Does Perioperative Bispectral Index Monitoring Decrease Time To Extubation In Patients Undergoing Coronary Artery Bypass Graft Procedures?

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Citation

Abstract
In a prospective randomized study the Bispectral index (BIS) was used to titrate propofol infusion during cardiopulmonary bypass (CPB) (between 40-50) and in the postoperative period in the ICU (between 60-70) until extubation. We studied a total of 40 patients undergoing cardiac surgery under CPB. They were randomized to 20 patients each in the BIS and standard therapy group (STG). In the STG group the propofol infusion was titrated to mean arterial pressures (MAPS) of 55 to 65 mm Hg during CPB and to a sedation score of zero on the Sedation-Agitation Scale (SAS). Patients in both groups had similar demographic characteristics, duration of CPB and surgery. The total amount of propofol used (BIS 1662mg, STG 1729 mg)] showed no statistical difference despite BIS monitoring. The time to the average time to eye opening (190 min), time to wean (210 min) and extubation (BIS 352 minutes, STG 380 minutes) were comparable in the both groups. Monitoring of hypnotic component with BIS during cardiac surgery failed to demonstrate an earlier time to recovery and extubation.

INTRODUCTION
Bispectral Index Monitoring (BIS) is a multifactorial parameter obtained from the electroencephalogram (EEG) and has been used as a monitor of sedation, hypnosis, and awareness. It employs processed electroencephalogram (EEG) signals to provide the user with a single number indicating the level of patient consciousness. BIS has been employed in patients undergoing CPB to reliably guide administration of amnestic drugs, as well as for sedation in the ICU.

BIS monitor has been increasingly used in the operating room to monitor hypnosis during anesthesia and as a tool to “fast track” recovery of patients. We studied the utility of using a BIS monitor perioperatively for patients undergoing coronary artery bypass grafting (CABG) under cardiopulmonary bypass (CPB).

Management strategies in patients undergoing cardiac surgery have undergone significant changes in an effort to be cost-effective and optimize use of resources. Despite use of different anesthetic techniques to expedite recovery, patients may still be overly sedated after cardiac surgery. In addition, maintenance of the appropriate level of sedation in the Intensive Care Unit (ICU) during ventilatory support and weaning is subjective and may result in prolonged ventilation secondary to excessive sedation.

We hypothesize that perioperative BIS monitoring during CPB and post-operatively in the ICU will result in earlier extubation and recovery than in the absence of perioperative BIS monitoring.

METHODS AND MATERIALS
After obtaining IRB approval and informed written consent, we studied forty consecutive patients scheduled for CABG involving CPB.

Selection criteria: Forty patients were divided into one of two groups by a computer-generated randomization. Patients included were greater than 18 years of age, scheduled for CABG on CPB and had a pre-operative ejection fraction of ≥40%. Patients with a history of alcohol or drug abuse, severe hepatic or renal disease, or severe neurologic disease were excluded from the study.

Preoperative sedation: Patients received standard pre-operative sedation, currently employed at our institution, which included midazolam, titrated to effect, to a maximum
dose of 10 mg. Enrolled patients were randomly assigned to one of two study groups as follows: the study treatment group (BIS) or the standard therapy group (STG).

Patients in the BIS group had the BIS electrode placed on the forehead prior to induction of general anesthesia.

Induction and maintenance of anesthesia: Propofol, (titrated to effect, to a maximum of 2 mg/kg), pancuronium (0.1 mg/kg), and fentanyl, (titrated to effect, to a maximum dose of 20 mcg/kg) were used for induction in both groups.

Anesthesia was maintained using a “balanced” technique consisting of isoflurane (MAC range 0.6 to 1.6) and fentanyl (up to 20 mcg/kg). Patients, in both groups, were maintained on a propofol infusion (50 to 100 mcg/kg/min), during CPB. In the BIS group the propofol infusion was titrated to maintain a BIS level 45 to 55. In the STG group, the propofol infusion was titrated to maintain MAP between 55 to 65 mm Hg. No volatile agents were used while on CPB.

Post CPB phase: At the conclusion of CPB, maintenance anesthesia for patients in both groups involved the “balanced” technique of isoflurane and fentanyl. BIS levels of 40 to 50 were maintained utilizing a propofol infusion, during closure of the sternum, suturing of skin and soft tissue.

