BALANCED FLUID REGIME VERSUS SALINE-BASED FLUID REGIME IN POST OPERATIVE SEVERE TRAUMATIC BRAIN INJURY PATIENTS: ACID BASE AND ELECTROLYTES ASSESSMENT

DR MOHAMAD HASYIZAN BIN HASSAN

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE

(ANAESTHESIOLOGY)

SCHOOL OF MEDICAL SCIENCES

UNIVERSITI SAINS MALAYSIA

2015

ABSTRACT

Title: BALANCED FLUID REGIME VERSUS SALINE BASED FLUID REGIME FOR POST OPERATIVE SEVERE TRAUMATIC BRAIN INJURY PATIENTS: ACID BASE AND ELECTROLYTES ASSESSMENT

Dr Mohamad Hasyizan

MMed Anaesthesiology

Department of Anaesthesia and Intensive Care,

School of Medical Sciences, Univertsiti Sains Malaysia,

Health Campus, 16150 Kelantan, Malaysia

Background:

Normal Saline is a common fluid of choice in neurosurgery and neurointensive care setting. It is widely being used as resuscitative and maintainence fluid due to its isoosmolarity to prevent development of cerebral oedema and secondary insult that worsened the outcome of post traumatic brain injury patients. However, balanced solution was invented with closer properties to plasma content gives a new alternative for fluid management in neurointensive care setting

Objectives:

This study aimed to compare between balanced and saline fluid regime on electrolytes, acid base, serum osmolarity and outcome in post operative traumatic brain injury patients in neurointensive care setting.

Methodology:

This is a prospective, randomized and single blinded trial on 64 patients underwent operation for severe traumatic brain injury and subsequently ventilated in neurointensive care for more than 24 hours. Group B only received balanced fluid (Sterofundin ISO ®) while group S received Normal Saline as the maintenance fluid in the ICU over 24 hours. Electrolytes and acid base parameters were assessed at 8 hours interval over 24 hours period whereas the serum osmolarity and IVC was taken at admission and after 24 hours of ICU stay. The outcomes of the patients were assessed up to 3 months period post hospital discharge.

Results:

In term of serum sodium level, there were significant differences in time comparison in normal saline and balanced group ($F=11.23$, $p<0.001$). As for chloride, results showed that there were significant differences in normal saline and balanced group in time comparisons ($F=9.02$, $p<0.001$). There was significant difference in mean chloride level between two different groups at 0 hours, 8 hours and 24 hours ($p<0.001$) based on time (time-treatment interaction) where normal saline resulted to increase while balanced solution leads to reduce chloride level from baseline. Regarding potassium, there were significant differences in mean difference in normal saline group at time comparisons ($F=7.56$, $p<0.001$). There was significant difference of mean serum potassium among two different group based on time ($F= 6.88$, $p<0.001$) at 8 hours and 24 hours where saline fluid leads to slight hypokalemia while balanced solution has stable potassium level compared to baseline. Furthermore, we found that there were significant differences only in normal saline group in term of serum calcium level ($F=0.76$, $p=0.015$). There was significant difference in mean calcium concentration between saline and balanced fluid

group at 24 Hr (p=0.003) with reduction trend in the former compared to baseline. The results showed that there was significant difference of magnesim level in both treatment groups on time comparisons (F=2.65, p=0.050). Upon within-between group comparison (time treatment interaction), there were significant differences seen at 0, 16 and 24 hours(F= 10.36, p<0.001). Concerning serum paCO2 level, the results showed that there was significant difference in normal saline group at time comparisons (F=3.78, p=0.020). There was significant difference of mean arterial pCO2 level among two different group based on time (F= 4.89, p= 0.004) at 0, 8 and 16 hours. In balanced solution group, there were significant difference in two comparisons in Base Excess level based of time (F=4.05, p=0.011). In time-treatment interaction, there was significant difference of base Excess concentration among two different group based on time (F= 2.78, p=0.049) at 0, 16 hours and 24 hours. In balanced solution group, there was significant difference of serum bicarbonate level based on time (F=5.94, p=0.001). There are significant difference of bicarbonate level (p=0.019) in between two groups with the mean difference of 1.15(0.20, 2.11) regardless of time. There was also significant time-treatment interaction (F= 4.65, p=0.031) in between those two group after infusion of fluids at 16 hours and at 24 hours duration. Regarding lactate level, there was a significant difference of mean lactate concentration within both treatment groups (F=25.62, p<0.001) based on time. Serum osmolarity after infusion of Normal Saline over 24 hours is significant (p<0.001) with the mean difference of 12.49(8.15, 16.12). Both mean difference of the IVC diameter after infusion of Normal Saline and balanced solution is statistically significant with the mean difference of 0.11cm(0.08, 0.14) (p<0.001) and 0.13cm(0.10, 0.16)(p<0.001) respectively. Concerning the outcome, there was no significant difference in the patients outcome between both groups.

Conclusion:

In conclusion, the saline based fluid leading more towards higher chloride and lower pH and Base Excess than balanced group. In contrast, balanced fluid resulted to more towards maintaining higher potassium, calcium, magnesium and bicarbonate level than saline fluid. Normal serum osmolarity is preserved in both groups. There was significant improvement of the IVC diameter in both fluid therapies. The outcome of the patients between both groups is insignificant.

Dr Wan Mohd Nazaruddin Wan Hassan: supervisor

Dr Rhendra Hardy Mohd Zaini : Co-supervisor

ACKNOWLEDGEMENT

(In the name of Allah, the Most Gracious, the Most Merciful)

All praises and thanks be to Allah (SWT), since purely due to His virtue was this dissertation possible to be completed.

Any large endeavour like this will not be settled successfully without help and support from various individuals. I would like to express my gratitude to the following individuals for their continuous support, input and guidance in helping me to complete this research.

