This guide will help you review the clinical evidence that supports the utility of the BIS™ complete monitoring system during surgery to:

- Optimize anesthesia
- Reduce the risk of postoperative delirium
- Reduce the risk of awareness
- Improve emergence and recovery
Anesthesia guided by BIS™ technology improves anesthetic delivery and postoperative recovery from deep anesthesia while reducing anesthetic consumption.

Bispectral index for improving anaesthetic delivery and postoperative recovery.

Punjasawadwong Y, Phongchiewboon A, Bunchungmongkol N.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Cochrane review and meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arms</td>
<td>Randomized or quasi-randomized controlled trials comparing the use of BIS™ monitoring technology to standard care (clinical signs or end-tidal anesthetic gas [ETAG] monitoring)</td>
</tr>
<tr>
<td>Objective</td>
<td>To assess whether BIS™-guided anesthesia can reduce the risk of intraoperative recall awareness, consumption of anesthetic agents, recovery times, and total cost of anesthesia</td>
</tr>
<tr>
<td>N</td>
<td>7,761 across 36 controlled trials</td>
</tr>
<tr>
<td>Population</td>
<td>Surgical patients undergoing general anesthesia</td>
</tr>
<tr>
<td>BIS™ target range</td>
<td>Variable by trial</td>
</tr>
</tbody>
</table>
| Results              | • BIS™ monitoring-guided anesthesia significantly reduced the requirement for anesthetic drugs by as much as 58.9%.
  – Propofol by 1.32 mg/kg/hr (n=672)
  – Volatile anesthetics (desflurane, sevoflurane, isoflurane) by 0.65 minimal alveolar concentration equivalents (n=985)
• Monitoring with BIS™ technology reduced recovery times. Time:
  – To eye opening reduced by 1.93 mins (n=2557)
  – For response to verbal command reduced by 2.73 mins (n=777)
  – To extubation reduced by 2.62 mins (n= 1501)
  – To orientation reduced by 3.06 mins (n=373)
• PACU stay was significantly reduced by 6.75 mins (n=1953).
• BIS™ monitoring technology did not significantly change discharge time.
• In studies using clinical signs as control, BIS™ monitoring guided anesthesia significantly reduced the risk of intraoperative recall awareness among surgical patients with high risk of awareness, with an OR of 0.24 (n=7761). This effect was not demonstrated in studies where BIS™ monitoring technology was compared to ETAG monitoring as standard practice. |
| Conclusions          | Anesthesia guided by BIS™ technology has been shown to improve anesthetic delivery and postoperative recovery from deep anesthesia, significantly reducing consumption of anesthetics and reducing the incidence of intraoperative recall awareness in patients compared to monitoring depth of anesthesia using clinical signs. |
Bispectral index (BIS) monitoring technology associated with improved postoperative recovery outcomes compared to non-BIS monitoring methods.

**Bispectral Index and non-Bispectral Index anesthetic protocols on postoperative recovery outcomes.**


<table>
<thead>
<tr>
<th>Study design</th>
<th>Systematic review of randomized control trials and two-arm prospective studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arms</strong></td>
<td>Bispectral index (BIS™) guided anesthesia monitoring</td>
</tr>
<tr>
<td></td>
<td>Non-BIS™ guided anesthesia monitoring</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>Compare BIS™- to non BIS™-guided anesthesia monitoring protocols on postoperative recovery outcomes.</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>9,537 patients in 26 RCTs</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Adult subjects undergoing surgery</td>
</tr>
<tr>
<td><strong>BIS™ target range</strong></td>
<td>Variable by trial</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>• Duration of anesthesia ranged from 47 minutes (min) to 3.2 hours</td>
</tr>
<tr>
<td></td>
<td>• BIS™-monitoring technology was associated with significantly shorter</td>
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<tr>
<td></td>
<td>– time to eye opening (-1.32 min [95% CI -2.14 to -0.51 min], p=0.001) in analysis of 14 studies</td>
</tr>
<tr>
<td></td>
<td>– time to extubation (-2.56 min, 95% CI -3.71 to -1.41 min, p&lt;0.001) in analysis of 16 studies</td>
</tr>
<tr>
<td></td>
<td>– time to orientation (-5.36, 95% CI -8.81 to -1.90 min, p=0.002) in analysis of 6 studies</td>
</tr>
<tr>
<td></td>
<td>• No significant differences between groups in hypoxemia, postoperative nausea and vomiting, time to oral fluid intake, and length of stay in post-anesthesia care unit</td>
</tr>
<tr>
<td><strong>Conclusions</strong></td>
<td>BIS™-monitoring technology reduces time to eye opening, extubation, and orientation compared to non-BIS™ monitoring technology methods.</td>
</tr>
</tbody>
</table>
### Study design

