COMPARISON OF INTRACEREBRAL AND SYSTEMIC HAEMODYNAMICS IN SEVERE TRAUMATIC BRAIN INJURED PATIENTS RECEIVING DEXMEDETOMIDINE OR PROPOFOL AS SEDATIVE AGENTS

BY

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ABSTRAK

Tajuk: Perbandingan intracerebral dan sistemic hemodinamik bagi pesakit-pesakit kecederaan otak yang teruk yang mendapat rawatan dexmedetomidine dan propofol sebagai ubat sedative.

Latarbelakang: Sedatif di unit rawatan rapi neurosurgeri adalah penting bukan sahaja untuk mengurangkan kegelisahan pesakit dan membantu pemberian ventilasi, tetapi ia mampu mengawal perubahan tekanan otak dan peredaran darah otak.

Objektif: Kajian ini dilaksana adalah untuk mengkaji keberkesanan dexmedetomidine berbanding propofol dalam pesakit kecederan otak yang teruk. Kajian ini akan mengfokuskan keberkesanan dexmedetomidine berbanding propofol kepada kesan perubahan jantung dan otak, penggunaan ubat tahan sakit dan masa ekstubasi.

Kaedah: Kajian prospektif melibatkan pesakit kecederan otak teruk yang telah menjalani pembedahan kepala dan telah diberi bantuan ventilasi di unit rawatan rapi neurosurgeri. Tiga puluh pesakit telah diagihkan secara rawak untuk menerima ubat sedatif dexmedetomidine (n=15) dan propofol (n=15). Ubat sedatif dititrasi untuk mencapai skor BIS diantara 60 hingga 70. Kesan terhadap jantung dan otak, penggunaan ubat tahan sakit dan masa ekstubasi telah diukur dan dibandingkan.

Keputusan: Data demografik diantara kedua-dua kumpulan adalah sama. Titrasi sedatif diantara dexmedetomidine and propofol telah mencapai purata SAS (Sedataion agitation Score) dan BIS skor yang sama. Tiada perbezaan yang ketara dalam perubahan purata BP, MAP, ICP dan CPP diantara dexmedetomidine dan propofol. Kadar denyutan jantung adalah rendah dalam dexmedetomidine (58.08 per min CI:51.54,64.62) berbanding propofol (77.06 per min; CI:70.52,83.60) dengan nilai $p<0.01$. Terdapat perbezaan dalam pengunaan ubat tahan sakit, di mana penggunaan ubat tahan sakit adalah rendah berbanding propofol walaupun perbezaan ini adalah tipis ($p=0.06$). Tiada perbezaan dalam masa ekstubasi diantara kedua-dua kumpulan.

Kesimpulan: Kajian ini telah menunjukan dexmedetomidine adalah setara dengan propofol di dalam pemberian kesan sedatif kepada pesakit kecederaan otak teruk lepasan pembedahan kepala. Dexmedetomidine adalah setara dengan propofol dalam kesan terhadap perubahan jantung dan otak kecuali dalam kadar denjutan jantung. Penggunaan ubatan tahan sakit juga adalah rendah dalam kumpulan dexmedetomidine walaupun ia tidak ketara dari segi statistik.

ABSTRACT

Title: Comparison of intracerebaral and systemic haemodynamic in severe traumatic brain injured patients receiving dexmedetomidine or propofol as sedative agent.

Background: Sedation in neurosurgical intensive care unit is crucial as it does not merely overcome anxiety and facilitate ventilation but may prevent deleterious changes in intracranial pressure and cerebral perfusion pressure.

Objective: The aim of this study is to explore the efficacy of dexmedetomidine compared to propofol for sedation in severe traumatic brain injured patients. This study will focus on the effects of dexmedetomidine compared to propofol on the cardiovascular haemodynamics, cerebral haemodynamics and sedation on severe traumatic brain injured patients.

