SIM. Perbezaan antara min (SD) untuk jumlah amaun cecair yang diberikan untuk kedua – dua kumpulan adalah signifikan secara statistic [2643.45 (1373.28) vs 4006.76 (2637.51),nilai *P* 0.004]. Di dalam kumpulan PVI, perbezaan antara min (SD) untuk laktat sebelum dan selepas pembedahan adalah signifikan secara statistic [1.23 (0.62) vs 1.06 (0.45), nilai *P* 0.012]. Perbezaan antara min (SD) untuk nilai sodium sebelum dan selepas pembedahan adalah signifikan secara statistic [137.45 (2.94) vs 139.76 (3.93), nilai $P < 0.001$].

Konklusi :

Pemberian cecair berpandukan PVI menunjukkan pengurangan jumlah amaun cecair yang digunakan serta nilai laktat yang signifikan berserta dengan peningkatan nilai sodium di dalam darah.

CHAPTER 1 INTRODUCTION

1.1 General Introduction

Perioperative fluid optimization and its effects on patients' postoperative outcomes are crucial in the day to day practice of an anaesthetist. Patients who undergo an elective surgery are often required to be fasted for at least six hours to prevent the incidence of pulmonary aspiration. This will usually be complicated with hypovolemia and electrolytes imbalances upon presentation to the operating theatre. The condition will be compounded in additional to the perioperative blood losses, insensible fluid losses and internal redistribution of fluids. (1-3) Increased length of hospitalization and costs with organ hypoperfusion are often associated with hypovolaemia while fluid overload complicates cardiorespiratory functions and wound healings which increases morbidity and mortality (4-6).

Goal directed fluid therapy utilizes the various types of invasive and non-invasive monitoring techniques to assist a clinician on fluid administration and provision of ionotropic support to achieve a stable perfusion and oxygenation. Recent studies had demonstrated that intraoperative goal directed fluid therapy does improve patients' outcomes and reduce morbidity, mortality and length of hospitalization (7-9). Previously, intraoperative fluid therapy was based by using clinical evaluations of blood pressure, heart rate, central venous pressure (CVP) and pulmonary artery catheters (PAC) which are invasive, costly and not effective as guidance for fluid resuscitation. It is not sensitive to detect fluid responsiveness. (10) Noninvasive dynamic techniques such as oesophageal doppler monitor (EDM), stroke volume variation (SVV), pulse pressure variability (PPV) and plethysmographic variability index (PVI) had been used effectively proven as guidance for goal directed fluid therapy and prevent complications. (11-13)

Plethysmographic Variability Index (PVI) is a noninvasive algorithm allowing for automated and continuous calculation of the respiratory variations in the pulse oximeter waveform amplitude and which can predict fluid responsiveness in mechanically ventilated patients.(14) PVI continuously calculates the respiratory variations in the photoplethysmogram from the data collected via a pulse oximetry sensor which is placed on the finger tip of a patient. The dynamic changes in Perfusion Index (PI) that occurs during a complete cycle is measured and continuously displayed.

There were studies done on patients who underwent major abdominal surgeries with the use of PVI which had shown a reduction in amount of fluids used and serum lactate levels. (15, 16) However, there were no published studies to show the efficacy of PVI in patients undergoing neurosurgical procedures.

In this study, we investigated whether PVI guided fluid therapy would reduce volume of fluids infused and serum lactate levels in patients undergoing neurosurgical procedures.

1.2 LITERATURE REVIEW

1.2.1 ANAESTHESIA FOR NEUROSURGERY

The vast expansion on the knowledge of neurosurgery had spurred great interest into the field of neuroanaesthesia. It can be as simple as a ventriculo-peritoneal shunt and as complicated as a craniotomy and tumour debulking and cervical spine laminectomy. This creates a challenge to an anaesthetist to be equipped with up to date knowledge and principles of patient undergoing neurosurgical procedures. Anaesthesia for neurosurgical procedures is a subspecialty field that needs a thorough knowledge on the cerebral and spinal anatomy and physiology. Maintenance of an adequate cerebral perfusion pressure (CPP) to promote continuous blood flow and oxygen supply to the brain is of importance. The CPP is usually maintained at 80-100mmHg in the presence of an intracranial mass. The cerebral blood flow (CBF) is autoregulated and maintained at about 50ml/100g/min in normal individuals at a wide mean arterial pressures (MAP) of 60 -160mmHg. (17) Beyond this limits, the blood flow becomes MAP dependent. MAP above 160mmHg can disrupt the blood brain barrier and cause intracerebral haemorrhage and cerebral oedema while MAP below 60mmHg can cause ischemia to the brain.

