Clinical Investigation

Bispectral index score and observer's assessment of awareness/sedation score may manifest divergence during onset of sedation: Study with midazolam and propofol

Address for correspondence:
Dr. Mohan Chandra Mandal, Department of Anaesthesiology, A-5, M.O. Qrts, North Bengal Medical College, Sushrutanagar, Darjeeling - 734 012, West Bengal, India.
E-mail: drmcmandal@gmail.com

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Dipanjan Bagchi, Mohan Chandra Mandal, Sabyasachi Das, Sekhar Ranjan Basu, Susanta Sarkar, Jyotirmoy Das

Department of Anaesthesiology, North Bengal Medical College, Sushrutanagar, Darjeeling, West Bengal, India

ABSTRACT

Background: Correlation between the clinical and electroencephalogram-based monitoring has been documented sporadically during the onset of sedation. Propofol and midazolam have been studied individually using the observer's assessment of awareness/sedation (OAA/S) score and Bispectral index score (BIS). The present study was designed to compare the time to onset of sedation for propofol and midazolam using both BIS and OAA/S scores, and to find out any correlation. **Methods:** A total of 46 patients (18-60 years, either sex, American Society of Anesthesiologists (ASA) I/II) posted for infraumbilical surgeries under spinal anaesthesia were randomly allocated to receive either injection propofol 1 mg/kg bolus followed by infusion 3 mg/kg/h (Group P, *n*=23) or injection midazolam 0.05 mg/kg bolus followed by infusion 0.06 mg/kg/h (Group M, *n*=23). Spinal anaesthesia was given with 2.5 ml to 3.0 ml of 0.5% bupivacaine heavy. When sensory block reached T6 level, sedation was initiated. The time to reach BIS score 70 and time to achieve OAA/S score 3 from the start of study drug were noted. OAA/S score at BIS score 70 was noted. Data from 43 patients were analyzed using SPSS 12 for Windows. **Results:** Time to reach BIS score 70 using propofol was significantly lower than using the midazolam ($P<0.05$). Time to achieve OAA/S score 3 using propofol was comparable with midazolam ($P=0.358$). **Conclusion:** A divergence exists between the time to reach BIS score 70 and time to achieve OAA/S score 3 using midazolam, compared with propofol, during the onset of sedation.

Key words: Bispectral index score, midazolam, observer's assessment of awareness/sedation score, propofol, sedation

INTRODUCTION

Supplementation of spinal anaesthesia with sedatives or anxiolytics has emerged as a standard protocol to alleviate the patient's anxiety and to produce amnesia of the surgical procedure.[1] There seems to be a seamless transition from mild to deep sedation and from there to a state indistinguishable from general anaesthesia (GA). Oversedation may expose the patients to the risk of cardio-respiratory depression and loss of airway control.[2] So, sedation warrants proper monitoring of the patient, especially in paediatric, elderly, and obese patients. Common methods of monitoring the depth of sedation are patient based (e.g., visual analogue scale), observer based (e.g., observer's assessment of awareness/sedation (OAA/S) score) and machine based (e.g., Bispectral index score (BIS)).[3-5] The OAA/S score has the disadvantage of frequent patient stimulation, which may alter the actual level of sedation. However, the BIS score gives a continuous objective assessment with minimal stimulation to patient. BIS monitor produces a single number to indicate the level of

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sedation. The derivation of the scale used by this electroencephalogram (EEG) based monitor is in fact not linear. Naturally, the score of this monitor cannot be expected to follow the progression of sedation linearly.

Midazolam, a benzodiazepine, has a property of rapid onset of action after intravenous (i.v.) injection. Propofol, a non-barbiturate anaesthetic agent, can produce rapid onset of sedation after i.v. administration in proper sub-hypnotic dose. There are studies comparing sedation with propofol and midazolam during regional anaesthesia.[6-9] Only a few studies have focused on finding the correlation between the BIS score and OAA/S score during the onset of sedation while using either drug.[4,10,11] These studies compared BIS scores at a fixed OAA/S score with variable correlation between the two scoring systems. However, a divergence between the OAA/S and BIS scores has been reported sporadically.[11-13]

Comparison between the time to onset of sedation measured with BIS and OAA/S scores and finding any correlation thereon would help to understand the sedation properties of these drugs and to use these in a better way where sophisticated instrumental monitoring is not available. Furthermore, it may open up a new dimension for future research. Hence, the present study was designed to compare propofol and midazolam in respect with the time to onset of sedation assessed with BIS monitor and OAA/S score. It was hypothesized that both the scores would tally during the onset of sedation. An endeavour was given to find out any correlation between the BIS score and OAA/S score during the onset of sedation with each drug.