ICU phase: After surgery, patients were transported to the cardiovascular intensive care unit. The propofol infusions were continued in both the BIS and STG groups. Propofol was titrated to a BIS level of 60 to 75 for patients in the BIS group. While in the STG group, propofol was titrated to a sedation score of zero on the Sedation-Agitation Scale (SAS). Postoperative pain was treated with intravenous morphine (2 to 4 mg as needed, based on the VAS scale).

Ventilatory settings and weaning criteria: The method of weaning from the ventilator was identical in both study groups. (See appendix 1 for details). Upon arrival in the ICU patients received mechanical ventilatory support in the following manner:

- **SIMV10**
- Tidal volume 10 ml/kg
- **FiO2 1.00**
- **PEEP 5cm water**
- Pressure support (PS) of 5cm of water

The following criteria were used to determine the appropriateness of discontinuation of mechanical ventilatory support (weaning):

- Patient awake and comfortable
- Hemodynamically stable
- Core temperature greater than 36C
- No signs of active bleeding
- No significant dysrhythmias
- No residual neuromuscular blockade

Presence of spontaneous respiration (respiratory rate less than 25 breaths per min (BPM), and minute ventilation greater than 5 liters per minute)

All sedation was stopped at the time of weaning from the ventilator.

Weaning was accomplished by decreasing the FiO2 and decreasing the number of mandatory breaths. Patients were reevaluated after 30 minutes. If above weaning criteria were met and oxygen saturation (SpO2) was greater than 96% on FiO2 of 50% or less, the mode of ventilation was changed from SIMV to PS of 5 cm/water. Arterial blood sampling (ABG) was obtained prior to extubation. The following parameters were considered appropriate for extubation.

- **pH**: 7.35-7.45
- **PCO2**: 35-45 mm Hg
- **PO2**: >80 mm Hg.

Endpoints: Primary clinical end points were i) time taken to extubation (from admission to ICU until extubation), and ii) total amount of propofol used in the operating room and ICU. Secondary endpoints included i) total amount of midazolam and fentanyl used intraoperatively ii) hypotension iii) number of patients reporting intraoperative recall.

Patients were evaluated for explicit awareness within 24 hours following extubation.

**STATISTICAL ANALYSIS**

Using an a priori power analysis, a patient population of 40 (20 per study group) was considered appropriate for
Does Perioperative Bispectral Index Monitoring Decrease Time To Extubation In Patients Undergoing Coronary Artery Bypass Graft Procedures?

- Detection of a difference of 25% in time to extubation between the BIS monitored group and the control group (no BIS) with a power of 0.92 and $\alpha = 0.05$.

Demographic variables were compared between groups using chi square analysis and Fischer’s exact test as appropriate. Time to extubation, total dose of propofol used and hemodynamic variables was compared using paired samples t test. A $P$ value of <0.05 was considered statistically significant.

RESULTS

Forty patients were studied with 20 patients randomly allocated in each group (20 patients in BIS, and 20 in STG).

Patients were randomized into two groups with the BIS group receiving titrated infusion of propofol to maintain BIS values of 40 to 50 in the OR and 60 to 75 in the ICU whereas the STG group receiving anesthetic drugs without the aid of BIS in the OR and sedation was titrated to SAS sedation of 0 in the ICU. The demographic characteristics (figure1) were similar with mean age of 64 years, and 75% males. The majority of patients were ASA 3 and 4 with ejection fraction of 50 to 60% .(Table 1) The average number of vessels bypassed was four in both groups.

The average anesthetic time (308 min), surgical time (258 min), CPB time (118 min) and cross-clamp (97 min) time were similar in both groups. (Table 2) The mean arterial pressure (MAP) and heart rate (HR) recorded in the OR and ICU did not show any differences. This correlates with the similar amounts of midazolam (average use of 8 mg) and fentanyl (BIS and control groups were 1660 and 1500 respectively) used in the OR in both groups.