Other than the MAP, the maintenance of normothermia, prevention of hypoxaemia and hypercarbia and normal levels of haemoglobin are pivotal to maintain adequate CBF.

The partial pressure of oxygen (PaO2) is maintained above 100mmHg and the partial pressure of carbon dioxide (PaCO2) is maintained at the range of 35- 45mmHg. Acute changes of these levels can be detrimental to the patient's cerebral physiology.

The anaesthetist should also be well versed with the pharmacodynamics and pharmacokinetics of anaesthetic drugs commonly used in neuroanaesthesia. Volatile anaesthetic agents such as isoflurane, sevoflurane and desflurane vasodilates the cerebral vessels and impair autoregulation in a dose-dependent manner. Thus, the final effect will be an increase in the intracranial pressure (ICP). They also decrease the cerebral metabolic rate (CMR) of the brain. Hence, with this uncoupling effect on the brain, the administration is termed luxury perfusion. Most intravenous anaesthetic agents such as propofol, etomidate, barbiturates and benzodiazepines reduce CBF and CMR. Ketamine produces increase in CBF and CMR which indirectly causes an increase in ICP. Of late, propofol and remifentanil had been effective in targeted controlled infusion (TCI) in maintaining haemodynamic stability and maintain adequate CPP. They are the mainstay of usage in neurosurgical procedures apart from other usage in surgeries involving the airway and assisting in awake fibreoptic intubation.

Neurosurgery also requires unique positioning of the patient to achieve optimal positioning and surgeon comfort to operate. Patients are often operated supine but often may need to be in prone, sitting and park bench position. These different types of positioning may have variable physiological effect on the CBF and the anaesthetist has to be knowledgeable in optimizing the CPP.

Apart from that, fluid handling is crucial in neuroanaesthesia too. Too much of a fluid will cause an increase in intracerebral blood volume thus causing increase in ICP. There are doubts and questionable benefits of hypervolaemia on CBF and brain tissue oxygenation regarding the impact of hypervolaemia on intracranial stability.(18) Anesthesiologists and neurosurgeons were advised to exercise caution on the usage of hypervolaemic therapy as a part of triple H therapy that comprises hypervolaemia, hypertension and haemodilution.

1.2.2 PERIOPERATIVE FLUIDS MANAGEMENT

Total body water (TBW) is the estimated contents of water in percentage in actual body weight in individuals. They vary between age, gender and adipose contents in the body. TBW in a healthy man with body weight of 70kg is about 40 liters, which means about 60% of his body weight is water. A healthy female contains lesser TBW which is about 55%. (19) The total body water is distributed between intracellular fluid (ICF) compartment that accounts for 40% of total body weight and extracellular fluid (ECF) compartment that constitutes 20% of body weight. ECF is sub divided into interstitial fluids and intravascular fluids (plasma). ICF is contained within cells and comprises about two thirds of TBW. Transcellular fluids constitute about 0.6% of TBW and contained within body cavities such as cerebrospinal fluids, ocular, synovial, peritoneal and pleural fluids. Plasma ions include sodium (Na^+), chloride (Cl^-) and bicarbonate (HCO_3^-) and lesser amounts of potassium (K^+), magnesium (Mg^{2+}), calcium (Ca^{2+}), phosphates, sulphates, organic acids and proteins.

Fluids are usually given intravenously via a good, reliable and functioning branula or central venous line to expand intravascular volume which is part of ECF. Commonly given fluids can be categorized into crystalloids, colloids and blood products. These have to be carefully titrated according to the general conditions of the patient, intraoperative bleeding and insensible losses generated. Therefore constant clinical evaluation and assessment of intravascular volume must be relied upon as precise measurements of fluid compartment volumes are not readily available. Laboratory examinations such as arterial blood gases, haemoglobin and haematocrite levels and renal profiles can be obtained from time to time to estimate physiological and pathological derangements intraoperatively.