METHODS

Patients of either sex (age 18-60 years, complying to ASA I/ASA II criteria) posted for elective infraumbilical operations (surgical, gynaecological, or orthopaedic) of approximate 90 min duration were included in this single blinded study. Patients refusing to participate in the study, accept spinal anaesthesia or receive sedation during the surgery were excluded. Other exclusion criteria included patients with contraindications for spinal anaesthesia, pregnant patients, and those with cardiorespiratory diseases, psychiatric illnesses or history of allergy to study drugs.

Based on a previous study regarding the onset of sedation with propofol and midazolam,[6] 40 patients were needed for the study, taking an α error of 0.05 and power of the study (1-β) to be 80%, and considering a difference of 20% regarding the time for the onset of sedation to be significant clinically. Expecting the possibility of dropout of 15%, a total of 46 patients were recruited during their pre-operative visits. They were divided into two groups of 23 patients each, utilizing a computerized random number table. Concealment was done by sealed opaque envelope method. They were to receive either injection propofol (Group P) or midazolam (Group M). The study commenced after approval from the Institute's Ethics Committee. After proper discussion with the patient regarding the nature of the anaesthetic and sedation procedures, informed consent was taken.

The anxiety grade of the patients was noted preoperatively based on the Amsterdam pre-operative anxiety and information scale[14] [Table 1]. Patients with a score of 4 were graded as mild, 5-10 as moderate and 11-20 to be severely anxious. In the literature,[5] it has been found that a BIS reading of 70-80 corresponds with a clinical state where patient is "able to respond to loud verbal, limited tactile stimulation" and BIS score of 60-70 corresponds with a state where patient is "responsive to loud verbal and more intense tactile stimulation." In OAA/S score of 3 the patient "responds only after the name is called loudly/or repeatedly."[13] For this reason, in the present study the OAA/S score 3 has been considered as a state of sedation on clinical observation and a BIS score 70 has been taken as a state of sedation when monitored instrumentally. Hence, the time to reach BIS score 70 and the time to achieve OAA/S score 3 was noted. The assessment of OAA/S score was carried out according to a 5-point scale[13,15] [Table 2].

The patients received injection Ranitidine 50 mg, injection Ondansetron 4 mg and injection tramadol

Table 1: The Amsterdam pre-operative anxiety and information scale

Scale	Anxiety status
1	I am worried about the anesthetic
2	The anesthetic is on my mind continually
3	I would like to know as much as possible about the anesthetic
4	I am worried about the procedure
5	The procedure is on my mind continually
6	I would like to know as much as possible about the procedure

The measure of agreement with these statements should be graded on a five-point Likert scale from 1=not at all to 5=extremely; The anxiety scale consists of four items (questions 1, 2, 4, 5), each of which could be scored from 1-5; The score of the anxiety scale is the sum of these four questions, with a scoring range from 4 to 20

Table 2: The observer's assessment of alertness/sedation score

Responsiveness	Speech	Facial expression	Eyes	Composite score
Responds readily to name spoken in normal tone	Normal	Normal	Clear; no ptosis	5 (alert)
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed or marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words	-	-	2
Does not respond to mild prodding or shaking	-	-	-	1

50 mg iv slowly as premedication around 30 min before surgery, in a side room under adequate monitoring. The monitors (non-invasive blood pressure, electrocardiogram, pulse oximeter) were attached and monitoring started. With proper backup for GA, preloading was started with warm Ringer's lactate solution 15 ml/kg over 30 min. The forehead and temples of the patient were cleaned with spirit and the 4 electrodes (elements) of BIS monitor (BIS XP, A-2000, Aspect) and the sensor were attached.[16]

