A COMPARATIVE STUDY BETWEEN A TARGET CONTROLLED INFUSION (TCI) AND MANUAL CONTROLLED INFUSION (MCI) OF PROPOFOL FOR SEDATION DURING CEREBRAL PROTECTION IN SEVERE TRAUMATIC BRAIN INJURED PATIENTS

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ABBREVIATIONS

TCI	Target Controlled Infusion
MDPE	Median Performance Error
MDAPE	Median Absolute Performance Error
SBP	Systolic Blood Pressure
MAP	Mean Arterial Pressure
HR	Heart Rate
$CMRO_2$	Cerebral Metabolic Rate Of Oxygen.
BIS	Bispectral Index
MCI	Manual Control Infusion
ICP	Intracranial Pressure
CPP	Cerebral Perfusion Pressure
NICU	Neurosurgical Intensive Care

ABSTRAK

Pendahuluan

Propofol adalah ubat penenang yang paling kerap digunakan kepada pesakit yang mengalami kecederaan otak dengan menggunakan teknik kawalan secara manual (TKM). Perkembangan teknik terbaru iaitu teknik kawalan secara mensasarkan kepekatan (TKK) telah membuka dimensi baru dalam pemberian ubat propofol yang belum diuji kepada pesakit kecederaan otak. Tujuan kajian ini adalah untuk membandingkan keberkesanan teknik TKM berbanding teknik TKK kepada pesakit yang mengalami kecederaan trauma otak untuk kesan penenang semasa proses pemulihan otak di Wad Rawatan Rapi Neurologi.

Metodologi

Di dalam kajian prospektif ini, seramai 50 orang pesakit yang mengalami kecederaan trauma otak dengan skor kesedaran di antara 3 hingga 8, berumur di antara 16 hingga 50 tahun, tidak mempunyai sejarah perubatan yang teruk dan perlu menjalani pembedahan kecemasan otak (kraniotomi) telah dibahagikan secara rambang kepada dua kumpulan (25 pesakit setiap kumpulan). Namun begitu seorang pesakit dalam kumpulan TKM telah dikeluarkan dari sampel kajian kerana terlalu tidak tenang walaupun ubat penenang telah diberi secukupnya sehingga memerlukan ubat melumpuhkan otot. Semasa pembedahan

otak, kedua-dua kumpulan diberikan protokol yang sama dan kajian bermula sebaik pesakit tiba di Wad Rawatan Rapi Neurologi. Kesan penenang diawasi menggunakan monitor Bispectral Index (BIS) dan skala sedasi (Sedation Agitation Scale). BIS index mencapai nilai diantara 60-70 dan skala sedasi 2-3 dipertimbangkan sebagai kadar penenang yang mencukupi. Parameter hemodinamik (tekanan darah dan denyutan jantung) serta parameter otak (tekanan dalam kranium serta tekanan perfusi) direkodkan setiap jam selama 24 jam. Parameter-parameter lain yang direkodkan adalah masa dan isipadu ubat yang digunakan untuk mencapai nilai BIS 70, jumlah isipadu keseluruhan untuk ubat propofol yang digunakan selama 24 jam. Masa yang diambil untuk mencapai nilai BIS 90 selepas 24 jam dan ubat diberhentikan direkodkan. Kedua–dua kaedah aliran ubat menggunakan mesin yang sama. Bagi ubat penahan sakit, fentanyl diberikan dan diberhentikan 4 jam sebelum masa kajian tamat (24 jam).

Keputusan

Terdapat perbezaan yang signifikan di antara dua kaedah pemberian ubat. Teknik TKK memberikan kesan penenang yang cepat 6.32 ± 2.28 minit berbanding kaedah TKM 19.71 ± 7.00 minit. Terdapat juga perbezaan yang bererti dari sudut masa yang diambil untuk mencapai aras BIS 90. Kaedah TKK mengambil masa 22.44 ± 11.50 minit berbanding TKM 57.29 ± 19.89 minit. Dari segi kesan terhadap tekanan di dalam otak (intercranial pressure) terdapat perbezaan yang bererti tetapi tiada perbezaan di antara dua kaedah ini dari sudut tekanan darah purata dan tekanan perfusi cerebral.