Propofol infusion was initiated at the onset of CPB and volatile anesthetic agent was discontinued. Propofol infusion was continued during transfer to ICU and was terminated when weaning criteria was established Hypothermia was routinely adopted during CPB with the lowest temperature of 28°C achieved in both groups. With presence of hypothermia propofol infusion alone was sufficient to sustain BIS values to less than 46. The amount of propofol use for both groups were recorded in the OR (1103mg BIS and 1159mg STG) and ICU (485mg BIS and 500mg STG) and were equivalent. (Table 4)

Morphine was used intermittently for analgesia in the ICU and administered in bolus dose of 1-4 mg intravenously every two hours and titrated to hemodynamic signs BP >120/90, HR>110/min. The amount of morphine (mg) used in BIS and control groups in ICU at the time of extubation were similar. (Table 4)

During weaning the average time to eye opening (190 min), time to wean (210 min) was similar in the both groups. Extubation times were 352 minutes BIS and 380 minutes in STG group . Time to extubation showed a trend to be less in the BIS group that was not statistically significant. (Figure2) Extubation within six hours following surgery was accomplished in 60% of BIS and 45% of control patients. Extubation within 6 hours when used as criteria to differentiate early versus late extubation did not show any difference. (Table 5)

The MAP values (mm Hg) of BIS and STG groups at baseline (95,124), intubation (81,79), incision (78,80), at start and end of CPB (68, 64) and at end of sternal wire (75,71) were similar. (Table 6) In BIS group values ranged BIS ranged from 40 to 45 in the OR. (Table 8)

MAPs of BIS and STG groups on admission to ICU and at 1,2,3,4, and 5, hours were similar. BIS values at time of eye opening and extubation was greater than 75. (Table 7)

We did not encounter any adverse intraoperative events such as hypoxia, or hypotension necessitating intra-aortic balloon pump during weaning from CPB.

Patients in the study were interviewed postoperatively and there was no history of recall.

Figure 1

Table 1. Patient demographics and ASA class
Does Perioperative Bispectral Index Monitoring Decrease Time To Extubation In Patients Undergoing Coronary Artery Bypass Graft Procedures?

Figure 2
Demographic characteristics of both groups studied included age, gender and ventricular ejection fraction and ASA class. No statistical differences were present.

Table 2: Surgical time (time in minutes from incision to last suture), and lowest body temperature during procedure (C)

<table>
<thead>
<tr>
<th>Variable</th>
<th>BIS</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical time</td>
<td>25.6</td>
<td>28.5</td>
</tr>
<tr>
<td>Lowest body temp.</td>
<td>34.2</td>
<td>35.5</td>
</tr>
</tbody>
</table>

WEANING DATA

Table 4: Propofol and morphine use in the ICU

<table>
<thead>
<tr>
<th>Propofol/morphine</th>
<th>BIS</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol infusion</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Morphine administration</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Morphine was used intermittently for analgesia in the ICU and administered in bolus dose of 1-4 mg intravenously every two hours and titrated to hemodynamic signs BP >120/90, HR>110/min

Table 5: Eye opening, time to wean and extubation time, and extubation within 6 hours

<table>
<thead>
<tr>
<th>Variable</th>
<th>BIS</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to eye opening</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Time to wean</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Extubation time</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Figure 5

Figure 6

Figure 7

Does Perioperative Bispectral Index Monitoring Decrease Time To Extubation In Patients Undergoing Coronary Artery Bypass Graft Procedures?

Figure 8
Table 6: Hemodynamic (MAP and HR) data in OR

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Patient A</th>
<th>Patient B</th>
<th>Patient C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>50</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>MAP At induction</td>
<td>60</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>MAP at start of CPB</td>
<td>70</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>MAP at end of CPB</td>
<td>80</td>
<td>90</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 9
Table 7: Hemodynamic (MAP) data in ICU

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Patient A</th>
<th>Patient B</th>
<th>Patient C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>50</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>MAP At induction</td>
<td>60</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>MAP at start of CPB</td>
<td>70</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>MAP at end of CPB</td>
<td>80</td>
<td>90</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 10
Table 8: Intraoperative and ICU BIS readings.