Methods: A prospective and randomized trial was conducted on post craniectomy patients with severe traumatic brain injury and who were ventilated in neurosurgical intensive care unit. Thirty patients were randomized to receive either dexmedetomidine (n=15) or propofol (n=15). The infusion rate was titrated to achieve bispectral index (BIS) of 60 to 70. Cardivascular and cerebral haemodynamics, analgesic requirement and extubation time were measured and compared.

Results: Demographic data were comparable in both groups. Titration of sedation in both groups was able to achieve the same mean of SAS score and BIS score. There were no

significant differences in mean BP, MAP, ICP and CPP between dexmedetomidine and propofol. Heart rates were found to be significantly low in dexmedetomidine group (58.08 per min CI:51.54,64.62) and propofol (77.06 per min; CI:70.52,83.60) with $p<0.01$. The analgesic requirement were marginally lower in dexmedetomidine compared to propofol ($p=0.06$). There were no differences in terms of extubation time between the two groups.

Conclusion: This study showed that dexmedetomidine was comparable to propofol in the provision of sedation in post craniectomy in severe traumatic brain injured patients. Dexmedetomidine was comparable in terms of cardiovascular and intracerebral haemodynamics except patient treated with dexmedetomidine has lower heart rates. There was also reduction in the needs for additional analgesia with dexmedetomidine even though it was not statistically significant.

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ABBREVIATION

ACE	Angiotensin Converting Enzyme
ATICE	Adaptation to the Intensive Care Environment
BIS	Bispectral index
BP	Blood pressure
cAMP	Cyclic adenosine monophosphate
$CMRO_2$	Cerebral metabolic rate of oxygen
CNS	Central nervous system
CPP	Cerebral perfusion Pressure
CVP	Central venous pressure
DBP	Diastolic Blood pressure
EEG	Electroencephalogram
GCS	Glasgow coma scale
HR	Heart rate
ICP	Intracranial Pressure
ICU	Intensive care unit
LC	Locus Cerleus
MAP	Mean arterial pressure
NSICU	Neurosurgical intensive care unit
SAS	Sedation Agitation scale
SBP	Systolic blood pressure
TBI	Traumatic Brain Injury

1 INTRODUCTION

The role of sedation in neurosurgical intensive care unit is to overcome anxiety and pain, to facilitate mechanical ventilation, facilitate frequent neurological assessment and provide sedation without causing deleterious changes in intracranial pressure (ICP) and cerebral perfusion pressure (CPP). Dexmedetomidine, a highly selective α_2 adrenoreceptor agonist, produces dose dependent sedation, anxiolysis and analgesia involving spinal and supraspinal region without respiratory depression (Khan *et al.*, 1999a). It also offers haemodynamic stability particularly over stressful extubation period (Venn & Grounds, 2001) and has only minor effect on cognitive functions (Hall *et al.*, 2000), thus allowing easy communication and cooperation between patients and medical staff. These clinical characteristics make dexmedetomidine a potentially attractive sedative in neurosurgical intensive care unit. However not many studies had compared dexmedetomidine with other traditional sedatives in neurosurgical patients.

Dexmedetomidine is also believed to exert some neuorprotective properties (Ma *et al.*, 2004). The reason for the neuroprotective effect of dexmedetomidine is thought to be due to its action in attenuating the massive release of catecholamines that occurs with cerebral hypoxic-ischemia in multiple parts of the brain. This action may be mediated by pre-synaptic a_2-adrenoceptors. Several animal studies have shown that dexmedetomidine improves neuronal survival after transient global or focal ischaemia (Kuhmonen *et al.*, 2001).

With the unique clinical characteristics and the neuroprotective properties of this novel sedative, dexmedetomidine would be very beneficial in the neurosurgical intensive care. Thus this study aims to explore the efficacy of dexmedetomidine compare to propofol as a sedative in post-craniectomy in severe traumatic brain-injured patients. This study will focus on the effects of dexmedetomidine compared to propofol on the cardiovascular haemodynamics, cerebral haemodynamics and sedation on severe traumatic brain injured patients.