Kesimpulan

Pemberian ubat propofol mengunakan kaedah TKK lebih effektif untuk kesan penenang kepada pesakit kecederaan otak kerana kesan penenang dapat diberikan dengn lebih cepat dan menggunakan jumlah isipadu yang sedikit. Kesan pemulihan daripada ubat penenang juga lebih cepat dipulihkan. Kaedah ini juga dapat mengurangkan tekanan dalam kranium lebih baik daripada kaedah TKM.

ABSTRACT

Introduction :

Propofol is the commonest sedative agent used in traumatic brain injured (TBI) patient using manual controlled infusion (MCI) technique. The development of target controlled infusion (TCI) technique has given a new dimension of propofol administration and it has never been tested in TBI patients. The aims of this study were to compare the effectiveness of different method of propofol infusion (TCI versus MCI) for sedation during cerebral protection in TBI patient in Neurosurgical Intensive Care Unit (NICU).

Methodology

In this prospective, double blinded, randomized controlled trial study, 50 patient who had traumatic brain injury with a Glasgow Coma Scale (GCS) between 3 to 8, age between 16 to 50 years old with no severe medical illness and undergoing craniotomy were randomized into two groups using block randomizations (25 patients in each group). However, one of the patients in MCI group had to be excluded due to very agitated state in spite of adequate sedation until the extend requiring muscle relaxant. During surgery, both groups received anesthesia with a standard protocol and the study started once patients admitted to Neuro ICU for cerebral protections. Sedations level was monitored using Bispectral index (BIS) monitor and Sedation Agitation Scale (SAS). BIS index of

60-70 and SAS score of 2-3 was considered as adequate sedation. Both groups used the same infusion pump which can operate either TCI or MCI and the drugs administrated via a dedicated central venous line lumen. Homodynamic parameters (blood pressure and heart rate) and neurological parameters (intracranial pressure and cerebral perfusion pressure) were recorded, time and volume used to achieve BIS 70, total volume of propofol used for 24 hours and time taken to achieve BIS 90 after stopping infusion at the end of cerebral protection were measured. Fentanyl infusion at 1 mcg/kg were given for pain relieve and was stopped four hours before the end of the study (24 hours).

Results

There are some significant differences between two modes of infusion. TCI mode achieved BIS 60-70 significantly faster than MCI with mean time 6.32 ± 2.88 minutes compared to MCI which is 19.71 ± 7.00 minutes. Time taken to recover from sedation to achieving BIS 90 was also significantly faster in TCI at 22.44 ± 11.50 minutes compared to MCI 57.29 ± 19.89 minutes. In view of ICP, there was a significant difference between two modes but no significant difference in MAP and CPP.

Conclusion

TCI mode of propofol is more effective in sedating neurotrauma patients as gives adequate sedation faster with a lesser volume and also faster recovery. It also lowers the Intracranial pressure (ICP) to less than 20mmHg better than MCI.

1. INTRODUCTION

Sedation and analgesia is used primarily in ICU to limit the stress response to critical illness, provide anxiolysis, improve ventilatory support and facilitate adequate ICU care. However, in neurosurgical ICU (NICU) there are many other reasons for the use of these agents. The goal of ICU care for the neurotrauma patients during cerebral protection is to provide adequate conditions that favor recovery of brain tissue and to prevent secondary neuronal damage due to increased intracranial pressure (ICP) or inadequate cerebral perfusion pressure (CPP)(Rhoney *et al,* 2001)

Propofol is one of the sedative agents commonly used in managing head injury patients. In terms of pharmacokinetics, it has rapid onset, high clearance rate and rapid recovery (Marinella, 1997). These are very helpful for rapid neurological assessment. The use of propofol sedation also allows for more rapid tracheal extubation compare to midazolam sedation (Hall et al., 2001). Physiologically, it reduces CBF, $CMRO_2$ and ICP in patients with or without intracranial disease (Herregods, 1988, Pinaud, 1990). However it can cause a dose-dependant decrease in MAP which is due to a drop in systemic vascular resistance (SVR), cardiac contractility and preload (Claeys, 1988).