An infusion pump (JMS syringe pump, model BP 500) was readied with a 20 ml disposable syringe filled either with injection propofol or injection midazolam as per the study group, and connected with the i.v. line via an infusion line and a three way stop valve. The patient was positioned in the left lateral decubitus position and spinal anaesthesia was given with 2.5 ml to 3.0 ml of 0.5% bupivacaine heavy using Quincke needle (26 G) at the L3-L4 interspinous space after local infiltration with 2 ml of 1% lignocaine. After positioning the patient, monitoring of the BIS values was started.

When the sensory block reached the T6 level, sedation as appropriate for the group of the study was initiated and the surgery started. The patients in the Group P received a bolus over 2 min of propofol (1 mg/kg) followed by an infusion of propofol 3 mg/kg/h. The patients in Group M received a bolus of midazolam (0.05 mg/kg) over 2 min and then an infusion of midazolam 0.06 mg/kg/h.[15,17] The time to reach BIS score 70 from starting the study drug was recorded. The time to achieve OAA/S score 3 from the start of the study drug was also noted. At the point of attaining the BIS score of 70, the OAA/S score was noted. All the above mentioned data were recorded by one experienced anaesthesiologist who was not otherwise involved in the study. The infusion was then titrated to maintain the BIS score between 65 and 70 for the rest of the operative period. The SpO_2, heart rate (HR), respiratory rate (RR) and BIS were monitored continuously, and the mean arterial pressure (MAP) continually at 5 min intervals until the end of surgery.

Observed data were entered into Microsoft Excel Workbook and analyzed using the SPSS 12.0 for Windows. Numerical data were analyzed using the independent sample *t* test. The categorical data were analyzed using the Chi-square test. A $P<0.05$ was taken to be of statistical significance.

RESULTS AND ANALYSIS

In the Group M, two patients had to be converted to GA. In the Group P, one patient needed GA. Hence, data from 43 patients were available for analysis. The study groups were found to be comparable in respect of age, sex, weight, height, and anxiety grades and ASA status [Table 3]. The groups were comparable in respect with MAP and HR.

The time to achieve BIS score 70 was found to be lower in the study Group P when compared to Group M ($P<0.05$). The time taken to reach OAA/S score of 3 was comparable in both the study groups. It was found that at a BIS score of 70, an OAA/S score of 1 was achieved in 38.1% of patients sedated with midazolam (vs. only 4.5% in Group P), which was statistically significant. An OAA/S score of 2 was achieved in 31.8% of patients in Group P versus 9.5% in Group M [Table 4].

The time needed to reach a BIS score of 70 was 20.6±8.6 min in severely anxious patients sedated with midazolam in contrast to 6.5±4.4 min in severely anxious patients sedated with propofol ($P=0.001$). The time to reach OAA/S score of 3 was comparable in both groups. At BIS score 70, the OAA/S score 1 was achieved in 63.6% of severely anxious patients in Group M compared to nil in Group P [Table 5].

Table 3: Demographic parameters, anxiety grades and ASA status of patients of study groups

Variables	Group P (*n*=22) (%)	Group M (*n*=21) (%)	*P* value
Age in years	33.2±9.8	35.6±10.6	0.546
Weight in kg	56.9±6.7	55.9±6.6	0.622
Height in cm	163.9±8.2	164.3±7.8	0.863
BMI	21.2±2.6	20.6±1.7	0.823
Male*	13 (59.1)	11 (52.4)	0.658
Female*	9 (40.9)	10 (47.6)	0.658
Anxiety (mild)*	6 (27.3)	3 (14.3)	0.295
Anxiety (moderate)*	8 (36.4)	7 (33.3)	0.835
Anxiety (severe)*	8 (36.4)	11 (52.4)	0.290
ASA I*	19 (86.4)	18 (85.7)	0.951
ASA II*	3 (13.6)	3 (14.3)	0.951