2 LITERATURE REVIEW

2.1 Sedation in Intensive-care Unit

Sedation is an imperative component in managing critically ill patients. Sedation is defined as the allaying of irritability and excitement, especially by administration of a sedative (Dorland, 1995). In the contexts of managing critically ill patients in the intensive care unit (ICU), sedation can be defined as the provision of analgesia and the satisfaction of anxiolytic, hypnotic and amnestic needs of these patients. Anxiety refers to the emotional and physical responses to real and imagined danger the patient experiences in the ICU, and anxiolysis is the reduction of these responses and implies a calm and tranquil state. Hypnosis refers to a state of minimal motor activity and appears similar to sleep. Amnesia is impairment of memory attributable to alteration in attention, arousal, or mood. Failure to meet these end-points may have deleterious effects on the critically ill patient (Young *et al.*, 2000).

2.1.1 Indications for sedation

There are numerous reasons for the administration of sedatives in mechanically ventilated patients. Predominantly, allaying anxiety is the main concern. The causes of anxiety in the intensive care units are multifactorials. These may include loss of the ability to interact and control the environment, worries about families, homes and finances, a fear and uncertainty regarding the implications of diagnoses and outcome, loss of the sense of time and habitual day-night cycles, fear of pain and death, and fear of mechanical life

support system failures (Turner *et al.*, 1990). Pharmacologic sedation may in itself exacerbate anxiety and confusion because of the disorientation it creates. Other factors include pain and physical discomfort from postoperative procedure, the presence of endotracheal tube, carinal stimulation, nasogastric and intubations, from prolonged immobility, and from periodic invasive procedures, such as tracheal suctioning and line placement (Szalados & Boysen, 1998).

Many patients requiring mechanical ventilation suffer from cardiopulmonary instability and impaired gas exchange. Abnormal elevations in oxygen consumption and carbon dioxide production may compromise such patients (Srivastava *et al.*, 1999). Sedatives and analgesics have been shown to reduce oxygen consumption and autonomic hyperactivity (Kress JP, 1996). The use of certain modes of ventilatory support, such as prolonged exhalation times in patients with severe obstructive disease; the use of high positive end expiratory pressure; inverse ratio pressure controlled ventilation; or high-frequency or oscillatory modes in patients with acute respiratory distress syndrome (ARDS) are the instances where deep levels of sedation may enhance ventilator synchrony (Pohlman *et al.*, 1994).

Amnesia has always been cited as an indication for sedation in mechanically ventilated patient but its importance is far less certain than during surgical procedure. Indeed, complete amnesia for extended periods of time during mechanical ventilation in the ICU has never been proven to confer benefit, and some data suggest that prolonged ICU amnesia may be detrimental to long-term neuropsychiatric recovery from critical illness. There is some evidence that lack of awareness related to sedation and/or underlying illness

is associated with development of posttraumatic stress disorder and that preservation of awareness during mechanical ventilation may reduce this problem. However, it is indisputable that complete amnesia is mandatory whenever neuromuscular blocking agents are administered.

2.1.2 Sedation in Traumatic Brain injury

Sedation is advocated in neurosurgical intensive care unit for patient with TBI with similar indications as those in general ICU. Apart from the similar indications, sedation and analgesia are given in TBI to minimized painful or noxious stimuli as well as agitation as they may potentially contribute to elevation of ICP.

Selections of pharmacological sedative in TBI are based upon their effects on the haemodynamics, ICP, $CMRO_2$ and effects on seizure threshold. It is often recommended that the sedative agent used should be short acting as to facilitate neurological assessment. Even a modest amount of sedative may mask neurological deficit (Mirski and Hemstreet, 2007).