Normally propofol for sedation in ICU is administered using manual controlled infusion (MCI) method. Nowadays, a new method of infusing drugs has been developed which is called target controlled infusion (TCI) method. The infusion pump that has a TCI method of infusion is incorporated with special design software that has been

developed based on pharmacokinetic profile of the drug and for propofol. The software is called 'Diprifusor' and it has been validated for use. Instead of starting MCI with recommended infusion regime in ml/h or μg/kg/min based on calculated dose in mg/kg, TCI was started by selecting a certain target of propofol concentration in the blood in μg/ml that can cause a certain clinical effect (McMurray, 2004). In simple word, MCI is the method of infusing propofol by targeting the dose, for example the dose between 0.3-4.0 mg/kg/h for sedative effect whereas TCI is the method that targeted to achieve certain blood concentration of propofol, for example 0.2-2.0 μg/ml for sedative effect.

The basic principle of TCI is the initial targeted blood concentration (TBC) of drug is set as required by the anesthesiologist and then infusion rates are altered automatically by the TCI pump according to a validation of pharmacokinetic model. 'Diprifusor' software consists of three-compartment pharmacokinetic model with a specific set of pharmacokinetic parameters for propofol and two independent infusion control algorithms (Gepts, 1998). The input data that must be set by anesthesiologist to run the TCI syringe pump are age of the patient, body weight of the patient and target blood concentration.Therefore, the anesthetists will need to set on the TCI infusion pump the level of propofol blood concentration they are aiming for. So that when the infusion pump is started, it will deliver certain amount of propofol based on automatic calculation of the software to achieve that concentration.

In general, TCI has several potential benefits over MCI technique. It has been described as more convenient in use, simple to operate, easy to titrate, good control of

depth of anesthesia and stable haemodynamically. There are few potential advantages of TCI over MCI technique of propofol in sedating TBI patients during cerebral protection. It provide more stable ICP, CPP and haemodynamic control as well as more rapid recovery for neurological assessment. The comparisons between TCI and MCI of propofol for anaesthesia have been previously described in few of the literatures. However there is no study comparing between these two methods for sedation in neurosurgical intensive care setting particularly for traumatic-brain injured patients.

1.1 OBJECTIVES

1.1.1 To compare the time taken to achieve adequate sedation .

1.1.2 To compare neurological monitoring parameters (ICP and CPP) between TCI and MCI techniques of propofol over 24 hours

1.1.3 To compare haemodynamic changes (MAP and heart rate) between TCI and MCI techniques of propofol over 24 hours

1.1.4 To compare the time of recovery after stopping the infusion between TCI and MCI techniques of propofol (the time from stopping infusion to the time of achieving awake state indicated by BIS > 90).

1.1.5 To compare the total amount of propofol consumption (in mg/kg/h) between TCI and MCI techniques of propofol during sedation.

2. LITERATURE REVIEW

2.1 HEAD INJURY

2.1.1 EPIDEMIOLOGY

Head injury is a major cause of morbidity and mortality worldwide with an ever rising trend. Severe head injury remains one of the leading causes of death and permanent disability among productive age group in Malaysia. Head injury directly causes a great burden and economic loss to the family and country. It is estimated that 23 to 24 million people are injured worldwide in road crashes and about 1.17 million deaths occur per year worldwide due to road traffic accident. The total number of road traffic accident in Malaysia exceeded 223, 000 in 1999 with an average of 16 deaths every single day. The cost involved is calculated at RM 4.6 million a day with a total of RM1.67 billion, making it a major public health problem in Malaysia.

2.1.2 PATHOPHYSIOLOGY

Primary brain injury is due to acceleration and deceleration of the head or the mechanical impact to scalp, skull, brain matter and blood vessels at the moment of injury in a focal, multi focal or diffuse pattern. The physical force at the time of injury commonly causes contusion and laceration of the brain which is in contact with the inner skull surface, mainly at the temporal pole and orbital surface of frontal lobe. In addition the diffuse

axonal injury that occurs at the subcortical surface and deeper structures is commonly seen in severe head injured patients. Extradural or epidural hematoma following head injury commonly occurs in the convexity of brain and mostly due to torn middle meningeal artery or bleeding from the skull fracture. Subdural hematoma is usually due to tearing of bridging vein or laceration of the cortical brain and it is not uncommon that subdural hematoma may be associate with underlying contusion. Intraparenchyma hematoma which manifested as a clot in the brain is commonly resulted from brain laceration. The intracranial hematoma may be multiple dependants on the site and velocity of impact. All this hematoma presented as mass lesion that contribute to the raised intracranial pressure and the sizeable clot need surgical evacuation.