- Dr Wan Mohd Nazaruddin bin Wan Hassan, my dissertation supervisor and Dr Rhendra Hardy Mohd Zaini my co-supervisor for their guidance, ffort and advice throughout my study period.
- Professor Dr Shamsul Kamalrujan Hassan, Head of Department and professor in Department of Anaesthesiology and Intensive Care.
- All lecturers of Department of Anaesthesiology, colleagues and friends who has been supporting me in recruiting the patients throughout the time the research was conducted.
- Dr Siti Azrin Bt Abdul Wahab, statistician in Biostatistic Department for guidance in data analysis and statitistical works.
- All the staffs in Operation Theatre, Neurointensive care ICU(2 Delima), General ICU (1 Mutiara) and Surgical ICU HUSM
- All the next of kin of the patients who involved in the study for their kind cooperation and contribution to my research
- My parents and siblings for their endless love, patience and support

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

2,3-DPG	2,3-diphosphoglycerate
ADH	Antidiuretic hormone
ANF	Atrial natriuretic factor
ASA	American Society of Anesthesiologist
ATOT	All anion charges of weak plasma acids
ATP	Adenosine triphosphate
BBB	Blood Brain Barrier
BE	Base Excess
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca2+	Calcium
Cl-	Chloride
CNS	Central Nervous System
CO2	Carbon Dioxide
COP	colloid oncotic pressure
CPP	cerebral perfusion pressure

CSF	cerebrospinal fluid
CSW	cerebral salt wasting
CVP	central venous pressure
DNA	Deoxyribonucleic acid
ECF	extracellular fluid
ECG	electrocardiogram
GCS	Glasgow Coma Scale
GDT	goal directed therapy
GOS	Glasgow Outcome Scale
HCO3-	bicarbonate
HCT	haematocrite
HES	hydroxyetyl starch
HR	heart rate
HUSM	Hospital Universiti Sains Malaysia
ICF	Intracellular Fluid
ICP	intracranial pressure
ICU	intensive care unit
IV	intravenous

IVC	inferior vena cava
K+	Potassium ion
LDH	Lactate dehydrogenase
LR	Lactated Ringer's
MAC	Minimal Alveolar Concentration
MAP	Mean Arterial Pressure
Mg2+	Magnesium Ion
MW	Molecular weight
Na+	Sodium ion
NaHCO3	Sodium Bicarbonate
NS	Normal Saline
OT	operation theatre
PCO2	partial pressure of carbon dioxide
PO2	partial pressure of oxygen
PO_4^{3-}	phosphate ion
RBC	red blood cell
RNA	ribonucleic acid
SAH	subarachnoid haemorrhage

SDH	subdural haemorrhage
SD	standard deviation
SIADH	syndrome of inappropriate ADH hormone
SID	strong ion difference
SpO2	oxygen saturation
TBI	traumatic brain injury
TBW	total body water
TCI	target control infusion
TIVA	total intravenous anaesthesia

ABSTRAK

Tajuk: Perbandingan antara cecair seimbang dan cecair berasaskan salin untuk pesakit kecederaan trauma kepala teruk selepas pembedahan: penilaian asid bes dan elektrolit.

Latarbelakang:

Cecair salin selalunya digunakan semasa pembedahan kepala dan di pusat rawatan rapi neuro. Cecair ini digunakan secara meluas semasa resusitasi dan hydrasi pesakit kerana mempunyai kepekatan yang sama dengan plasma dan mengelak berlakuya kebengkakan otak dan kecederaan susulan. Namun, cecair seimbang telah dicipta dengan mempunyai kandungan yang lebih menyerupai plasma dan memberikan alternatif baru kepada pengurusan cecair di unit rawatan rapi.

Objektif:

Kajian ini bertujuan untuk membandingkan antara cecair seimbang dan cecair salin dari seg elektrolit, asid bes, kepekatan serum, dan kesan kepada pesakit selepas pembedahan di pusat rawatan rapi neuro.

Tatacara:

Kajian ini merupakan kajian prospektif, rawak dan 'single blinded' di kalangan pesakit selepas pembedahan yang diventilasi selama lebih 24jam. Kumpulan B hanya memnerima ceair seimbang (Sterofundin ISO ®) manakala kumpulan S menerima cecair salin sebagai cecair hidrasi di ICU selama 24 jam. Kajian terhadap elektrolit dan asid bes dilakukan pada selang lapan jam selama 24 jam manakala kepekatan serum dan IVC diamil pada waktu masuk dan selepas 24 jam. Kesan kepada pesakit sehingga 3 bulan selepas keluar dari hospital dibuat.

Keputusan:

Terdapat perbezaan signifikan dalam kumpulan salin dalam perbandingan masa (F=11.23, p<0.001) pada tahap Natrium. Untuk klorida, terdapat perbezaan dalam kedua-dua kumpulan dalam perbandingan masa (F=9.02, p<0.001). Terdapat perbezaan dalam tahap klorida diantara kedua-dua kumpulan pada jam ke 0, 8 dan jam ke 24 (p<0.001). berkenaan Kalium, terdapat perbezaan dalam kumpulan (F=7.56, p<0.001). Terdapat perubahan diantara kedua-dua kumpulan pada 8 jam dan 24 jam (F= 6.88, p<0.001) dimana salin menyebabkan sedikit hipokalemia. Tambahan, terdapat perbezaan dalam kumpulan salin bagi segi kalsium berdasarkan masa (F=0.76, p=0.015). Terdapat juga perbezaan dalam tahap purata kalsium diantara kedua-dua kumpulan pada 24 jam (p=0.003). Keputusan juga menunjukkan perbezaan dalam kedua-dua kumpulan bagi segi magnesium (F=2.65, p=0.050). Pada perbandingan diantara kumpulan mengikut masa, terdapat perbezaan pada 0, 16 dan 24 jam (F= 10.36, p<0.001). Mengenai tahap PaCO2, keputusan menunjukkan perbezaan dalam kumpulan salin dalam perbandingan masa (F=3.78, p=0.020). Terdapat perbezaan dalam purata pCO2 antara dua kumpulan pada 0, 8 dan 16 jam (F= 4.89, p= 0.004). dalm kumpulan cecair seimbang, terdapat perbezaan tahap lebihan bes berdasarkan masa (F=4.05, p=0.011). terdapat juga perbezaan diantara kedua-dua kumpulan pada 0, 16 dan 24 jam (F= 2.78, p=0.049). Dalam kumpulan cecair simbang, terdapat perbezaan dalam serum bikarbonat (F=5.94, p=0.001). Terdapat perbezaan interaksi rawatan-masa diantara kedua-dua kumpulan pada 16 dan 24 jam (F= 4.65, p=0.031). Berkenaan tahap laktat, terdapat perbezaan dalam purata laktat dalam kedua-dua kumpulan berdasarkan masa (F=25.62, p<0.001). Osmolariti serum selepas infuse salin slama 24 jam dijumpai signifikan (p<0.001) denagn purata perbezaan 12.49(8.15, 16.12). Kedua-dua purata perbezaan saiz diametr IVC dilihat signifikan dengan 0.11cm(0.08, 0.14) (p<0.001) bagi cecair salin dan 0.13cm(0.10, 0.16)(p<0.001) badi cecair seimbang. Tidak