Usually, fluid maintenance is given as per the Holliday Segar formula. The first 10kg is 4ml/kg/hour, second 10kg is 2ml/kg/hour and subsequent weight is 1ml/kg/hour. This precise fluid therapy is especially important in the paediatrics and elderly patients. (20)

One of anesthetists' major challenges is a good perioperative fluid optimization. Maintenance of intravascular volume is important to achieve optimal perioperative outcomes. (21-23) Both hypovolaemia and hypervolaemia are known to cause increased perioperative morbidity and mortality; therefore, assessment of the patients' actual haemodynamic status can guide appropriate therapy. Inadequate fluid resuscitation leads to hypovolaemia and is the most avoidable cause of organ dysfunction and death. Prolonged inadequate tissue perfusion and delay in fluids resuscitation may lead to worsening haemodynamic parameters, reduced microcirculation and organ dysfunction. Hypovolaemia is associated with improper organ perfusion which will lead to increased perioperative mortality and morbidities. More often than not, it is common to administer large amount of fluids intraoperatively, which will lead to increased intravascular space expansion, improve organ perfusion and tissue oxygenation.(24). Excessive fluids administration will also result in increased perioperative complications such as acute pulmonary edema, pneumonia, prolonged time to first bowel movement and increased length of hospital stay. (25)

There had been evidences which suggest that perioperative fluid balance has significant impact on patient outcomes. There had been a few published studies which suggested that goal directed fluid therapy (GDFT) can reduce organ specific complications in the acutely ill and those going for major surgeries. (8, 26).Evidences are mounting to suggest the titration of fluid therapy based on patients' individual fluid responsiveness may improve their outcome.(21)Literatures had suggested that perioperative goal directed therapy (GDT) based on flow related haemodynamic parameters improves patients outcome.(27)

1.2.3 MONITORINGS IN ANAESTHESIA

Invasive and non-invasive monitoring such as intra-arterial blood pressure, central venous pressure and urine output are usually helpful to gauge fluid needs in major surgical procedures with large fluid shifts. This is vital to prompt recognition of any haemodynamic changes and to intervene earliest as possible to avoid unnecessary complications. Intra-arterial blood pressure gives precise beat to beat changes of the blood pressure. It is also useful for the anaesthetist to obtain blood samples intraoperatively.

Currently, there are many variables that are designed to assess fluid responsiveness. Static measurements such as central venous pressures (CVP), pulmonary artery occlusion pressure (PAOP), left ventricular end diastolic area and cardiac index are invasive type of monitor. It needs to be carefully threaded into the patients' radial or brachial artery or into the central veins. Real time, sophisticated and noninvasive methods also called dynamic measurements, involves pulse pressure variability (PPV), systolic pressure variability (SPV), stroke volume variability (SVV) and plethysmographic variability index (PVI). A systematic review of the role of central venous pressure (CVP) measurement in fluid therapy concluded that neither the CVP number nor the rate of change of CVP was accurate in assessing blood volume or in predicting the response to a fluid challenge. Therefore, caution should be exercised in interpreting CVP data to guide fluid administration. (28)

1.2.4 PLETHYSMOGRAPHIC VARIABILITY INDEX (PVI)

Non-invasive monitoring continues to rule and be the main option of choice to predict fluid responsiveness in the operating theatre.(6) The study showed that goal directed intraoperative fluid administration guided by systolic flow time measurements obtained from oesophageal Doppler monitoring results in earlier return of bowel function, lower incidences of postoperative nausea and vomiting and decrease in length of postoperative hospital stay.Many other studies have also demonstrated positive postoperative outcomes when patients are managed well and guided by dynamic parameters of hemodynamic function such as Pulse Pressure Variability (PPV) and Stroke Volume Variability (SVV) in surgeries such as hip fracture repair, gastrointestinal surgery and many other major surgeries.(12, 29, 30)