Base on guidelines for management of severe traumatic brain injury 2007, produced by Brain Trauma Foundation, proprofol has been widely used as sedative in the neurosurgical intensive care unit. Its rapid onset and short duration of action would not obscure neurological assessment. In addition, propofol had been shown to reduce $CMRO_2$ and control ICP thus has a putative neuroprotective effect. With these features, the

guidelines recommend propofol as a sedative, for the control of ICP. However propofol did not show any significant improvement of mortality or 6 month outcome. This out-come study was based on a double-blind, randomized controlled trial conducted by Kelly et al. comparing endpoints for patients who receive either propofol or morphine (Kelly PF, 1999). On the contrary, Chui et al, found that propofol showed a higher survival rate (36% vs 28%, $p<.001$) than the non-propofol group (Chiu *et al.*, 2006).

The Guidelines for the Management of severe Traumatic Brain Injury 2007, recommend that high dose of barbiturates should be administrated to control elevated ICP refractory to maximum standard medical and surgical treatment. However prophylactic administration of barbiturates to induce burst suppression EEG is not recommended (Bratton *et al.*, 2007).

2.2 Sedation monitoring

Achieving and maintaining a sufficient level of sedation and analgesia is the cornerstone of the management of critically ill patients including those with TBI. Although the sedative drugs used currently have good therapeutic indices, they can result in an unappropriate level of sedation if administered without any control and monitoring. Both undersedation and oversedation may result in an obvious effect on morbidity and mortality in critically ill patients (Jacobi et al., 2002). The consequences of undersedation and oversedation are shown in Table 2-1. Avoiding these consequences the effects of sedative should always be monitored and tailored to individual patient's need. In general practice

only 43% of ICU systematically used some methods of sedation monitoring (Soliman *et al.*, 2001).

Table 2-1 Consequences of under and oversedation.

Undersedation	Oversedation
Stress	Comatose state
Anxiety	Hypotension
Agitation	Bradicardia
Hypertension	Hypoperfusion
Hypoxia	Depressed or even abolition respiratory drive.
Hypercarbia	Prolonged Weaning
Ischaemic Heart Disease	Increase risk for respiratory tract infection
Intracranial Hypertension	

Methods for sedation monitoring can be classified into subjective methods and objective methods. An ideal method of evaluating sedation should have validity, applicability, responsivity, intra-rater reliability and inter-rater reliability (Carrasco, 2000, De Jonghe *et al.*, 2000). Validity is the ability of the method to actually measure the genuine level of sedation in patients and applicability means it can be so easily used in the clinical setting and allow routine monitoring by physician and nurse. The responsivity of a sedation monitoring method is represented by its ability to identify the variations of sedation over relevant time period. Intra-rater reliability requires that if the level of sedation is the same at different times, the same observer should obtain similar measures, while inter-rater reliability allows different observers to obtain similar measures of a determined level of sedation. Reliability is necessary in ICU, to allow the development of sedation protocols that can be used by every physician and every patient (Carrasco, 2000).

2.2.1 Subjective monitoring methods

Subjective monitoring methods are based on the clinical evaluation of the level of sedation. Direct clinical evaluation by the physician allows rough distinction between adequate, excessive and inadequate sedation, thus it has poor validity and reliability. The most studied are the Ramsay Scale, the Glasgow Coma Scale (GCS) modified by Cook and Palma, the Sedation Agitation Scale (SAS), the Richmond Agitation and Sedation Scale and the Adaptation to the Intensive Care Environment (ATICE) scale.

Ramsay et al. proposed a scale to evaluate the sedative effects in 1974 (Table 2-2), of alphaxolone/alphadolone in 30 ICU patients (Ramsay MA, 1974). To date it remains the most commonly used scale, although it has some well-described limitations. It is simple to use at the bedside, but results in indistinguishable levels of sedation, when depth and quality of consciousness are evaluated in the same item. As emphasized by Hansen-Flaschen *et al.*, 1994 and De Jonghe *et al.*, 2000 a patient can be so deeply sedated as to how only a brisk response to glabella tap or loud auditory stimulus (level 4 of the Ramsay scale) yet at the same time he can be agitated (level 1 of the Ramsay scale).