The pathophysiological process following primary impact that causes secondary brain damage is the development of vicious cycle of brain edema with subsequent increase in intracranial pressure (ICP), reduction in blood supply and oxygen delivery causing cerebral ischemia, energy failure and further edema enhancing the primary brain damage and poor outcome. Other factors that enhance the brain damage following primary impact are pyrexia, anemia, vasospasm, seizure, infection and hyponatremia. Autopsy study has demonstrated ischemic brain damage in 80-92% of patients who died following head injury (Pillai *et al.*, 2004, Graham and Adams, 1971).

The process that occurs at cellular level in the brain following severe head injury includes the release of amino acids, glutamate and aspartate, free radicals, lactate and hydrogen ion above toxic level. These processes eventually result in influx of calcium ions into cells and subsequently lead to cell swelling. In addition, the damage of blood brain

barrier leads to increase transcapillary exudation. Therefore the presence of intracranial hematoma with combination of cytotoxic and vasogenic cerebral edema distort the anatomy of brain and blood vessels which worsen the cerebral hypoxia, responsible for inflammation and microvascular dysfunction. The extravascular blood also releases free radicals, predisposing to large vessel spasm hence further reduction in cerebral blood flow, hypoperfusion and ischemia (Ikeda and Long, 1990, Kiening *et al.*, 2002).

2.1.3 COMPUTED TOMOGRAPHY (CT) SCAN IN SEVERE HEAD INJURY.

The standard non contrast enhanced computerized tomography (NCECT) scanning of the brain is an invaluable diagnostic tool and help in the management of severe head injury. A focal mass lesion such as epidural, subdural, intraparenchymal hematoma, brain contusion and associated lesions can be clearly demonstrated on CT brain. Emergency evacuation of hematoma can the be planned accordingly. The progressive enlargement of hematoma and swelling of the brain tissue resulted in shifting of the brain and displacement of the midline structure. The mass lesion in the supra tentorial compartment may cause brain herniation through the tentorial hiatus.. The herniation can be demonstrated on the CT scan as the effaced basal cistern.

Classification of brain injury according to the structural changes demonstrated on CT scan has been published based on the status of basal cistern, midline shift and hematoma of less than 30mls (Marshall *et al.*, 1992). The system defines brain injury into 4 categories from DI I, II, III and IV. A modified Marshall system has added DI V and VI

which includes the non evacuated mass of more than 30mls and evacuated mass lesion respectively. Midline shift and effacement of basal cistern as demonstrated on computed tomography correlate with the degree of cerebral edema and are predictors of lowering the cerebral compliance and perfusion pressure along with developing intracranial hypertension and the eventual outcome of severely brain injured patients (Toutant *et al.*, 1984, Miller *et al.*, 2004).

2.1.4 EVACUATION OF MASS LESION.

Craniotomy or craniectomy and evacuation of blood clot remove significant amount of mass lesion, such as epidural, subdural, intraparenchymal hematoma and contusion, hence restoring the brain anatomy, reducing intracranial volume and ICP with eventual improvement of outcome (Zhang *et al.*, 2001, Schneider *et al.*, 2002). Removal of this primary injury factor is crucial to prevent secondary brain damage. In addition, surgical evacuation of hematoma may result in reduced cerebral edema and minimize micro vascular dysfunction and large vessel spasm. In the extreme cases of refractory intracranial hypertension, decompressive craniectomy has been shown to normalize cerebral compliance and pressure volume index in patients who survive severe head injury.

2.1.5 INTRACRANIAL PRESSURE

Monitoring of ICP in severe head injury is recommended and associated with decreased death rate (Lane *et al.*, 2000). ICP monitoring in patients with GCS score of 8 and below forms the guideline in the management of severe head injury and is widely practiced throughout the world. One can monitor the ICP continuously and management of severe head injury is done accordingly. In addition to the intracranial hematoma that formed following head injuries, other factors that contribute to the raised ICP are cerebrovascular congestion, brain edema and development of acute hydrocephalus. ICP was found to be an independent factor that significantly relate to the outcome. Intracranial pressure varies following head injury. Normal ICP in adult during resting i horizontal position ranges between 7 and 15 mmHg. A sustained elevation of ICP of more than 20 mmHg in severe head injured patient is considered abnormal and treatment should be initiated before the ICP reaches 25 mmHg (Ratanalert *et al.*, 2004). Treatment protocol in severe head injury should aim to maintain ICP below 20 mmHg (Juul *et al.*, 2000). ICP between 20 and 40 mmHg is considered moderate and may result in poor outcome and elevation of ICP more than 40 mmHg is severe and usually fatal (Lundberg, 1960). The increased ICP in cases of diffuse injury without associated mass lesion is not as common as other severe head injured patients which harbor mass lesion (Cremer *et al.*, 2005). Evacuation of mass lesion thus may result in normal ICP provided the secondary insults and hydrocephalus are well controlled.