Plethysmographic Variability Index (PVI) is a dynamic index that is noninvasively used to allow for the continuous estimation of respiratory variations in the pulse oxymeter forms in patients who are mechanically ventilated. PVI continuously calculates the respiratory variations in the photoplethysmogram from the data collected noninvasively via a pulse oximetry sensor. The dynamic change in Perfusion Index (PI) that occurs during a complete respiratory cycle is measured and automatically calculated.(31) The pulse oximetry uses red and infrared light and a constant amount of light from the pulse oximeter is absorbed by skin, tissues and non-pulsatile blood whereas a variable amount is absorbed by the pulsating arterial inflow. The dynamic change in Perfusion Index (PI) that occurs during a complete respiratory cycle is measured and automatically calculated as PVI. It is displayed continuously in the machine and derived from [$(PI_{max} – PI_{min})$ / P_{max}] x100. PVI can also be used to predict fluid responsiveness in those ventilated patients undergoing major surgeries. Cannesson et al., 2008 had demonstrated the ability of PVI to predict fluid responsiveness in the operating theatre. In addition, they also managed to prove that CVP and Cardiac Index (CI) are poor predictive ability at the same clinical settings.(32)PVI represents the first noninvasive, continuous, widely available and easy to use index that can be used to predict fluid responsiveness in patients who are sedated under positive pressure ventilation.

There has been increasing interests on the availability of PVI to gauge fluid responsiveness for patients undergoing major surgeries. A study conducted in Seoul National University Hospital in 2012 demonstrated that PVI was being able to predict fluid responsiveness in children who are mechanically ventilated undergoing neurosurgeries.(33) In the year 2010, Forget and colleagues showed that PVI directed fluid management reduced the volume of intraoperative fluids infused and reduced intraoperative and postoperative serum lactate levels compared to the standard of care group in patients undergoing major abdominal surgeries. (15)

1.2.5 LACTATE METABOLISM

Lactate is a byproduct of anaerobic metabolism, elevated in hypoperfusion states when pyruvate cannot enter the Krebs cycle due to insufficient oxygen supply and it is shunted to lactate. Lactate production greatly exceeds the rate of metabolism in states of global hypoperfusion, which will result in the increase in serum lactate levels. Imbalance between oxygen delivery and demand to the tissues is characteristic of acute hypoperfusion. Inability to satisfy the basic metabolic and oxygen requirement will result in organ dysfunction and failure. (1)

Multiple experiments and clinical assessments had shown that serum lactate will start to increase whenever oxygen delivery is inadequate to maintain basic normal tissue oxygenation.(34) Serum lactate levels are closely related to a poor outcome in critically ill patients.

Traditionally, resuscitation of surgical patients has always been guided by the normalization of vital signs, such as blood pressure, heart rate and urine output; and only when haemodynamic instability persists, invasive monitoring is required such as central venous pressure and arterial lines. Ideally, the marker of adequate resuscitation should be able to assess resolution and improvement of hypoperfusion. The aim for an early correction seems to improve outcome.(35,36) Elevated serum lactate levels in haemodynamically stable surgical patients are associated with a higher mortality rates and postoperative complications.(37) A goal-oriented protocol targeting a normal blood lactate can shorten the length of hospitalization and decrease mortality rates.(38, 39)

The use of serum lactate as an endpoint of resuscitation is based on a substantial literatures, including multiple prospective studies in trauma and surgical patients and also the critically ill patients in the Intensive Care Unit and operating theatres. However, there were no studies done yet on the implication of PVI in neurosurgical patients.

1.2.6 ELECTROLYTES IMBALANCES AND NEUROSURGERIES

The most common electrolyte imbalance seen in neurosurgical patients is hyponatraemia. It is multifactorial and most common causes are syndrome of inappropriate antiduretic hormone (SIADH) or cerebral salt wasting syndrome (CSWS). It may also be common to see hypernatraemia in this group of patients especially in neuro trauma or postoperative care. Cranial diabetes insipidus (DI) is a common cause of death in the neurosurgical ICU. Careful titration of fluids as per requirement to content the hypo or hypernatraemia is of outmost importance. Correction of these incidences is crucial so as to prevent cerebral oedema or cerebral pontine myelinolysis.