terdapat perbezaan signifikan terhadap kesan kepada pesakit diantara kedua-dua buah kumpulan.

Kesimpulan:

Kesimpulannya, cecair salin membawa kepada kepekatan klorida yang lebih tinggi dan lebihan bes yang lebih rendah. Sebaliknya, cecair seimbang mengekalkan paras kalium, kalsium, magnesium dan bikarbonat yg leih tinggi. Osmolarity darah dikekalkan dan saiz IVC meingkat dalam kedua-dua kumpulan. Kesan kepada pesakit dalam kedua-dua kumpulan adalah tidak signifikan.

ABSTRACT

Title: Balanced Fluid Regime versus Saline-based Fluid Regime for post operative severe traumatic brain injury patients: Acid Base and Electrolytes Assessment

Background:

Normal Saline is a common fluid of choice in neurosurgery and neurointensive care setting. It is widely being used as resuscitative and maintainence fluid due to its isoosmolarity to prevent development of cerebral oedema and secondary insult that worsened the outcome of post traumatic brain injury patients. However, balanced solution was invented with closer properties to plasma content gives a new alternative for fluid management in neurointensive care setting

Objectives:

This study aimed to compare between balanced and saline fluid regime on electrolytes, acid base, serum osmolarity and outcome in post operative traumatic brain injury patients in neurointensive care setting.

Methodology:

This is a prospective, randomized and single blinded trial on 64 patients underwent operation for severe traumatic brain injury and subsequently ventilated in neurointensive care for more than 24 hours. Group B only received balanced fluid (Sterofundin ISO ®) while group S received Normal Saline as the maintenance fluid in the ICU over 24 hours. Electrolytes and acid base

parameters were assessed at 8 hours interval over 24 hours period whereas the serum osmolarity and IVC was taken at admission and after 24 hours of ICU stay. The outcomes of the patients were assessed up to 3 months period post hospital discharge.

Results:

In term of serum sodium level, there were significant differences in time comparison in normal saline and balanced group ($F=11.23$, $p<0.001$). As for chloride, results showed that there were significant differences in normal saline and balanced group in time comparisons ($F=9.02$, $p<0.001$). There was significant difference in mean chloride level between two different groups at 0 hours, 8 hours and 24 hours ($p<0.001$) based on time (time-treatment interaction) where normal saline resulted to increase while balanced solution leads to reduce chloride level from baseline. Regarding potassium, there were significant differences in mean difference in normal saline group at time comparisons ($F=7.56$, $p<0.001$). There was significant difference of mean serum potassium among two different group based on time ($F= 6.88$, $p<0.001$) at 8 hours and 24 hours where saline fluid leads to slight hypokalemia while balanced solution has stable potassium level compared to baseline. Furthermore, we found that there were significant differences only in normal saline group in term of serum calcium level ($F=0.76$, $p=0.015$). There was significant difference in mean calcium concentration between saline and balanced fluid group at 24 Hr ($p=0.003$) with reduction trend in the former compared to baseline. The results showed that there was significant difference of magnesim level in both treatment groups on time comparisons ($F=2.65$, $p=0.050$). Upon within-between group comparison (time treatment interaction), there were significant differences seen at 0, 16 and 24 hours($F= 10.36$, $p<0.001$). Concerning serum paCO2 level, the results showed that there was significant difference in normal saline group at time comparisons ($F=3.78$, $p=0.020$). There was significant difference of

mean arterial pCO2 level among two different group based on time (F= 4.89, p= 0.004) at 0, 8 and 16 hours. In balanced solution group, there were significant difference in two comparisons in Base Excess level based of time (F=4.05, p=0.011). In time-treatment interaction, there was significant difference of base Excess concentration among two different group based on time (F= 2.78, p=0.049) at 0, 16 hours and 24 hours. In balanced solution group, there was significant difference of serum bicarbonate level based on time (F=5.94, p=0.001). There are significant difference of bicarbonate level (p=0.019) in between two groups with the mean difference of 1.15(0.20, 2.11) regardless of time. There was also significant time-treatment interaction (F= 4.65, p=0.031) in between those two group after infusion of fluids at 16 hours and at 24 hours duration. Regarding lactate level, there was a significant difference of mean lactate concentration within both treatment groups (F=25.62, p<0.001) based on time. Serum osmolarity after infusion of Normal Saline over 24 hours is significant (p<0.001) with the mean difference of 12.49(8.15, 16.12). Both mean difference of the IVC diameter after infusion of Normal Saline and balanced solution is statistically significant with the mean difference of 0.11cm(0.08, 0.14) (p<0.001) and 0.13cm(0.10, 0.16)(p<0.001) respectively. Concerning the outcome, there was no significant difference in the patients outcome between both groups.