Systematic review of 42 randomized controlled trials

### Arms

Randomized controlled trials utilizing the BIS™ monitor, E-Entropy™ monitor (GE Healthcare), and Narcotrend™ Compact M monitor (MT MonitorTechnik)

### Objective

To determine the clinical and cost-effectiveness of EEG monitors compared with standard clinical monitoring, in patients receiving general anesthesia

### N

Systematic review encompassing 31 previously reviewed randomized controlled trials of monitoring with BIS™ technology, with an additional 11 published randomized controlled trials

### Population

Patients receiving general anesthesia, including pediatric patients

### BIS™ target range

Variable by trial

### Results

Statistically significant outcomes in the BIS™ monitoring group compared to clinical monitoring:

- Mean difference in total intravenous anesthesia (TIVA) consumption was slightly reduced
  - The mean difference (in MAC equivalents) in inhaled anesthetic consumption was reduced −0.15
  - The mean difference in intravenous anesthetic consumption was −1.33 mg/kg/h
- Time to extubation was reduced by 0.5 mins to 5 mins in five trials with BIS™ monitoring technology
- Time to discharge from recovery room was reduced by 6.7 mins to 30 mins in all NICE trials, including four conducted in children
- Mean difference in the Cochrane Review article was −7.63 mins in favor of BIS™ monitoring technology
- The high-risk-of-awareness group had a lower incidence of confirmed awareness in the group with BIS™ monitoring technology and TIVA
- For patients at high risk of adverse outcomes from TIVA, the cost-effectiveness ratio for BIS™ monitoring technology exceeded that of the competitors and grew increasingly more cost-effective as patient risk factors were added to the assessment model.

### Conclusions

- EEG-based depth of anesthesia monitors help provide the appropriate level of anesthesia to patients, helping to avoid inadequate or excessively deep levels of anesthesia.
- NICE recommends EEG-based depth of anesthesia monitors, including the BIS™ monitor, as an option for all patients receiving TIVA.
- NICE recommends monitoring because it’s cost-effective and measuring ETACs in TIVA patients isn’t possible.
- Anesthetists using EEG-based depth of anesthesia monitors should have appropriate training and experience with these monitors, and understand the potential limitations of their use in clinical practice.
Using BIS™ monitoring technology to provide light sedation can help reduce the relative risk of postoperative delirium by more than 50%.

**Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair.**


<table>
<thead>
<tr>
<th>Study design</th>
<th>Single-center randomized controlled trial (US)</th>
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</table>
| **Arms**     | Deep sedation: BIS™ monitoring-guided anesthesia titrated to a BIS™ value of approximately 50  
               Light sedation: BIS™ monitoring-guided anesthesia titrated to a BIS™ value of ≥ 80 |
| **Objective**| Compare the risk of postoperative delirium between patients receiving deep and light sedation |
| **N**        | 114                                           |
| **Population**| Elderly patients (≥ 65 years) undergoing hip fracture repair with spinal anesthesia |
| **BIS™ target range** | Deep sedation: BIS™ index value of 50  
                              Light sedation: BIS™ index value of ≥ 80 |
| **Results**  | • Light sedation was associated with:  
                             – Lower incidence of delirium (19% vs. 40%; p=0.02)  
                             – Shorter duration of delirium (0.5 days vs. 1.4 days; p=0.01)  
                             – Lower propofol dose (2.5 mg/kg vs. 10.2 mg/kg; p<0.001)  
                             – Greater use (19% vs. 5%; P=0.04) and dose (5.53 mg/kg vs. 1.26 mg/kg; p=0.02) of midazolam  
                             • Deep sedation was identified as a predictor of delirium  
                              – For every 4.7 patients receiving light sedation, 1 case of delirium is avoided |
| **Conclusions** | Using BIS™ monitoring technology to deliver light propofol sedation was associated with a 50% decrease in postoperative delirium compared to deep sedation. Light sedation may be a safe and cost-effective method for preventing postoperative delirium in elderly patients. |
Combination of light general anesthesia and peripheral nerve block is associated with lower incidence of postoperative delirium