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>At start of CPB</td>
<td>70</td>
<td>15</td>
</tr>
<tr>
<td>At end of CPB</td>
<td>80</td>
<td>20</td>
</tr>
</tbody>
</table>

The BIS readings at baseline, intraoperatively and in the ICU as noted in the BIS group shows patient lightly sedated at baseline, below 45 during surgery and moderately to lightly sedated postoperatively in the ICU prior to readiness for ventilator weaning.

DISCUSSION

BIS has been introduced to the operating room to improve anesthesia providers’ ability to administer anesthetic drugs, decrease emergence times and improve patient outcome by earlier discharge from the recovery room facility. Johansen examined the impact of BIS on perioperative care. Anesthesia was maintained at BIS values between 50 and 65 (for at least 34% of time) with surgical duration of about 1 hour and was associated with earlier emergence and recovery from general anesthesia. In the current study, we failed to demonstrate any effect of BIS monitoring on recovery parameters in our group of patients undergoing myocardial revascularization. In particular, we were unable to demonstrate any reduction in time to spontaneous eye opening, earlier ventilator weaning, and extubation times.

Unlike surgery in outpatient setting patients undergoing cardiac surgery may require increased depth of anesthesia commensurate with level of surgical stimulus such as sternotomy and pericardiotomy and BIS was designed to be maintained between 40 and 50 range. In our study BIS values dropped significantly to below 45 range after induction and remained significantly lower throughout pre
CPB, CPB and post CPB period. Scmidlin\textsuperscript{11} noted a much lower BIS value (median of 41) during hypothermic CPB (32C) with propofol sedation. He attributed it to brain cooling or increased propofol levels due to slow pharmacodynamics during cooling.

Johansen\textsuperscript{10} noted that hypnotic maintenance at BIS less than 50 did not confer any clinical advantage over unmonitored cases. The lower BIS values obtained in our study could partially explain lack of significant differences in recovery parameters compared to control group.

BIS monitoring has been used by numerous investigators in outpatient surgery, to titrate anesthetic depth, reduce exposure to anesthetic agents and facilitate early recovery and discharge.\textsuperscript{3,10,11,12,13} Patient population in our study focused on a more select group comprising of older male patients in the age range of 60 to 70 years, predominantly ASAIII and IV and undergoing exclusively elective coronary artery bypass grafting. A longer duration of anesthesia (300 minutes) and physiologic variables associated with CPB [hypothermia (28 to 32C), hemodilution with changes in drug concentration] would be confounding variables, which preclude comparison with other studies that were performed on relatively healthy patients undergoing outpatient surgery.

Other studies have investigated the effects of BIS monitoring on emergence and recovery in the inpatient setting. Wong\textsuperscript{12} examined 68 elderly patients undergoing lower extremity joint replacement surgery where patients were similarly randomized in BIS and non-BIS group. Isoflurane usage was 30% lower in BIS which resulting in faster emergence (9.5 vs 13.1 minutes) but no difference in time to discharge from the PACU was observed. Pavlin\textsuperscript{21} reported 11% faster recovery in males when BIS was used to titrate sevoflurane. Gan\textsuperscript{9} reported that titrating propofol with BIS monitoring during balanced anesthesia decreased propofol use by 22% and significantly improved recovery. Our study did not show any benefit of BIS monitoring in significantly reducing the amount of midazolam, fentanyl and propofol administered to patients perioperatively. Possible reasons for lack of differences in anesthetic doses in BIS and non-BIS groups could be related to decreased overall anesthetic requirements in elderly population with more comorbidities. Hypothermia during CPB (lowest core temp was 28 C in both groups) would also reduce anesthetic requirement.

Anesthetic agents administered in our study were also different from other studies where volatile agents were maintained throughout the procedure. Isoflurane was used only pre-CPB and post CPB, whereas propofol infusion was used during CPB and continued in ICU till patient was ready to be weaned from mechanical ventilation. Intraoperative use of midazolam, fentanyl and propofol and ICU use of propofol were similar in BIS and non BIS groups. The use of anesthetics and sedatives with weaning and extubation in the ICU is a different clinical scenario unlike other published studies where patients were extubated prior to transfer to post-anesthesia unit.

Pavlin\textsuperscript{15} failed to demonstrate any impact of BIS monitoring on recovery parameters in 1580 inpatients. There was no reduction of time spent in operating room at end of surgery, and time spent in PACU before discharge to ward.