Conclusion:

In conclusion, the saline based fluid leading more towards higher chloride and lower pH and Base Excess than balanced group. In contrast, balanced fluid resulted to more towards maintaining higher potassium, calcium, magnesium and bicarbonate level than saline fluid. Normal serum osmolarity is preserved in both groups. There was significant improvement of the IVC diameter in both fluid therapies. The outcome of the patients between both groups is insignificant.

CHAPTER 1

INTRODUCTION

Saline based solution classically being used in neurosurgery and neurointensive care setting. It is widely being used as resuscitative and maintainence fluid due to its isoosmolarity. In nerosurgery and intensive care, maintaining normovolaemia and preventing reduction of plasma osmolality is essential in order to prevent development of cerebral oedema. It is important to prevent secondary insult that worsened the outcome of post traumatic brain injury patients. Thus, maintaining hemodynamic stability with control of factors influencing the intracranial pressure is essential to improve patients survival. Plasma osmolarity should be taken care properly since reduction in plasma osmolality results in oedema of normal and abnormal brain (TOMMASINO, MOORE et al. 1988).

Normal saline (NS) solution is more preferable as compared to lactated Ringer's (LR) solutions since the latter is slightly hypoosmolar and hence worsening the cerebral edema. However, usage of normal saline is not without side effect. It is a matter of fact that dose dependent normal saline infusion contributes to hyperchloremic metabolic acidosis (McFarlane and Lee 1994, Kellum 2002). Producing severe hyperchloremic acidosis by giving large amount of unbalanced fluid may mask diagnosis of perfusion deficit or may result in inappropriate clinical intervention due to erroneous presumption of ongoing tissue hypoxia secondary to hypovolumia (Mythen and Hamilton 2001). In the study of intensive care unit patients, the base excess(BE) was shown to predict outcome and to identify patients who

have a high risk for mortality (Smith, Kumar et al. 2001). Williams, Hildebrand et al. (1999) also reported, apart from developing metabolic acidosis, Normal Saline infusion also increase time to first urination significantly. Scheingraber, Rehm et al. (1999) and colleagues studied patients undergoing elective lower abdominal gynaecologic surgery who received approximately 6000mls of either Normal saline or Ringers Lactate. NS treated patients showed a smaller urine output than Ringer's Lactate treated patients. On a group of patients undergoing abdominal aortic aneurysm repair who received either Ringers Lactate or Normal Saline in a double blinded fashion, (Waters, Gottlieb et al. 2001) the NS treated patients developed hyperchloremic acidosis and they needed significantly more blood product than RL group. Nevertheless, some authors emphasised that infusion related hyperchloremic acidosis is benign (Kellum 2002). However, avoiding therapy related hyperchloremic metabolic acidosis is always desirable when managing hypovolumic patients.

The total balanced concept of fluid is a new approach to resuscitation (Boldt 2007). There is evidence that balanced fluid concept offers important effect of acid base and electrolyte. When used in plasma adapted volume replacement strategy (balanced crystalloid plus balanced HES) and given in high doses, this had better effect with regards to electrolyte concentration and Base Excess (BE) compared with non balanced strategy (Boldt 2006). Apart from that, balanced high molecular weight (MW) hydroxyetyl startches (HES) (Hestend(R)) impaired coagulation significantly less than a conventional high MW HES prepared in saline (hexastarch) (Roche, James et al. 2006). Saline based HES may also alter the platelet function (Wilkes, Woolf et al. 2002). Martin G et al. in 2002 reported that HES

prepared in NS (hexastarch) resulted in significantly more impaired thromboelastographic data than HES prepared in balanced solution (Hestend ®) (Boldt 2007). Balanced colloidal volume replacement regime may also have other beneficial effects. In a prospective, randomized double blinded clinical trial for patients undergoing elective surgical procedure, the balanced HES formulation improved gastric mucosae perfusion more than conventional HES (Wilkes, Woolf et al. 2001).

Based on various literature reviews of consequences of infusing saline-based fluid regime, alternative fluid solutions may be administered particularly in prolonged neurosurgical procedures and neurointensive care setting which involves significant blood loss and fluid shift in order to maintain stable acid base and electrolyte parameters without giving any consequence result of cerebral edema.

It is inevitable that further studies have to be conducted in order to assess and rationalize usage of balanced fluid solution in neurosurgery and neurointensive care setting. The current approach of fluid replacement is directed towards balanced, plasma-adapted crystalloid and colloid solutions (Boldt 2007). Whether choosing a total balanced volume replacement strategy would beneficially influence organ function, morbidity or even mortality must be evaluated in large controlled studies. It also remains to be elucidated whether repetitive use of such a fluid replacement concept, for example in the ICU patients would be advantageous. Up to date, there are still lacks of clinical trials done to evaluate

effects of balanced solutions toward neurosurgical patients and in neurointensive care management.

The aims of this study are to assess postoperative acid-base, electrolytes and serum osmolality changes between balanced fluid regime and saline-based fluid regime groups. Apart from that we are trying to evaluate differences of morbidity and mortality of post traumatic brain injury patients in term of ventilator days, duration of ICU and hospital stay and Glasgow Outcome Scale (GOS) post operatively. The study is design for 24 hours in duration allowing better analysis and prediction of outcome in neurointensive care after administration of prolong and large volumes of fluid therapies.

CHAPTER 2

LITERATURE REVIEW

2.1 Traumatic brain injury: An Overview

In this modern and hectic world, it is a matter of fact that traumatic brain injury (TBI) is a major cause of mortality and severe neurological sequale. It is inevitable that this situation plays a very significant consequence to the community and the healthcare system. Based on the study conducted by Helmy, Vizcaychipi et al. (2007), traumatic brain injury accounted for 15 to 20% of death in population ages 5 to 35 years and responsible for 1% of all adult death. Apart from that, the management of traumatic brain injury involved multidisciplinary team including neurointensivist, neuroanesthetis, neurosurgeon and other support groups. In order to achieve better prognosis and outcome, avoidance of the secondary injury, maintenance of cerebral perfusion pressure (CPP) and optimization of cerebral oxygenation is crucial. Currently, advancement in medicine and improved equipment and trauma care has led to more patients arrived to neurosurgical and intensive care but nevertheless resulted in increased number of patients with neurological disability. In America ifself, the CDC has estimated at least 5.3 million American has suffered from TBI with lifelong dependence in activity of daily living (Grathwohl, Black et al. 2008).