*Categorical data; analyzed with Chi-square test: Values expressed in *n* (%); Rest are numerical data; analyzed with independent *t* test: Values expressed in mean±SD; *P*<0.05 is taken to be significant; Group P received inj. propofol, Group M received inj. Midazolam; ASA – American society of anesthesiologists; BMI – Body mass index

Table 4: Characteristics of onset of sedation

Variables	Group P (*n*=22)	Group M (*n*=21)	*P* value
Time to reach BIS score 70 (min)	4.8±3.3	14.9±9.9	0.000
Time to achieve OAA/S score 3 (min)	3.5±1.9	5.3±2.9	0.358
OAA/S 1 at BIS score 70* [*n*(%)]	1 (4.5)	8 (38.1)	0.007
OAA/S 2 at BIS score 70* [*n*(%)]	7 (31.8)	2 (9.5)	0.072
OAA/S 3 at BIS score 70* [*n*(%)]	12 (54.5)	10 (47.6)	0.650
OAA/S 4 at BIS score 70* [*n*(%)]	2 (9.1)	1 (4.8)	0.578

*Categorical data; analyzed with Chi-square test: Values expressed in *n* (%); Rest is numerical data; analyzed with independent *t* test: Values expressed in mean±SD; *P*<0.05 is taken to be significant. Group P received inj; propofol, Group M received inj. midazolam; BIS – Bispectral index score; OAA/S – Observer's assessment of alertness/sedation

Table 5: Characteristics of onset of sedation in patients with severe anxiety

Variables	Group P (*n*=8)	Group M (*n*=11)	*P* value
Time to reach BIS score 70 (min)	6.5±4.4	20.6±8.6	0.001
Time to achieve OAA/S score 3 (min)	4.7±2.3	6.4±3.5	0.267
OAA/S 1 at BIS score 70* [*n* (%)]	0 (0)	7 (63.6)	0.005
OAA/S 2 at BIS score 70* [*n* (%)]	4 (50)	1 (9.1)	0.046
OAA/S 3 at BIS score 70* [*n* (%)]	2 (25)	3 (27.3)	0.912
OAA/S 4 at BIS score 70* [*n* (%)]	2 (25)	0 (0)	0.080

The number of patients with severe anxiety in Group P is 8 out of total 22; in Group M it is 11 out of total 21; *Categorical data; analyzed with Chi-square test: Values expressed in *n* (%); Rest is numerical data; analyzed with independent *t* test: Values expressed in mean±SD; *P*<0.05 is taken to be significant; Group P received inj. propofol, Group M received inj. midazolam; BIS – Bispectral index score; OAA/S – Observer's assessment of alertness/sedation

The comparative graphs between the time to reach BIS score of 70 and OAA/S score of 3 in the two study groups are depicted in the Figure 1. Spearman's correlation between time to reach OAA/S score of 3 and time needed to reach BIS score of 70 was calculated separately in either of the groups. In Group P, it was 0.875 (strong, P=0.000) and in Group M it was 0.582 (moderate, P=0.006). For severely anxious patients, the Spearman's correlation between the time to reach OAA/S score of 3 and time needed to reach a BIS score of 70 in Group P was 0.571 (moderate, P=0.139) and in Group M was 0.305 (low moderate to low, P=0.361), which depicts a poorer correlation in Group M. The poor correlation between the time to reach OAA/S score 3 and time needed to reach BIS score 70 in Group M is also evident from these comparative graphs. The comparative graphs of the time to reach BIS score 70 and OAA/S score 3 in severely anxious patients are also depicted in the same Figure.

Graphs A and B compare the times in total patient population in study Groups P and M respectively. Graphs C and D compare the times in patients who were severely anxious in study Groups P and M. The time to reach BIS score 70 and time to reach OAA/S 3 show a big divergence in Group M patient population in comparison to Group P. Group P received inj. propofol; Group M received injection midazolam. The haemodyanamic parameters of the patients remained stable during the study procedure as is depicted in Figure 2 below.