In 1987 Cook and Palma modified the GCS to evaluate the response of ventilated patients to external stimuli (Cook S, 1989) and the scale validity, applicability, and reliability was confirmed by Carrasco et al (Carrasco G, 1995). The modification made includes the scoring of eye opening (resembling that of GCS), response to nursing procedure (resembling the motor response of GCS adapted to the ICU), respiration, and cough. The major advantage over the Ramsay scale is the introduction of respiration and cough scores that can be useful in titrating sedation in mechanically ventilated patients. The major disadvantage is the absence of an agitation scoring that precludes its use in agitated patients.

The Sedation Agitation Scale (SAS) was first introduced in 1994 by Riker et al (Riker *et al.*, 1994) (Table 2-3). In 1999, Riker et al. demonstrated good validity and reliability with SAS and a good correlation between SAS and the Ramsay scale, as both have evident similarities in content and structure (Riker *et al.*, 1999). The main difference, as underlined by Riker et al., is that while agitation corresponds to just one category in the

Ramsay scale (score 1), it is stratified into three different categories (score 5, 6 and 7) in SAS, therefore SAS could provide additional information in agitated patients.

Table 2-2 Ramsay score

Patient awake, anxious, agitated or restless	1
Patient awake, cooperative, orientated and tranquil	2
Patient drowsy with response to commands	3
Patient asleep, brisk response to glabella tap or loud auditory stimulus	4
Patient asleep, sluggish response to stimulus	6
No response to firm nail-bed pressure or other noxious stimuli	7

Table 2-3 Sedation Agitaion Scale (SAS)

Dangerous agitation (pulling at ET tube, trying to remove catheters, climbing over bed rail, striking at staff)	7
Very agitated (requires physical restraints, biting ET tube)	6
Agitated (anxious or mildly agitated, attempting to sit up, calms down to verbal instructions)	5
Calm and cooperative (calm, awakens easily, follows command)	4
Sedated (difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands)	3
Very sedated (arouses to physical stimuli but does not communicate or follows command, may move spontaneously)	2
Unrousable (minimal or no response to noxious stimuli, does not communicate or follows commands)	1

The Richmond Agitation Sedation Score (RASS) has also been evaluated in a prospective cohort study to test its validity and reliability by Ely EW et al. in 2003. The study found that the reliability was similar as those of Ramsay Scale. It was also shown that RASS provides a method for goal-directed delivery of medication. The score of RASS ranges between +4 (corresponding to a combative patient) and -5 (corresponding to an unrousable patient); 0 corresponds to a patient alert and calm. Agitation is stratified in 4 categories, one more than the SAS. Sedation is divided in 5 categories, 2 more than SAS and one more than the Ramsay scale. Therefore, RASS may offer a more detailed description either in agitated patients or in sedated ones.

The Adaptation to the Intensive Care Environment scale or ATICE was developed and validated by De Joganhe (De Jonghe *et al.*, 2003). The ATICE is specifically designed to evaluate mechanically ventilated patients and is very useful for titrating sedation in patients submitted to mechanical ventilation. ATICE includes five items: awakeness and comprehension combined in a consciousness domain, and calmness, ventilator synchrony and face relaxation combined in a tolerance domain. According to S. Rinaldi, ATICE is a more complicated clinical scale than its predecessors and further studies of ATICE are needed as it does not include the assessment of delirium (Consales *et al.*, 2006).