Glasgow coma scale (GCS) after resuscitation is the most well-known classification to grade the TBI. TBI is further classified to mild, moderate or severe according to this classification(table 2-1). As a result of insult to the brain, the inflammatory cascade is initiated and caused in worsening oedema with vasogenic, cytotoxic and osmotic component(Unterberg, Stover et al. 2004). Since the skull is the fixed compartment, increase in intracranial pressure will develops. Generally, TBI is classified into two distinct periods: primary and secondary brain injury. The primary insult results from direct impact of the trauma causing shearing, compression and impact to neuronal, glial and vascular tissue. Subsequently, integrity and haemostasis and permeability of the cell will be effected (Stiefel, Tomita et al. 2005). On the other hand, the secondary injury is described as the results of further physiological insult, such as ischemia, reperfusion and hypoxia to the associated area (Moppett 2007).

The prognosis of the TBI patients are closely related to several factors including GCS at presentation, advance age, associated hypotension during admission and fixed and dilated pupils (Ghajar 2000). Apart from that, CT scan finding linked directly to severity of the head injury and influence the outcome of the patients. Among the most common abnormality detected are midline shift, effacement of basal cistern and traumatic subarachnoid haemorrhage (SAH). The most widely accepted grading system in reporting the CT scan finding is Marshall system(table 2-2). However, this grading predict mortality instead of functional recovery (Marshall, Marshall et al. 1991). In addition, Glasgow Outcome Scale (GOS) is developed to assess the outcome of TBI patients (table 2-3). It is

usually measured at 3 months post trauma and up to 1 year. GOS 4-5 is labelled as good outcome whereas GOS 1-3 is classified in poor outcome group (King Jr, Carlier et al. 2005).

Table 2.1 Glasgow Coma Scale

Description	Response	score
Eye open	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Best verbal response	Orientated	5
	Words	4
	Vocal sounds	3
	Cries	2
	None	1
Best motor response	Obeys orders	6
	Localize to pain	5
	Flexion (withdrawal) to pain	4
	Decerebrate (abnormal flexion to pain)	3
	Decorticate (extension to pain)	2
	None	1

Table 2.2 Marshall CT scan classification for traumatic brain injury

Marshall class		Description	Mortality (%)
Class I	Diffuse injury I (no visible pathology)	No visible pathology on CT scan	6.4
Class II	Diffuse injury II	Cistern are present with midine shift 0-5mm and/or lesion densities present No high or mixed density lesion > 25cc may include bone fragments and foreign bodies	11
Class III	Diffuse injury III (swelling)	Cistern compressed or absent with midline shift 0-5mm, no high or mixed density lesion >25cc	29
Class IV	Diffuse injury IV (shift)	Midline shift >5mm, no high or mixed density lesion	44
Class V	Evacuated mass lesion	Any lesion surgically evacuated	30
Class VI	Non evacuated mass lesion	High or mixed density lesion >25cc, not surgically evacuated.	34

Table 2.3 Glasgow Outcome Scale

Score	Description
1	Death
2	Persistent vegetative state. Patient exhibits no obvious cortical function
3	Severe disability. Conscious but disabled. Patients depends on others for daily support
4	Moderate disability. Disabled but independent. Patient is independent as far as daily life. Disabilities include varying degrees of dysphasia, hemiparesis, ataxia as well as intellectual ad memory deficits and personality changes
5	Good recovery. Resumption of normal activities even though there may be minor neurologic or psychological deficits.

2.2 Roles of surgical decompression in traumatic brain injury

It is a matter of fact that prevention of secondary injury is crucial in the management of traumatic brain injury in order to improve the patients' outcome and survival. In the management of traumatic brain injury, several aspects and factors are taken care of properly to ensure secondary insult is diminished. Among these crucial aspects are, field resuscitation after TBI, expeditious triage, emergent surgical evacuation of mass lesion, control of ICP and support of the CPP, multimodal monitoring and neurointensive care, and optimization of physiological environment (Curry, Viernes et al. 2011). Perioperative period on the other hand is also important where it provides opportunity to correct the insult and to optimize the resuscitation. However, surgery and anaesthesia is not without risk. It may predispose the patients for further insult such as intraoperative hypotension due to surgical massive blood loss, effects of inhalational anaesthetic gasses and other anaesthetic drugs, and electrolyte imbalances and hyperglycemia intraoperatively. All these factors should be tackled seriously to avoid adverse outcome.

The patients with TBI can be treated either conservatively or surgically. Craniotomy or craniectomy is performed according to surgical judgement. Among the indications of surgical decompression craniotomy or craniectomy are:

1. GCS less than 9
2. Mass lesion more than 30 cm^3 epidural hematoma regardless of GCS
3. Mass lesion more than 10mm thickness subdural hematoma

4. Presence of midline shift more than 5mm
5. Evidence of intracranial hypertension
6. Assymetrical or fixed and dilated pupils

(Bullock et al. 2006).