Ahmad et al\textsuperscript{13} compared the impact of BIS monitoring on fast tracking of 99 outpatients undergoing laparoscopic surgery. The study was similar to our study where patients were divided into 2 groups with or without BIS monitoring. Authors found no statistical difference between the groups with respect to number of patients who successfully bypassed the phase 1 recovery area, length of hospital stay and cost of hospitalization.

Zohar et al\textsuperscript{16} used intraoperative BIS monitoring for sevoflurane titration in elderly outpatient surgical population and found no difference in early and intermediate recovery endpoints. He suggested that the anesthesiologist’s standard technique allowed patients in the control group to maintain BIS in the targeted range without additional information provided by BIS monitor.

Our study results reflect a similar situation and could be explained by the following: 1.) A standardized anesthetic regimen by a skilled anesthesiologist with use of fast tracking techniques and propofol titration during postoperative sedation is as effective as other techniques where BIS values are used to guide depth of anesthesia. 2.) The anesthesiologist using the BIS monitor did not significantly alter their standard anesthetic drug administration technique and therefore use of BIS failed to make a difference.

An additional advantage of BIS is that it helps clinician reduce the incidence of awareness with recall.\textsuperscript{17} The incidence of awareness under anesthesia in multiple studies ranges from 0.1 to 0.2\textsuperscript{18} Ekman et al studied a large cohort of 4945 surgical patients undergoing anesthesia with muscle...
Does Perioperative Bispectral Index Monitoring Decrease Time To Extubation In Patients Undergoing Coronary Artery Bypass Graft Procedures?

relaxants who were monitored with BIS values kept between 40 and 60. The BIS monitored group when compared to a historic group without BIS monitoring showed a 77% reduction in the incidence of explicit recall. In our study we did not observe any incidence of explicit recall in BIS and control groups.

There are a number of limitations to our study. Our study design did not include concealed BIS monitoring in control group. BIS values have been higher in BIS monitored groups compared to control groups.9,12

Clinically the use of BIS monitors in the OR and ICU requires continuous monitoring.

This is difficult for the anesthesiologist as the BIS numbers change frequently with changes in level of surgical stimulus, body temperature –cooling during CPB and rewarming. BIS titration requires constant visual attention and may be difficult as the anesthesiologist’s attention may be diverted in maintaining hemodynamic stability during weaning from CPB, monitoring cardiac status with EKG, pulmonary artery catheter and transesophageal echocardiography.

The BIS algorithm has changed since its inception but is not a perfect tool. Some clinical situations can be confusing with false variations in BIS. BIS should be monitored in the clinical context as impaired cerebral perfusion from low cardiac output, hypothermia, hypoglycemia, erroneous placement, electrical interference may provide misleading information to the anesthesiologist.\cite{25,20}

CONCLUSIONS

We hypothesized that BIS monitoring in patients undergoing anesthesia for CABG would show earlier postoperative recovery when anesthetic drugs are titrated to the target organ ‘brain’. A well-validated cerebral monitor such as BIS did not demonstrate objective findings of early extubation, faster recovery or decreased use of hypnotics, analgesics and sedatives.

We speculate that advantages in BIS monitoring were minimized by the complex nature and duration of cardiac surgery, hypothermia, CPB, inability to initiate ventilator weaning in immediate postoperative period unlike surgery in ambulatory setting. The benefits of BIS monitoring in non-cardiac patient population may not be extrapolated to patients undergoing cardiac surgery. Anesthesia providers are now increasingly aware and conduct the anesthetic with a view to fast track cardiac surgery patients thereby minimizing any advantages accrued from anesthetic depth titration with the use of BIS monitor.

APPENDIX 1

Sedation Agitation Score

- +2 : Dangerously agitated, does not follow commands
- +1 : Agitated, but follows commands
- 0 : Calm and follows commands
- -1 : Deep sedation
- -2 : Oversedated

References

13. Ahmad S, Yilmaz M, Marcus R-J, Glisson S, Kinsella A:
Impact of Bispectral Index monitoring on fast tracking of gynecologic patients undergoing laparoscopic surgery. Anesthesiology 2003; 98:849–52
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