DISCUSSION

When using injection propofol, the achievement of OAA/S score 3 was closely followed by a fall in BIS score to 70, even when patients were severely anxious. Thus, a moderate to strong correlation between the instrumental and clinical monitoring seems to exist regarding the onset of sedation using the propofol. This was not the case with midazolam, where a divergence between the time to reach BIS score 70 and time to achieve OAA/S score 3 was evident and was supported by a poor correlation between the two. The time to reach BIS score 70 was lower for sedation with propofol (4.8±3.3 min) than with midazolam (14.9±9.9 min). Similarly, in severely anxious patients in both the groups, the difference to reach BIS score 70 was strikingly high (6.5±4.4 min with propofol vs. 20.6±8.6 min with midazolam). The time to achieve OAA/S score 3 was 3.5±1.9 min with propofol sedation and 5.3±2.9 min with midazolam, the values being comparable. Likewise, the time to achieve OAA/S score 3 was also comparable in severely anxious patients receiving propofol (4.7±2.3 min) or midazolam (6.4±3.5 min).

Comparing sedation with propofol and midazolam while monitoring with BIS, Khurana *et al*.[8] found the time to onset of sedation (BIS score of 75) with injection propofol to be 6.2±0.2 min and that with injection

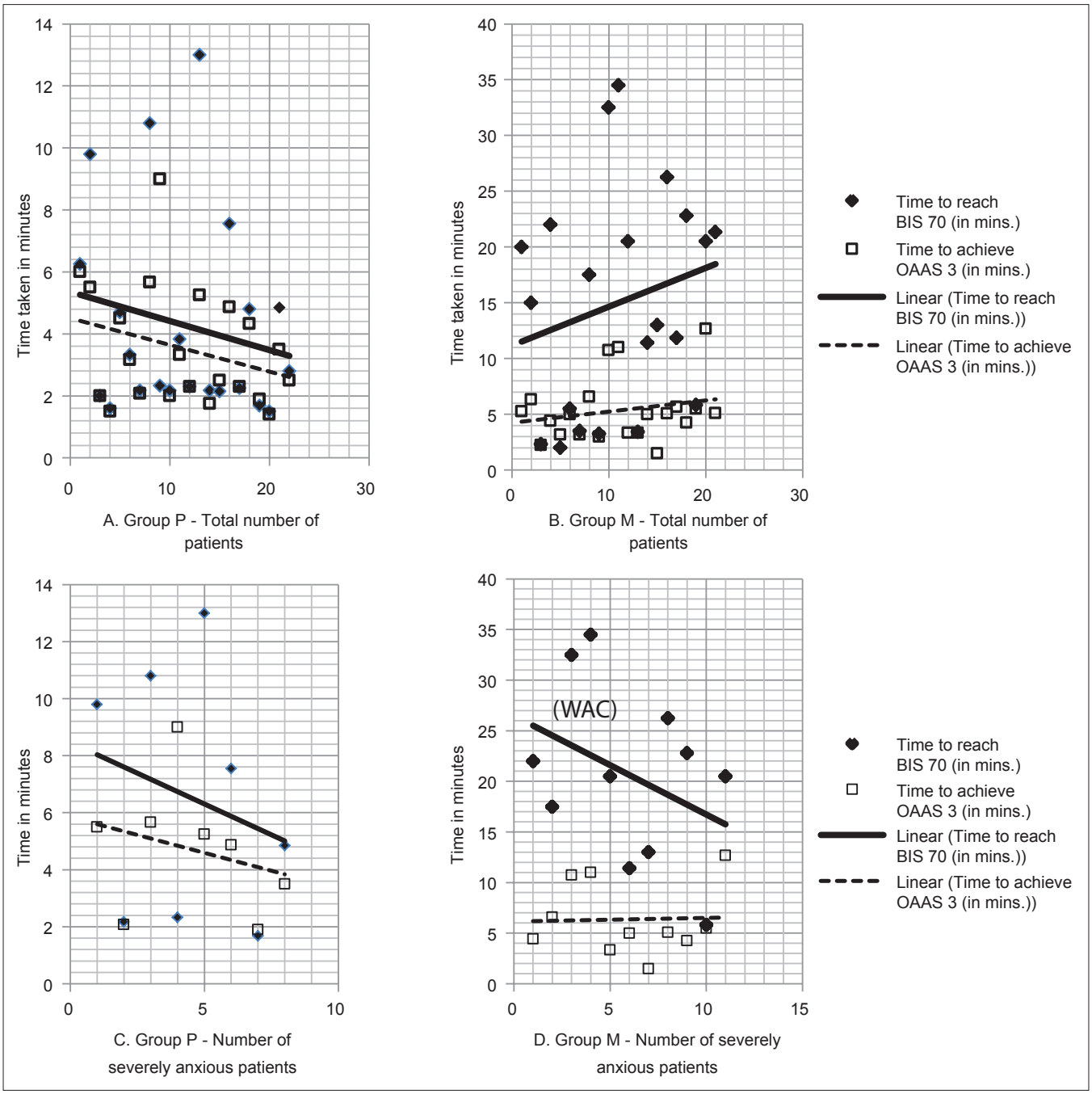

Figure 1: Comparison between time to reach BIS 70 and time to achieve OAA/S score 3. Graphs A and B compare the time in total patient population in study groups P and M respectively. Graphs C and D compare the time in patients who were severely anxious in study group P and M. The time to reach BIS score 70 and time to reach OAA/S 3 show a big divergence in group M patient population in comparition to group P. Group P received inj. Propofol; group M received inj. Midazolam