Table 2-4 Richmond Agitation Sedation Scale (RASS)

Combative—overtly combative, violent, immediate danger to staff	+4
Very agitated—pulls or removes tubes or catheters, aggressive	+3
Agitated—frequent non-purposeful movement, fights ventilator	+2
Restless—anxious but movements not aggressive vigorous	+1
Alert and calm	0
Drowsy—not fully alert but has sustained (410 s) awakening to voice (eye opening/eye contact)	-1
Light sedation-briefly (10 s) awakens with eye contact to voice	-2
Moderate sedation—movement or eye opening to voice (no eye contact)	-3
Deep sedation—no response to voice, but movement or eye opening to physical stimulation	-4
Unarousable—no response to voice or physical stimulation	-5

Table 2-5 The Adaptation to the Intensive Care Enviroment (ATICE)

Consciousness domain				Tolerance domain					
Awakeness (graded 0–5)		Comprehension (sum of the 1 point responses)		Calmness (graded 0–3)		Ventilator synchrony (sum of the 1 point responses)		Face relaxation (graded 0–3)	
Eyes closed, no mimic	0	Open/close your eyes	1	Lifethreatening agitation	0	No blockade of the inspiratory phase of ventilation	1	Permanent grimacing	0
Eyes closed, only face mimic after strong painful stimulation	1	Open your mouth	1	Agitation, does not respond to verbal order	1	No R espiratory Rate >30	1	Severe provoked grimacing	1
Eyes opening after strong painful stimulation	2	Look at me	1	Agitation, responds to verbal order	2	No cough	1	Moderate provoked grimacing	2
Eyes opening after light painful stimulation	3	Nod yes with your head	1	Calm	3	No use of accessory respiratory muscles	1	Relaxed face	3
Eyes opening after verbal order	4	Close your eyes and open your mouth	1						
Eyes opening spontaneously	5								

2.2.2 Objective monitoring methods

Objective methods are based on the measure of variables recorded from the patient, because sedation and agitation are experienced by the patients, and are the product of alteration of cerebral function. Thus it does not require the opinion of the physician to quantify the level of sedation (Consales *et al.*, 2006). Objective methods of monitoring sedation include:

- Pharmacokinetics methods
- Lower oesophageal sphincter (LES) contractility measurement.
- Heart rate variability
- Neurophysiology methods (frontalis muscle electromyogram, evoked potentials, electroencephalography and derived parameters).

The pharmacokinetic method is based upon the knowledge of the therapeutic range of the sedative drug employed and of its relation with the pharmacodynamic effects. The major problems were encountered with this method was that there are high inter-patient variability of pharmacodynamic effect seen in the critically ill patients. In addition to this, it is not possible to obtain real time result, so the method has a poor applicability to clinical practice.

In 1984, Evans proposed lower oesophageal contractility as a guide to the depth and adequacy of anaesthsia, as the lower oesophageal smooth muscle remain active despite muscle paralysis produced by muscle relaxant (Evans *et al.*, 1984). Deepening of anaesthsia

resulted in progressive suppression of lower oesophageal contractility. In 1987, Sinclair et al. used this method to identify excessive sedation in patients with renal impairment (Sinclair & Suter, 1987).

Respiratory induced heart rate variations or respiratory sinus arrhythmias had been shown to be related to the depth of anaesthsia. Pomfrett in 1993 demonstrated that changes in the degree of respiratory sinus arrhythmia could be used as an index of depth of anaesthsia (Pomfrett *et al.*, 1993). He had shown that there were correlation between electroencephalogram (EEG) and respiratory sinus arrhythmia in patients undergoing propofol anaesthsia. Wang *et al.*, 1993, and Chase *et al.*, 2004, had also demonstrated significant correlation between the degree of respiratory sinus arrhythmia and level of sedation. But both studies involved small sample size.

Frontalis muscle electromyogram is able to detect the disappearance of frontalis muscle during induction of anaesthsia and administration of sedations. This method was first proposed by Edmonds et al. in 1985 as a method for evaluating level of anaesthsia and depth of sedation (Edmonds *et al.*, 1986). However, the "all-or-none" behavior of the method and the low sensitivity of the frontalis muscle electromyogram render the lack of clinical usefulness of the particular method.

Electroencephalography (EEG) is the recording of electrical activity along the scalp produced by the firing of neurons within the brain. Based on the assumption that the cerebral electrical activity is a sensitive index of brain function, therefore EEG allow a noninvasive objective measurement of cerebral function and the variation induced by

sedative and anesthetic drugs. The modifications of EEG traces induced by sedatives were first described by Gibbs and Brown, 1948.