In a proportion of the patients the association between hypernatraemia and death is accounted for by the presence of central diabetes insipidus.(40). Hypernatraemia occurs less commonly than hyponatraemia and it is more common in brain-injured patients and is often an indicator of the severity of the underlying disease.(41) Diabetes Insipidus (DI) is associated with TBI, SAH, intracerebral haemorrhage, and pituitary surgery. Causes of hypernatraemia for neurosurgical patients should be carefully delineated in order to treat and prevent the complications. Most common cause is the infusion of hypertonic saline and application of triple H therapy (hypervolaemia, hypertension and haemodilution) for treatment of cerebral vasospasm. In fact, the choice of fluids for resuscitation in neurosurgical patients is limited to crystalloids (normal saline 0.9%, half saline 0.45% or Sterofundin) or colloids (Gelafundin) solutions only. It is due to the risk of cerebral oedema with lactate containing solutions of Hartman's saline which prevented its use in resuscitating neurosurgical patients. Normal saline contains 154mmol of sodium per liter of solution, which contributes to excessive sodium ions in plasma and not physiological. Hypernatraemia will result in neuronal cellular injury and cerebral oedema. Therefore appropriate monitoring of sodium levels intraoperatively is crucial to contain this problem in order to improve prognosis of patients undergoing elective craniotomies. Maintaining as near perfect electrolytes analysis on neurosurgical patients are important to maintain neuronal firing and integrity.

1.3 OBJECTIVES

1.3.1 GENERAL OBJECTIVES

To evaluate the efficacy between PVI guided and standard invasive monitoring in patients undergoing elective neurosurgical procedures.

1.3.2 SPECIFIC OBJECTIVES

1) To compare haemodynamics parameters (MAP and HR) between PVI guided and standard invasive monitoring in patients undergoing elective neurosurgeries.

2) To compare the mean differences of serum electrolytes and serum lactate levels between PVI guided and standard invasive monitoring pre and post operatively.

3) To compare the total volume of fluids infused to patients intraoperatively between PVI guided and standard invasive monitoring.

1.3.3 STUDY HYPOTHESIS

H0 : There are no differences in haemodynamic changes between PVI guided and standard invasive monitoring groups.

H0 : There are no differences in the levels of serum electrolytes and lactate between PVI guided and standard invasive monitoring.

H0: There are no differences in the amount of fluids infused intra operatively following the usage of PVI as compared to standard invasive monitoring.

1.4METHODOLOGY

1.4.1 STUDY DESIGN

This was a single blinded, randomized control trial in which the study protocol was designed and presented to the Human Research Ethics Committee of Health Campus Universiti Sains Malaysia for approval.

1.4.2 STUDY PERIOD:

The study was started from March 2015 until February 2016

1.4.3 STUDY SETTING:

The study was performed in the operation theatre, Hospital Universiti Sains Malaysia

1.4.4 STUDY POPULATION:

Study subjects were recruited from patients who were scheduled for elective neurosurgical procedures based on inclusion and exclusion criteria set out as below:

1.4.4(a) Inclusion Criteria:

- Consenting adults aged between 18 to 65 years old
- American Society of Anaesthesiologists (ASA) physical status of 1 to 2
- Patients scheduled for elective craniotomies under general anaesthesia

1.4.4(b) Exclusion Criteria:

- Extreme age of less than 18 or more than 65 years old
- Patients with heart diseases or abnormal cardiac functions detected on electrocardiogram or echocardiography
- Patients with permanent cardiac arrhythmias with pacemakers
- Patients undergoing emergency surgeries
- Previous or current history of heart failure
- Uncontrolled Diabetic and / or Hypertension with signs and symptoms of end organ damage.
- Patients who are pregnant.

1.4.5 SAMPLE SIZE CALCULATION

The sample size calculation was performed using the Power and Sample Size Calculation system (PS), with a type 1 error of 0.0500. From previous studies by Forget t.al 2010, the mean detectable difference for the total amount of crystalloids infused between control and study is 524mililiters with an SD of 813 mililiters for the control group. Using the PS calculation, n will be 42 for each group of patients.

1.4.6 SAMPLING METHOD

Consented patients were randomized into 2 groups: group A and group B. Group A is PVI which then received PVI sensor for intra operative fluid monitoring or no PVI sensor. Group B is SIM without PVI sensor applied during surgery. Simple randomization method was employed during the procedure as mentioned below:

1) 42 cards were labelled as PVI and another 42 cards were labelled as SIM. The cards are then mixed and put into a black envelope.
2) The patients were required to pick a card from a bag by a GA nurse. This means that 42 patients will be randomized into either PVI or SIM group with a total of 84 patients.