Decompressive craniectomy or craniotomy is one with control of several important factors. The CPP should be maintained and further increase in ICP mst be avoided. Apart from that, optimal surgical condition and prevention of secondary insults such as hypoxemia, hyper or hypocarbia and optimal glucose control of 6 to 10mmol/L should be done. Adequate analgesia and amnesia is also crucial(Bedell and Prough 2002, Curry, Viernes et al. 2011). Anesthetic goal is achieved with vigilant intraoperative monitoring such s invasive blood pressure, echocardiography (ECG), oxygen saturation monitoring (SpO2), anesthetic gas monitoring including minimal alveolar concentration(MAC) and end tidal carbon dioxide monitoring (ETCO2), bispectral index (BIS) and temperature monitoring. Invasive blood pressure is needed to monitor beat to beat variability of hemodynamics due to effect of anaesthetic agents and blood loss during the operation. Central venous pressure(CVP) is also installed in several cases to have the rough estimation of the intravascular volume during the operation. Continuous urine output measurement is also essential to monitor any depletion of intravascular volume by means of reduction in renal perfusion. Additionally, presence of invasive arterial line may allow the anaesthetist to do the blood sampling for monitoring of haemoglobin level, acid base and electrolyte status, and ventilation parameters including PaO2 and PaCO2 level intraoperatively (Bedell and Prough 2002).

Surgical decompression in severe diffuse TBI is associated with reduction in the intracranial pressure and length of intensive care unit (ICU) stay(Maas, Stocchetti et al. 2008). However, it showed more unfavourable outcome in GOS compared to those patients who was not operated. Nevertheless, the rates of mortality at months are similar between these two group (Copper et al. 2011). Decompressive craniectomy is associated with intracranial and extracranial complication. Intracranial complication includes expansion of the hemorrhagic contusion, evolution of contralateral mass lesion, external brain herniation, subdural effusion and infected wound(Stiver, 2009) while the latter leads to electrolytes imbalances, pneumonia and neurogenic pulmonary edema, shock, coagulopathy and sepsis (Piek, Chesnut et al. 1992).

2.3 Anaesthesia in neurosurgery

The traumatic brain injury patient might not only presented with intracranial haemorrhage but developed associated cerebral oedema as well. The mass effect secondary to intracranial bleeding with tight brain will increase the intracranial pressure according to Monroe Kelly Doctrine principle. Thus, vigilant and thorough anaesthetic practice is important in order to provide cerebral protection towards increase in intracranial pressure (ICP). It is essential to maintain optimal cerebral perfusion pressure (CPP) to prevent secondary brain injury and neuronal cell death.

Maintenance of anesthesia can be achieved either by inhalational technique or total intravenous anaesthesia. In the past most of the neurosurgical operation is conducted with inhalational anaesthesia. However, with emergence of total intravenous anaesthesia (TIVA) and target controlled infusion (TCI) technique, most anaesthetist are now comfortable of using these methods over traditional maintenance by using inhalational agents. Propofol and remifentanyl are the most common drugs used in TIVA/TCI technique. Propofol has unique pharmacokinetics and pharmacodynamics properties. Based on its' pharmacokinetic properties of three compartment model, anaesthesia can be maintained throughout the surgery and predictable offset time according to its' context sensitivity half time. On top of that, inhalational agents provoke increase in ICP when the concentration is more than 1.5 MAC and has uncoupled effect on the cerebral blood flow(CBF) with the cerebral metabolic rate (CMRO2).

Hemodynamic stability, reduction incerebral metabolic rate, preservation of cerebral autoregulation and prevention of increase in intracranial pressure is crucial to promise better prognosis to the patients and ensure rapid recovery (Talke, Caldwell et al. 2002, Magni, Baisi et al. 2005). Apart from that neuroprotenction and anticonvulsive properties should be considered to prevent further secondary insult. Anaesthesia should also aim to provide brain relaxation and minimal electrophysiological interference (Hans and Bonhomme 2006). Neuroprotection can prevent further brain activity that can increase cerebral metabolic rate and epileptical activity (Engelhard and Werner 2006).

2.4 Intensive care management of traumatic brain injury

2.4.1 General Approach

There are various factors that contribute to the secondary insult in traumatic brain injury patient. They can be either from systemic or intracranial causes and may occur at any level of treatment including during initial resuscitation and stabilisation phase or even during operation and intensive care period. Management of TBI in intensive care is targeted at optimizing the cerebral perfusion, oxygenation and preventing secondary insults. Based on a study by Elf, Nilsson et al. (2002), the outcome after TBI is improved by an organised and standardized managements of care in order to avoid secondary insults. Thus, several protocols was constructed in order to provide good basic intensive care and interventions to target cerebral perfusion pressure (CPP) and intracranial pressure (ICP).

2.4.2 ventilatory support, sedation, analgesia and paralysis

Severe head injury patients require mechanical ventilation in order to maintain arterial PaO2 above 80mmHg and arterial PaCO2 between 35 to 38mmHg (Oertel, Kelly et al. 2002). Regarding the usage of positive end expiratory pressure (PEEP), there is no absolute contraindication to the use of PEEP in hypoxemic patient unless the increase in thoracic venous pressure causes an unacceptable increase in intracranial pressure (ICP). On the other

hand, permissive hypercapnea should be avoided because of its cerebral vasodilatory effect that increase the ICP.

Apart from that, adequate sedation is important in order to minimize pain, anxiety and agitation and facilitating the mechanical ventilation. Sedations may also reduce cerebral metabolic rate of oxygen consumption. A short acting benzodiazepine such as midazolam is commonly used, which is very effective as a sedative and as an anticonvulsant, although accumulation is a problem. The other most common sedative agent being used is propofol. On the other hand, propofol may have benefits over midazolam because of its superior metabolic suppression effect with relatively short half life. However, propofol is not recommended in hypothermic patients since it has a tendency to accumulate and causing hyperlipidemia. There are also reports saying that the propofol can precipitate cardiovascular collapse (Warden and Pickford 1995). Propofol infusion as sedative agent may leads to propofol infusion syndrome and causes metabolic acidosis, rhabdomyolysis and bradycardia (Kumar, Urrutia et al. 2005). Barbiturate is reserved as a sedation when the other methods of controlling the ICP has failed. It is used in a lesser extend because of the risk of cardiovascular depression and infections (Eisenberg, Frankowski et al. 1988).