Peripheral nerve block as a supplement to light or deep general anesthesia in elderly patients receiving total hip arthroplasty: a prospective randomized study.


<table>
<thead>
<tr>
<th>Study design</th>
<th>Single-center randomized controlled trial (China)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arms</td>
<td>General anesthesia (GA) alone</td>
</tr>
<tr>
<td></td>
<td>GA (light sedation) plus lumbosacral plexus block</td>
</tr>
<tr>
<td></td>
<td>GA (deep sedation) plus lumbosacral plexus block</td>
</tr>
<tr>
<td>Objective</td>
<td>Evaluate combination of general anesthesia and peripheral nerve blockage in elderly patients undergoing hip arthroplasty.</td>
</tr>
<tr>
<td>N</td>
<td>203</td>
</tr>
<tr>
<td>Population</td>
<td>Patients aged ≥ 65 years undergoing total hip arthroplasty</td>
</tr>
<tr>
<td>BIS™ target range</td>
<td>Deep sedation: BIS™ index value 40 – 60</td>
</tr>
<tr>
<td></td>
<td>Light sedation: BIS™ index value 60 – 80</td>
</tr>
<tr>
<td>Results</td>
<td>• The following comparisons in the incidence of postoperative delirium were made:</td>
</tr>
<tr>
<td></td>
<td>– deep GA plus lumbosacral plexus vs. GA alone (38% vs 40%, P&gt;0.99)</td>
</tr>
<tr>
<td></td>
<td>– light GA plus lumbosacral plexus vs. GA alone (17% vs. 40%, P=0.007)</td>
</tr>
<tr>
<td></td>
<td>– light GA plus lumbosacral plexus vs. deep GA plus lumbosacral plexus (17% vs. 38%, P=0.007)</td>
</tr>
<tr>
<td></td>
<td>• There was no difference in complications between groups ≤ 30 days post-surgery.</td>
</tr>
<tr>
<td>Conclusions</td>
<td>In elderly patients undergoing total hip arthroplasty, the combination of light general anesthesia and lumbosacral plexus block was associated with significant reduction in incidence of postoperative delirium compared to nerve block with deep sedation, and general anesthesia alone.</td>
</tr>
</tbody>
</table>
**BIS™-guided anesthetic delivery is associated with 42% lower odds of postoperative delirium**

**BIS™-guided anesthesia decreases postoperative delirium and cognitive decline.**
Chan MT, Cheng BC, Lee TM, Gin T; CODA Trial Group.

| Study design | Multicenter randomized controlled trial (China)  
*Cognitive Dysfunction After Anesthesia (CODA)* Trial |
|----------------|---------------------------------------------------|
| **Arms** | Control: Blinded monitoring; routine care to manage anesthetic delivery  
Intervention: BIS™ monitoring-guided anesthesia titrated to a BIS™ value of 40 – 60 |
| **Objective** | Determine the association between BIS™ monitoring-guided anesthesia and the risk of postoperative cognitive dysfunction (POCD) and delirium |
| **N** | 921 |
| **Population** | Elderly patients (≥ 60 years) undergoing elective major surgery ≥ 2 hours and expected to stay in the hospital ≥ 4 days |
| **BIS™ target range** | BIS™ monitoring-guided anesthesia (n=462) utilized titration of anesthetics to achieve a BIS™ monitoring value of 40 to 60 |
| **Results** |  
- 20% of patients developed postoperative delirium  
- BIS™ monitoring-guided anesthesia was associated with  
  - less propofol and volatile anesthetic gas use  
  - higher mean BIS™ values (53.2 vs 38.6; *p*<0.001)  
  - shorter duration with a BIS™ value < 40 (7.2 mins vs 22.8 mins; *p*<0.001)  
- Fewer patients experienced postoperative cognitive issues in the BIS™ monitoring group  
  - 38% lower odds of developing POCD at 3 months (*p*=0.02)  
  - 35% relative reduction in the risk of postoperative delirium (15.6 vs 24.1%; *p*=0.01)  
  - 42% lower odds of developing postoperative delirium (*p*=0.01)  
- In 1000 elderly patients undergoing major surgery, use of BIS™ monitoring-guided anesthesia is expected to prevent 23 cases of POCD and 83 patients of postoperative delirium |
| **Conclusions** | Use of BIS™ monitoring-guided anesthesia reduced the time spent with BIS™ values < 40, subsequently reducing the risk of postoperative cognitive issues |
Use of BIS™ monitoring technology is associated with a reduced incidence of deep anesthesia and 22% lower relative risk of postoperative delirium

Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction.
Radtke FM, Franck M, Lendner J, Krüger S, Wernecke KD, Spies CD.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Single-center randomized controlled trial (Germany)</th>
</tr>
</thead>
</table>
| Arms               | Control: Blinded monitoring; routine care to manage anesthetic delivery  
 | Intervention: BIS™ monitoring-guided anesthesia |
| Objective          | Determine the association between BIS™ monitoring-guided anesthesia and the risk of postoperative delirium |
| N                  | 1,155 |
| Population         | Elderly patients (≥ 60 years) undergoing elective major surgery ≥ 1 hour |
| BIS™ target range  | BIS™ monitoring-guided anesthesia (n=575): Titration of anesthetics to achieve a BIS™ monitoring value of 40 to 60 |
| Results            | • BIS™ monitoring-guided anesthesia was associated with:  
 | | - Lower incidence of delirium (16.7% vs. 21.4%; p=0.036)  
 | | - Trend toward lower incidence of POCD at 7 days (18.1% vs. 23.9%; p=0.062)  
 | | - Lower average number of BIS™ monitoring values < 20 (3.7 vs. 5.6; p=0.04)  
 | | • Delirium was associated with increased mortality after 3 months (OR=2.05; p=0.015)  
 | | • Percentage of episodes of BIS™ monitoring value < 20 was an independent predictor of delirium (OR=1.027; p=0.006)  
 | | • Mean average BIS™ monitoring values in both groups did not differ, and were below the prespecified target range of 40 to 60 |
| Conclusions        | BIS™ monitoring technology was associated with a reduced incidence of low BIS™ values and a reduced risk of postoperative delirium |
Processed EEG monitoring-guided anesthesia is associated with a 29% reduction in the risk of postoperative delirium and cognitive dysfunction.

Processed electroencephalogram and evoked potential techniques for amelioration of postoperative delirium and cognitive dysfunction following non-cardiac and non-neurosurgical procedures in adults.


<table>
<thead>
<tr>
<th>Study design</th>
<th>Systematic review and meta-analysis of randomized controlled trials studying the effect of depth of anesthesia monitoring on postoperative delirium and postoperative cognitive dysfunction (POCD)</th>
</tr>
</thead>
</table>
| Arms         | Control: routine care to manage anesthetic delivery  
Intervention: monitoring-guided anesthesia (all studies included in the meta-analysis were performed with the BIS™ monitor) |
| Objective    | Evaluate the effectiveness of guiding anesthesia with depth of anesthesia monitoring (processed EEG or auditory evoked potentials) to reduce the risk of postoperative delirium and POCD |
| N            | 3 studies reporting postoperative delirium: 2,197 patients  
3 studies reporting POCD: 2,270 patients |
| Population   | Adult non-cardiac and non-neurosurgical patients undergoing general anesthesia (patients in the included studies were all > 60 years of age) |
| BIS™ target range | Variable by trial |
| Results      |  • BIS™-monitoring guided anesthesia was associated with:  
  – A 29% reduction in the risk of postoperative delirium (RR 0.71; 95% CI 0.59 to 0.85)  
  – A 29% reduction in the risk of POCD at 12 weeks post-surgery (RR 0.71; 95% CI 0.53 to 0.96)  
  • The authors did not find a significant reduction in POCD at 1 week post-surgery  
  • The number needed to treat (NNT) to prevent one case of the outcomes of interest were as follows:  
  – Postoperative delirium NNT = 17  
  – POCD NNT = 38  
  • The evidence quality was rated as moderate due to lack of blinding of the anesthesia providers and some incomplete outcome data |
| Conclusions  | In non-cardiac and non-neurological surgery in patients > 60 years of age, processed EEG monitoring was associated with a reduced risk of postoperative delirium and POCD. |
Multi-component interventions and monitoring the depth of anesthesia using BIS™ technology was effective in reducing incident delirium