1.4.7 STUDY FLOW

Upon obtaining approval from the Human Research Ethics Committee of Health Campus, Universiti Sains Malaysia, a written informed consent was obtained from 84 patients aged between 18 and 65 years old with American Society Anesthesiologists (ASA) physical status 1 and 2 who were to undergo elective neurosurgical procedures. Exclusion criteria for this study are patients age less than 18 or more than 65 years old, emergency surgeries, patients with significant cardiorespiratory and renal diseases and pregnant women.

The patients are randomized into PVI guided and non PVI guided group (standard care). Each would have 42 patients. In both groups of patients, standard intraoperative monitoring of electrocardiogram (ECG), nasopharyngeal core temperature probes, end tidal CO2 (ETCO2), pulse oximetry and non invasive arterial blood pressure (BP). Invasive monitors such as arterial lines, central venous access catheter and a continuous bladder drainage CBD was inserted. A Masimo Rainbow SET Pulse Oximeter version, Radical 7 (Masimo Co., Irving, California**)** is placed on patient's index finger for PVI monitoring. General anaesthesia was induced with IV Fentanyl 2mcg/kg , IV Propofol 2mg/kg and IV Rocuronium 0.6mg/kg. The trachea is intubated with an appropriate sized endotracheal tube. Maintenance of anaesthesia with oxygen/air with total flow of 2Liters/ minute with FiO2 0.35 to 0.4. Target controlled infusion (TCI) of remifentanil and propofol were used and adjusted according to the depth of anaesthesia and hemodynamics stability.

In the PVI group of patients, 500ml of normal saline 0.9% is preloaded over 10minutes prior to induction of anaesthesia. It is then followed by maintenance of the fluid at a rate 4ml/kg/ hour for the first 10kg, followed by 2ml/kg/hour for the next 10kg and 1ml/kg/hour for the subsequent weights as per Holliday Segar formula. PVI values which were more than 14% for more than 5 minutes, were given a bolus of Normal Saline 0.9% of 4ml/kg over 5 minutes and if the PVI was still more than 14%, another similar volume of the solution is infused over 5minutes. The dose is repeated every 5 minutes whenever the PVI is more than 14% until a maximum amount of 20ml/kg of Normal Saline 0.9% is given. HES 6% Gelafundin will be given in similar steps until the maximum of 20ml/kg if there were no responses to Normal Saline 0.9%. Blood products were given in patients with a MAP of less than 70mmHg, massive blood loss and evidences of a drop in hemoglobin levels. Vasoactive agents such as Noradrenaline will be started should the MAP is still low despite the fluid resuscitation above as accordance to the PVI values (please refer to Chart 1).

In the control group, a volume preloading with 500ml of normal saline 0.9% over 10 minutes prior to induction of anaesthesia. Fluid maintenance with normal saline 0.9% as per Holliday Segar formula was followed as the PVI group. A bolus of 250ml of fluids as per experience and preferences of the anesthetist with either normal saline 0.9%, colloids (HES 6% Gelafundin) or blood products as needed if the MAP is less than 70mmHg , central venous pressure (CVP) less than 12cmH20, urine output less than 0.5ml/kg/hour and Hemoglobin of less than 8g/dl. A repeat of the fluid is given every 5 minutes if any one of the indicators were met. If the MAP does not respond to fluids boluses, vasoactive agent noradrenaline will be commenced to maintain MAP above 70mmHg.

The patient’s arterial blood samples were taken for arterial blood gases (ABG) sampling at the time of skin incision, every 2 hours during surgery until the end of surgery.

These samples were analysed for the concentrations of hemoglobin levels, sodium (Na+) , potassium (K+) and serum lactate. They were all integrated in the blood gas ABL 800 analyzer (Radiometer, Copenhagen, Denmark).

The patients' intra operative vital signs (blood pressure, heart rate, saturation and CVP), blood losses, total amount and types of fluids and blood component infused together with preoperative and intraoperative serum lactate and electrolytes levels and any ionotropic supports were compiled and analyzed.