Analgesia is also important in traumatic brain injury patients. Analgesia is provided with regular doses of acetaminophen and infusion of opiod, such as remifentanyl, fentanyl, or morphine. These analgesic have minimal effects on cerebral hemodynamics in adequately resuscitated patients (Sperry, Bailey et al. 1992). Neuromuscular blocking agents are

occasionally utilized to minimize coughing and straining which may increase ICP and is provided with boluses or infusion of atracurium or rocuronium. Apart from that it may also confer better management in patients with high ventilator setting.

2.4.3 Hemodynamic support

Hemodynamic disturbances in traumatic brain injury patient are caused by various factors. The injury itself may cause depletion in intravascular volume and trauma to the myocardium secondary to high impact injury may lead in primary pump failure. Maintenance of hemodynamic stability is important as the injured brain may lose the capability for vascular autoregulation, either globally or locally. Hypotension must be avoided since it causes a reduction in cerebral blood flow and subsequently results in cerebral ischaemia (Chesnut, Marshall et al. 1993). In contrast, hypertension is also detrimental since it may exacerbate vasogenic edema and increase ICP (Grande, Asgeirsson et al. 1997).

Firstly, intravascular volume should be maintained with the target central venous pressure (CVP) of 5 to 10 mmHg by using isotonic crystalloid and colloid. (Ghajar 2000). Subsequently, vasoactive drugs should be instituted if the hemodynamic is still inadequate. Furthermore, a pulmonary artery catheter or non invasive cardiac output monitor should be considered in patients with increasing needs for inotropic and vasopressor support and evolving shock is inevitable. Adrenal insufficiency is not uncommon after severe TBI, and in

patients with high inotropic requirements, a short synacthen test should be done before initiation of empirical steroid replacement (Bernard, Outtrim et al. 2006).

Intracranial pressure monitoring is also instituted to maintain cerebral perfusion pressure (CPP) to avoid secondary insult in certain cases. The target MAP is then determined according to the CPP. Concerning the treatment to achieve target CPP, the short acting beta blocker is the agent of choice and should be titrated against blood pressure. These agents do not cause cerebral vasodilatation, when compared to nitrates and calcium channel blocker, and therefore do not increase cerebral blood volume and ICP.

2.4.4 Nutritional support

Early nutritional support is recommended if the patient is hemodynamically stable. A Cochrane review suggested that early feeding is associated with beter outcomes interm of survival and disability (Perel, Yanagawa et al. 2006). Early feeding stimulates immunological function by increasing the CD4 cells, CD4-CD8 ratio and T Lymphocyte responsiveness (Sacks, Brown et al. 1995). Borzotta, Pennings et al. (1994) reported that there is no significant differences in the patient's outcome if the feeding started via the enteral route or parenterally. Ideally, the total calorie requirement is about 25 to 30 kcal/kg/day. On top of that, according to Eastern Association for Surgery of Trauma (EAST) Practice Management Guideliness, 15% of the calories should constituted of protein.

Nevertheless, enteral formulas are preferable unless in the case of high gastric residual volume or associated intraabdominal trauma. The enteral nutrition is apparently more physiological and safer as compared to parenteral nutrition. However, appropriate metabolic monitoring is essential to avoid side effects for example, hyperglycemia, gastric intolerance, ketoacidosis, diarrhea, and relative hypovolumia which compromise hemodynamic stability.

2.4.5 Glycemic control

Hyperglycemia is common is post traumatic brain injury patient. It is related to the stress response which further generates a hypercatabolic states and rapid muscle protein breakdown (McCowen, Malhotra et al. 2001). At cellular level, there are deleterious effect on macrophage and neutrophil function with axonal dysfunction.

Adequate level of glucose in plasma is associated with improve morbidity and outcome. The suggested blood glucose level is between 4 to 10mmol/L. Van den Berghe, Wilmer et al. (2006) and colleagues in large randomised control trial demonstrated that tight glycemic control reduced the number of deaths from multiple organ failure with sepsis. In TBI patients, hyperglycemia is associated with higher in ICP, worse neurological sequale, prolong hospitalization and in general reducing the survival (Rovlias and Kotsou 2000). Clayton and colleagues demonstrated relative reduction of intensive care mortality of

around 30% of the patient after maintain the glucose level of 4 to 7 mmol/L. Thus, optimal glucose control is essential in management of traumatic brain injury patients.

2.4.6 Peptic ulcer prophylaxis

The incidence of Cushing's ulcer in traumatic brain injury patient accounted of round 10%. Thus, regular prescription of peptic ulcer prophylaxis is important but the ideal agent of choice, dosage or route of administration is yet unclear (Devlin, Claire et al. 1999).

2.4.7 Coagulopathy and deep venous thrombosis

Disseminated intravascular coagulation (DIC) is a well known compaction of severe head injury patients. It can also be the results of polytrauma itself, massive blood transfusion during initial resuscitation phase and as a complication of gram negative bacterial sepsis. Systemic release of high cerebral parenchymal concentrations of tissue thromboplastin and other agents in TBI patients are responsible of inducing consumptive coagulopathy (Piek, Chesnut et al. 1992).

Deep venous thrombosis (DVT) is reported in various extend in post traumatic brain injury patients. The incidences are as low as 3% in isolated head injury rising to approximately 23% in polytrauma cases (Rogers, Cipolle et al. 2002). Among the measures of preventing DVT includes, stockinette, sequential compression devices, low dose

unfractionated heparin (UH), low molecular weight heparin (LMWH), vena cava filters or a combination of these. Evolution can happened after cerebral contusion and influenced by coagulopathy and anticoagulation thus, timing of initiation of venous thrombosis prophylaxis may influence the outcome after TBI. However, most authors agreed that commencement of DVT prophylaxis should be considered after 72 hours of insult whereas the drug might be as well started as early as 24 hours after blunt closed head injuries (Norwood, McAuley et al. 2002). Although LMWH seems to be better than UH in preventing DVT, the incidence of adverse effect is low in both option.