The interpretation of the rough EEG tracing to monitor sedation is difficult. Therefore, an approach was formulated to analyze and process the EEG signal into a derived parameters. An example of this is the Bispectral Index Scale (BIS) monitoring device which the first and only technology approved by the U.S. Food and Drug Administration (1996) for marketing as an EEG based monitor of anesthetic effect. There are other EEG derived parameters. These include Narcotrend, Patient State Index (PSI), and Entropy. For the relevance of the discussion, BIS will only be discussed.

2.2.3 Bispecteral Index Scale (BIS)

The BIS is a statically derived variables of the EEG expressed as a score between 0 (isoelectrical) and 100 (fully awake). It is based on a statistical technique called bispectral analysis, as the name suggest, that allows the study of phenomena with nonlinear character. The first studies of EEG bispectral analysis were published in 1971 (Barnett *et al.*, 1971).

The process by which BIS was derived is shown schematically in Figure 2-1. The EEG was recorded onto a computer and was time-matched with clinical endpoints and, where available, drug concentrations. The raw EEG data were inspected, sections containing artifact were rejected, and spectral calculations were then performed to produce both bispectral and power spectral variables. Following statistical ranking, the variables

correlating best with the clinical endpoint were chosen. These were then fitted to a multivariate statistical model using the maximum likelihood solution to a logistic regression analysis to produce a continuous series of BIS values. This index was then tested offline in a prospective manner on a new database, and studies evaluated its clinical utility.

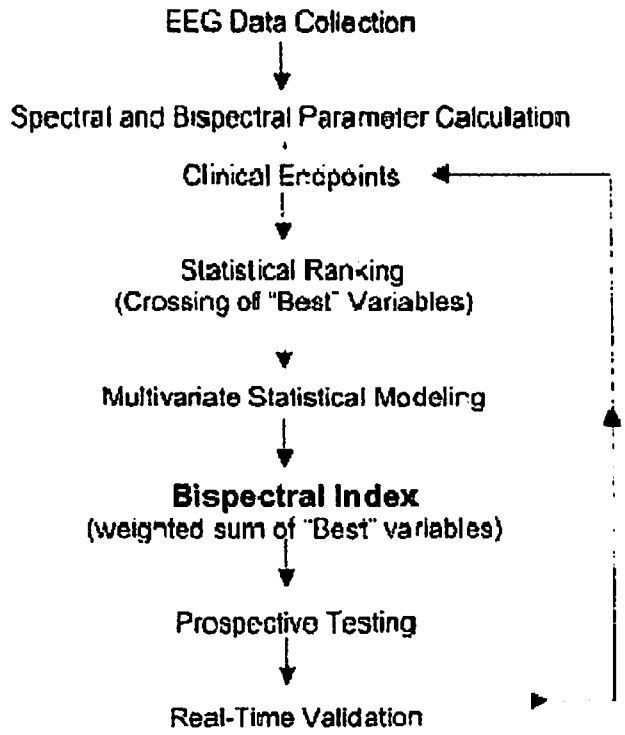

Figure 2-1 BIS development process

In conclusion, BIS is an empiric measurement, statically derived, based on the large EEG database recorded in volunteers and patients who were given one or more anaesthetic drugs (Glass *et al.*, 1997).

The BIS value ranges from 0 to 100 where 0 corresponds to isoelectricity and 100 corresponds to the awakening state Figure 2-2. A correlation between BIS values and the administered dose of intravenous and inhalational anaesthetics has been demonstrated: the progressive deepening of anaesthesia induces a corresponding progressive reduction in BIS values (Johansen & Sebel, 2000).