midazolam to be 11.0±0.5 min. The present study, with a cut-off value of BIS score 70, reflects a similar trend. In severely anxious patients, this difference was strikingly high. Yaddanapudi *et al*.[6] found the onset of sedation (time to achieve OAA/S score 3) with propofol to be 13.0±4.2 min against 18.8±4.2 min with midazolam using lower bolus doses. The present study, with higher bolus doses, demonstrates a similar lower trend for propofol compared to midazolam.

Park *et al*.[13] opined that BIS monitor would not be sensitive enough to adequately reflect the depth of sedation and hypnosis when using N_2O alone for sedation. Clinical indices like the OAA/S scale were found to be more suitable to determine the dose requirement and the adequacy of depth of sedation and hypnosis. Although Liu *et al*. observed that the bi-spectral index corresponded well with OAA/S scores during onset of sedation with midazolam[4] and

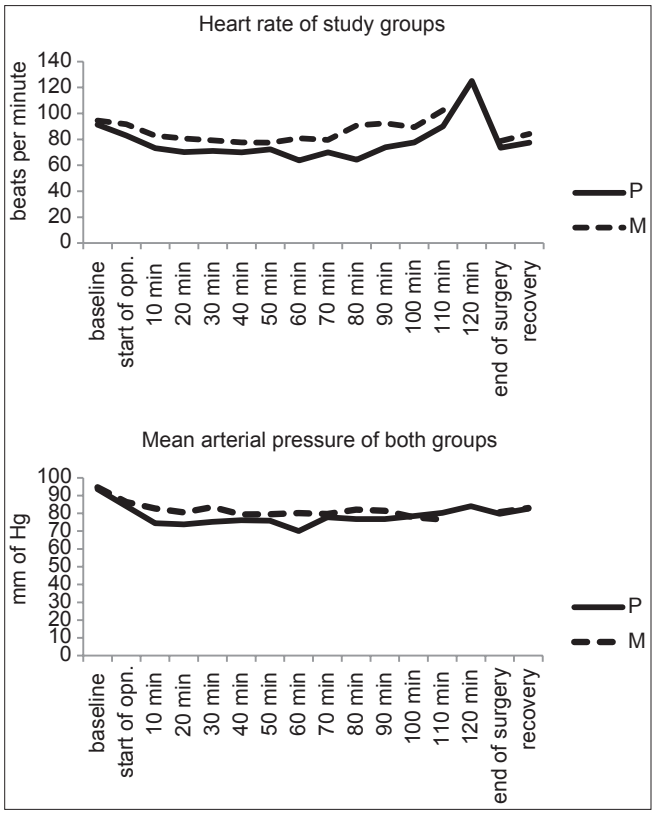

Figure 2: Comparison of the MAP and HR in both the study groups. Both MAP and HR were comparable in both the groups. Group P received inj. Propofol; group M received inj. Midazolam

with propofol,[10] Ibrahim *et al*.[11] found that BIS was a better predictor for sedation with propofol than with midazolam. It might be possible that propofol being a hypnotic, suppressed cerebral activity faster and more predictively.[17,18]