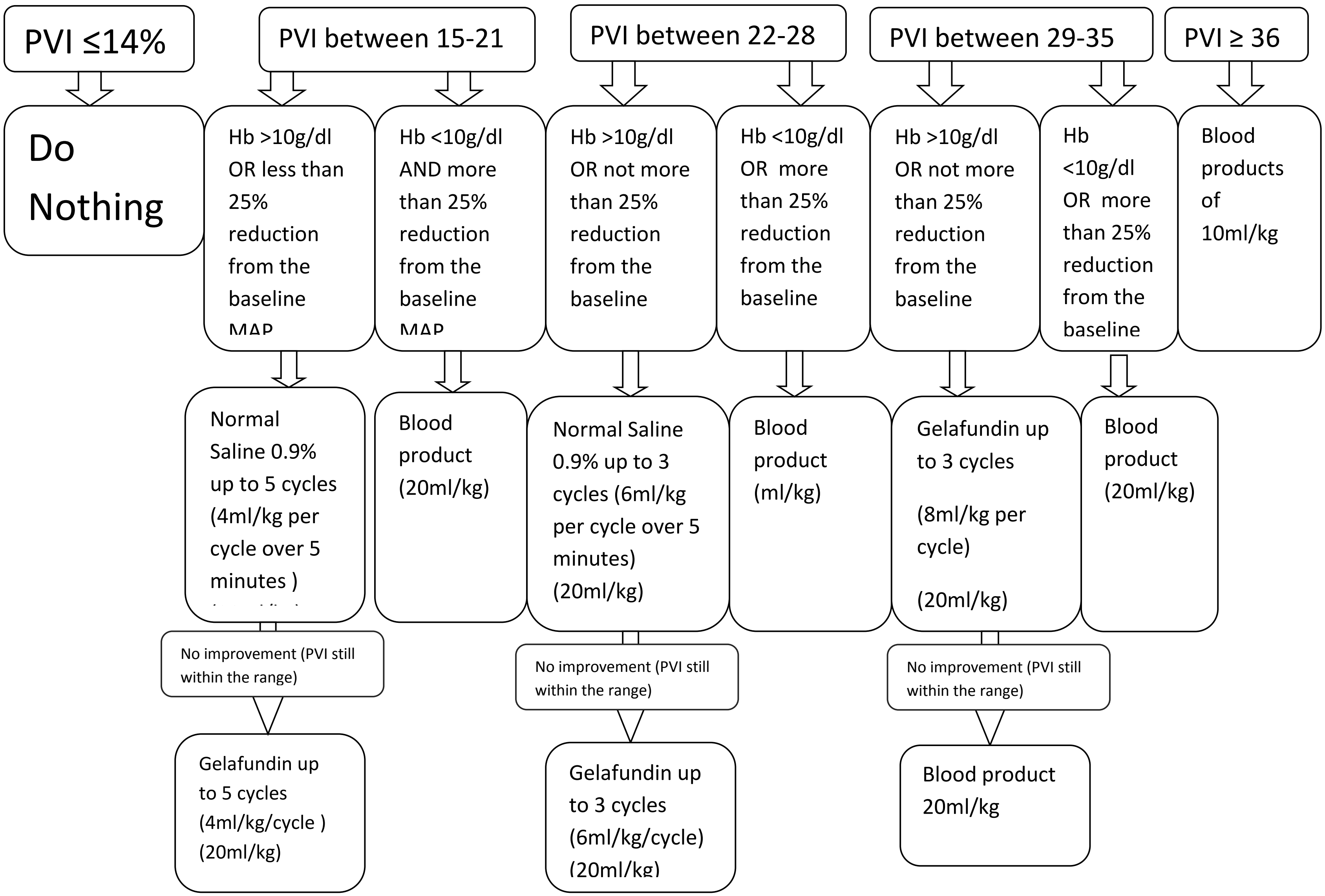
The patients were transferred to the Intensive Care Unit (ICU) for postoperative stabilization and monitoring by anaesthetist and surgeon.

1.4.8 FLOW CHART

1.4.8(a) FLOW CHART OF THE STUDY

Reference Population

Adult patients scheduled for elective neurosurgical procedures



1.4.8(b) Fluid Protocol for Various PVI Values