The usage of BIS to monitor sedation in ICU has been extensively studied. The results of these studies are varied, some studies concluded that BIS is useful in monitoring sedation in ICU (Consales *et al.*, 2006, Arbour, 2006) and some studies showed otherwise (LeBlanc *et al.*, 2006, Nasraway, 2005, Weatherburn *et al.*, 2007). Arbour et al. concluded that BIS may have a role in sedation assessment and BIS value should be interpreted with caution as many factors seem to confound BIS score (Arbour *et al.*, 2009).

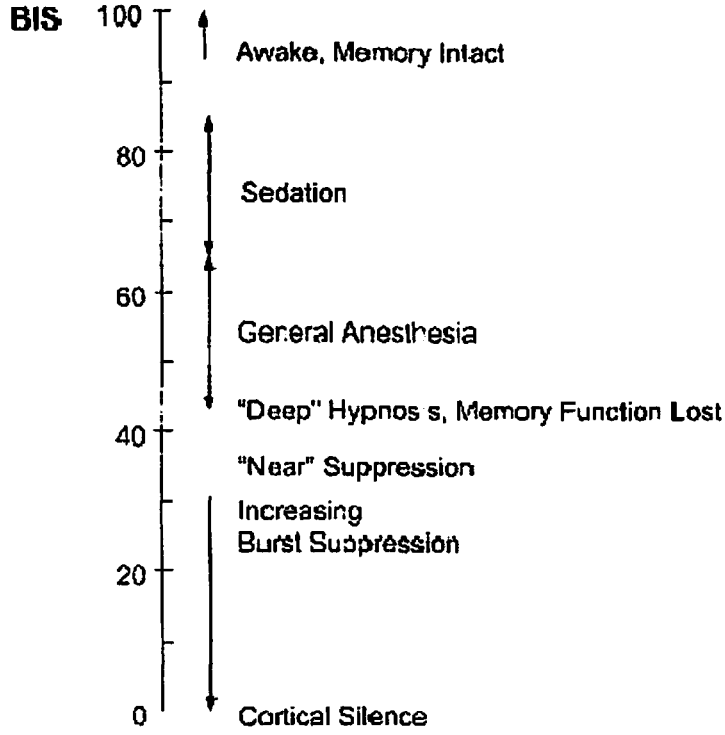

Figure 2-2 The Bispectral Indexmedetomidine Scale (BIS).

BIS value of 65-85 have been recommende for sedation, where as values of 40-65 have been for general anaesthsia. At BIS value below 40, cortical suppression become discernible in raw EEG as burst suppression pattern.

Numerous medical and physiological conditions may alter electroencephalography (EEG), such as hypoglycaemia, hypothermia or hypovolaemia, and result in the BIS monitor indicating an incorrect hypnotic state (Dahaba, 2005).

Not all sedative or hypnotic drugs have correlating effect with BIS monitoring. An example is katamine, a dissociative anesthetic with an excitatory effect on EEG. When given a dose of 0.25mg/kg – 0.5mg/kg sufficient to produce unresponsiveness did not reduce BIS as expected (Morioka N, 1997). Propofol and midazolam when used, shows a significant correlation between sedation level and BIS values (Liu *et al.*, 1996). However the effects of opioids on BIS is uncertained (Johansen and Sebel, 2000).

2.2.4 Role of BIS in Monitoring Patient with Head Injury

Few studies have investigated the role of BIS monitoring in patient with head injury (Gilbert *et al.*, 2001). O'Connor and co-workers reported large variances in BIS scores in their study of 29 patients with neurological diseases (O'Connor *et al.*, 2001). Rikers and co-worker also noted asymmetrical BIS score in patients with abnormal computed tomography scans (Riker *et al.*, 2001). On the other hand, Fabergas and colleague reported that BIS monitoring to be a good outcome predictor in severely brained damage unconscious patients (Fabregas *et al.*, 2004). Anupa *et al* in 2004 found that the BIS monitoring correlate well with standard clinical sedation scales in the neurosurgical intensive care units (Deogaonkar *et al.*, 2004). They also found that, the potential advantage of BIS monitoring

is that it offers a continuous real-time assessment of the level of consciousness that does not require time-consuming physical examination.