Propofol was found to suppress the alpha rhythm to theta and delta rhythms. Higher doses of the drug efficiently produced burst-suppression.[17] Midazolam usually converted the alpha rhythm to a beta rhythm within 60s. By 60 min of infusion, this rhythm either developed into a resistant beta rhythm of low amplitude or reverted back to alpha rhythm. This pattern of change in cerebral activity was typical of the benzodiazepines.[17] Anxious patients had heightened cerebral activity. So, the benzodiazepines took a longer time for cerebral suppression. It is worth mentioning that the BIS score is derived from analysing the EEG, i.e., the cerebral activity. A longer time to suppress the cerebral activity especially in severely anxious patients might cause a delayed decrease in BIS scores in patients sedated with midazolam despite the patient being clinically asleep. This resulted in a great divergence between the time to reach BIS score 70 and time to achieve OAA/S score 3 in patients sedated with midazolam, although much explanation remains to be sought for. From the above findings, it is apparent that OAA/S scores may not correlate with BIS score during onset of sedation using midazolam.

In the present study, the distribution of OAA/S scores at BIS score 70 were compared between the groups. At BIS score 70, OAA/S score 1 was found in 38.1% of patients sedated with midazolam, compared to only 4.5% of patients sedated with propofol. In severely anxious patients this was 63.6% with midazolam versus nil with propofol. At an OAA/S score of 1, when patients are deeply asleep, not responding to even gentle prodding, and having a higher risk of losing control of airway, the BIS score still remained 70. Thus the patients were deeply sedated clinically though the BIS monitor indicated apparently light sedation. This discrepancy was more with midazolam. An OAA/S score 2 was found in 9.5% of patients sedated with midazolam, and 31.8% of patients sedated with propofol (9.1% with midazolam versus 50% with propofol in severely anxious patients). An OAA/S score of 2 indicated deep sedation and might be associated with loss of airway reflexes in some patient population. However, even then the BIS score was 70. Thus, if only BIS is used as the sole monitor for measuring the depth of sedation, dangerously deep levels of clinical sedation may be reached with either propofol or midazolam and specially so with midazolam. Although EEG-based monitor of sedation demonstrated a correlation with the clinical monitoring of sedation and responsiveness at the extremes of sedation, Chisholm *et al*.[19] did not find a good correlation in the area of clinical interest, namely, at scores between 61 and 80 when one would like to measure light to moderate sedation. The use of BIS to monitor sedation is appealing. However, the conventional clinical assessment of sedation is important as patient contact is maintained. BIS monitoring should be employed as an adjunct to clinical assessment rather than as the primary monitor. The combination of both methods of monitoring can provide complementary facts ensuring a better understanding of the patient's response to sedation than when using either method singly.[12] Simply looking at an EEG based monitor and ignoring the clinical signs of oversedation will not be prudent.

CONCLUSION

A divergence exists between the time to reach BIS score 70 and time to achieve OAA/S score 3 using midazolam, compared to propofol, during onset of

sedation. Monitoring sedation with BIS score and OAA/S score demonstrates poor correlation during onset of sedation using midazolam. Better correlation was found while using the propofol. Clinical sedation is our area of interest. Hence, relying solely on an EEG based monitor to attain a number on the screen may not be wise enough as this might end in an inappropriate level of sedation with loss of airway control.

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Upcoming Conferences

Name of the conference: 4th Annual Conference of All India Difficult Airway Society

Date: 8th, 9th and 10th November 2013

Venue: North Bengal Medical College, Siliguri, West Bengal

Difficult Airway Workshop: 8th November 2013

Organising Secretary: Dr. Sabyasachi Das

E-mail: secynac2013@gmail.com

Name of the conference: 15th Annual Conference of Indian Society of Neuroanaesthesiology and Critical Care (ISNACC-2014)

Date: 31st January - 2nd February 2014

Venue: Jaipur, India

Organising Secretary: Dr. Shobha Purohit

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