2.4.8 Miscallenous

Supportive care plays an important role in intensive care patients. These include chest and limb physiotherapy, frequent turning, eye care, positioning, and full hygiene. Various protocol such as ventilator care bundles and sepsis bundles are developed in order to improve patient outcome. Frequent dressings of catheters are also crucial to minimize the risk of infection. Apart from that, boluses of sedation or analgesic in the patients with refractory intracranial hypertension are also essential during various procedures in the intensive care setting.

2.5 specific managements in neurointensive care

2.5.1 Intracranial pressure (ICP) and Cerebral perfusion pressure (CPP) thresholds

Based on Monroe Kelly Doctrine principle, the intracarial compartment consist of brain, cerebral spinal fluid(CSF) and blood within the rigid skull vault. The volume of these contents exerts a pressure which is known as intracranial pressure. The measuremet of ICP is essential to identify evolving mass and also important in regulation of the cerebral perfusion pressure (CPP). CPP can be calculated from the formula of CPP= MAP-ICP. It is a matter of fact that ICP is also plays an important role as independent predictor of outcome although many studies are more directed towards targeting the CPP. The ICP shoul be controlled below 20mmHg as many literatures found out that ICP is a discriminatory factor toward the outcome of the patients (Hiler, Czosnyka et al. 2006).

Control of cerebral perfusion pressure (CPP) is a most important factor to avoid cerebral ischaemia. Rosner and colleagues in 1996 had inciently demonstrated a better outcome in patients with CPP more than 70mmHg and brought the huge influence in management of traumatic brain injury. Although the ideal CPP target is yet to be determined, the Brain Trauma Foundation has concluded that the ideal CPP should be more than 70mmHg. However, increasing CPP in injured brain can also be deleterious. In traumatic brain injury patients, there was dissociation between cerebral blood flow (CBF) and its metabolic requirement on top of impaired vascular autoregulation. Thus, increasing CPP will cause increment of blood vessel diameter, cerebral blood volume and consequently

ICP. ICP can also be enhanced by increasing the hydrostatic pressure across the capillary bed that subsequently causes vasogenic edema. Furthermore, driving MAP with fluids and inotropic drugs to maintain CPP is associated with cardiorespiratory complications. Based on the study conducted by Robertson, Valadka et al. (1999), increased fluid intake with higher dose of inotropes is associated with five folds increase in incidence of acute respiratory distress syndrome (ARDS). Nevertheless, the study by (Coles, Steiner et al. 2004) and colleagues by using oxygen-15 positron emission tomography has evaluated that increasing CPP from 70 to 90mmHg acutely reduced ischaemic brain volume, although the clinical benefit of this observation in unclear.

Generally, ICP and CPP can be regulated in various ways, including reduction in metabolic rates by means of sedations, induce hyperventilation, hyperosmolar therapy, hypothermia, and surgical interventions.

2.5.2 Induced hyperventilation

Partial pressure of carbon dioxide (PaCO2) plays the major determinant of cerebral vessel calibre. A reduction in PaCO2 causes cerebral vasoconstriction, reduction in cerebral blood volume and ICP. However, excessive hyperventilation may further reduce the PaCO2 and causing cerebral ischemia especially in the first 24 hours (Muizelaar, Marmarou et al. 1991). A PaCO2 target of 35 to 38mmHg should be aimed in patients with increased ICP with hyperventilation with PaCO2 at 30 to 35mmHg is reserved for those with intractable

intracranial hypertension. Furthermore hyperventilation is reserved in neurointensive care setting with appropriate monitoring and jugular venous bulb oxygen installation (Oertel, Kelly et al. 2002).

2.5.3 hyperosmolar therapy

Hyperosmolar therapy is one of the established measures to reduce the cerebral edema and the intracranial pressure after traumatic brain injury. Mannitol, a well-known osmotic diuretic has been used in numerous conditions in order to minimize the secondary insult after the trauma. It has the fast onset and rapid effect by its mechanism as plasma expander. Mannitol exerts its osmotic gradient between the plasma and the brain tissue and reducing the cerebral edema by draining the water from the interstitial into the intravascular space (Nath and Galbraith 1986). This situation is particularly true in intact blood brain barrier (BBB) based on the Starling mechanism. However, repeated administration of mannitol is dangerous since plasma osmolarity of more tht 320mmol/L is associated with neurological and renal complications (Bullock 1995). Apart from that, mannitol infusion may lead to severe intravascular volume depletion that subsequently causing hypotension and hemodynamic disturbances. Mannitol can also cause hyperkalemia (Manninen, Lam et al. 1987) and rebound increase in intracranial pressure (Marshall, Smith et al. 1978).

Hypertonic saline is the emerging alternative to the mannitol as hyperosmolar therapy in reducing intracranial pressure. However, it is available in wide concentration range and the optimal dose of the hypertonic saline is still under discussion. Hyperonic saline produces reduction in cerebral edema by moving the water out of the cells and reducing the tissue pressure. In addition, hypertonic saline improves cerebral blood flow (CBF independent to ICP by reducing the endothelial cell volume, improving the diameter of capillary lumens, and reducing the erythrocyte size thus, improving the blood rheology (Shackford, Zhuang et al. 1992). As compared to mannitol, hypertonic saline is a better volume expander with no hyperkalemia and impaired renal function as a complication (Qureshi, Suarez et al. 1999). It is also being use in control of ICP in patients refractory to mannitol (Suarez, Qureshi et al. 1998).

2.5.4 Salt and Water Balance

Traumatic brain injury may lead to alteration in salt and water balance. It can cause various pathology including central diabetes insipius (DI), cerebral salt wasting (CSW) syndrome and syndrome of inappropriate ADH (SIADH). The situation is further complicated with excessive administration of the sodium in the maintenance fluid therapy. However, low sodium solution or synthetic ADH hormone should be administered in the context of severe hypernatremia with serum sodium of more than 160mmol/L (Cole, Gottfried et al. 2004). However, the correction of sodium should be done with caution since rapid decrease of sodium will leads to cerebral oedema.