2.1.6 CEREBRAL PERFUSION PRESSURE

CPP measurement can be obtained manually by subtracting the ICP from the MAP and in usual circumstances already calculated by the patient's monitoring device. Therefore CPP is directly influenced by blood pressure and ICP. Arterial hypotension due to hypovolemia, cardio depressant drug and septicemia and those that increase ICP as mentioned above will compromise CPP. Cerebral perfusion pressure targeted therapy has been shown to produce better survival outcome in severe head injury (Huang *et al.*, 2007, Juul *et al.*, 2000). Maintenance of baseline CPP between 60 to 70 mmHg reduces the possibility of cerebral ischemia. This CPP oriented protocol generally requires vasopressors. High CPP reduces the ICP as long as the cerebral autoregulation remains intact. Autoregulation of cerebral blood flow is the mechanism by which a constant and steady blood flow is delivered to the brain over a certain range of MAP or CPP. Normal condition, cerebral pressure autoregulation remains intact as long as the CPP is kept between 50 mmHg and 140 mmHg.

2.1.7 PROPOFOL IN TRUMATIC BRAIN INJURY

Propofol a substituted phenol, is a relatively new intravenous induction agent and also as a sedative agent. It has achieved widespread popularity, largely because of short effective half life and hence a rapid onset and offset of action with short recovery.

The effect on cerebral blood flow (CBF) are probably secondary to a reduction in cerebral metabolic rate (CMR), but the effective mass of propofol in reducing raised ICP may be less in CMR-CBF coupling is impared by traumatic brain injury.

Carbon dioxide(CO_2) reactivity and autoregulation of CBF appear reasonably well preserved during propofol administration. Normal brain, CBF is not greatly affected by changes in CPP between 50 and 150mmHg. This may not be so in the head injury if cerebral autoregulation is impaired (Bouma et al, 1992).

The potentially beneficial cerebral effects of propofol and its brief duration of action even after prolonged administration make it suitable for maintaining sedation by infusion. Therefore propofol has fewer tendencies to accumulate which allow regaining early recovery. This is particularly relevant for early postoperative neurological assessment requirement.

In head injury patient with raised ICP, rapid induction with propofol may reduce ICP and improve oxygenation. This may prevent the marked, through relatively brief ICP increases that may occurs with endotracheal intubation.

Propofol can cause dose dependent cardiovascular depression and systemic hypotensive especially when anesthesia is rapidly induced by bolus drug administration. Hypotensive is partly due to systemic vasodilatation (Persada et al, 1993) but may be also be due to direct myocardium depression and decreased cardiac output (Lindgren 1993).

This may induce cerebral ischemia by one of two mechanisms. If autoregualtion is intact, a reduction in mean arterial pressure will produce reflex cerebral vasodilatation and further risk further an increased ICP and a fall in CPP. If autoregulation is impared, hypotensive may produce a critical decrease in CPP and CBF. The risk of hypotensive is greater in presence of hypovolemia due to either multiple injury or deliberate dehydration for ICP control.

Because of cardiovascular effects and brief duration of action, propofol required a careful choice of dose regimen for induction in order to avoid hypotensive or raised ICP at laryngoscopy.

A slow rate of administration may provide great cardiovascular stability (Stokes *et al,*1991) and allow titration of dose against effect, but this is usually not possible in patients with head injury because of the risk of regurgitation in the fasted patient and the danger of hypoventilation and hypercarbia.

Infusion regimens which provide stable planes of anesthesia without prolonged recovery time, have been developed for propofol. For the similar reasons, propofol infusion is becoming more popular for sedation in ventilated patient in intensive care.

Weather used in anesthesia or for sedation, hypotension with propofol need to be carefully avoided by aggressive fluid and pharmacological therapy.