**Interventions for preventing delirium in hospitalised non-ICU patients.**

<table>
<thead>
<tr>
<th>Study design</th>
<th>Systematic review of 39 RCTs of single and multi-component interventions on the incidence of delirium in non-ICU patients.</th>
</tr>
</thead>
</table>
| Arms         | Control: Usual care or placebo interventions  
Interventions: Multicomponent interventions, pharmacological, OR anesthetic interventions |
| Objective    | Evaluate the effectiveness of non-pharmacological and pharmacological interventions for preventing delirium in hospitalized non-ICU patients. |
| N            | Total of 16,082 patients in 39 randomized controlled trials |
| Population   | Patients aged >16 years admitted to acute general hospitals and at risk of developing delirium |
| BIS™ target range | Variable by trial |
| Results      | • In terms of incidences of delirium,  
  – multi-component interventions reduced the incidences of delirium in comparison to usual care (p=0.02)  
  – administration of cholinesterase inhibitors (p=0.57), antipsychotic treatments (p=0.81), melatonin (p=0.25), and other pharmacological (citicoline and methylprednisolone) showed no significant reduction in delirium incident  
• Selecting one anesthetic agent over another showed no clear evidence in preventing delirium  
• BIS™ monitoring-guided anesthesia significantly reduced the occurrence of delirium (p=0.0002) |
| Conclusions  | Multi-component interventions and using BIS™ technology to monitor and control anesthesia can reduce the incidence of postoperative delirium. |
Low BIS™ is associated with mortality in observational studies with ≥ 1 year follow-up periods

Relation between bispectral index measurements of anesthetic depth and postoperative mortality: a meta-analysis of observational studies
Zorrilla-Vaca A, Healy RJ, Wu CL, Grant MC.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Meta-analysis of 8 observational studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arms</td>
<td>Observational studies that examine the association between depth of anesthesia and mortality</td>
</tr>
<tr>
<td>Objective</td>
<td>To quantitatively evaluate the relationship between depth of anesthesia and mortality</td>
</tr>
<tr>
<td>N</td>
<td>40,317 patients across 8 observational studies</td>
</tr>
<tr>
<td>Population</td>
<td>Patients undergoing anesthesia and monitored by BIS™ technology</td>
</tr>
<tr>
<td>BIS™ target range</td>
<td>Low BIS™ value &lt;45</td>
</tr>
<tr>
<td>Results</td>
<td>Three studies utilized a 30-day follow-up period and five studies utilized a ≥ 1-year follow-up period</td>
</tr>
<tr>
<td></td>
<td>Anesthesia depth with a low BIS™ value (&lt;40-45) is associated with mortality (N=40,317, 95% CI, 1.07-1.38, p=0.003)</td>
</tr>
<tr>
<td></td>
<td>The significance of the association between low depth of anesthesia (low BIS™ value) and mortality varied by follow-up time</td>
</tr>
<tr>
<td></td>
<td>– Follow-up ≥ 1 year was significant (n=23,347; 95% CI, 1.00-1.21, p=0.04)</td>
</tr>
<tr>
<td></td>
<td>– Follow-up at 30 days was not significant (n=16,970; 95% CI, 0.81-2.36, p=0.24)</td>
</tr>
<tr>
<td>Conclusions</td>
<td>There is a significant association between depth of anesthesia measured by BIS™ monitoring technology and mortality.</td>
</tr>
<tr>
<td></td>
<td>Although the association between low BIS™ values and mortality was significant only with the ≥ 1 year follow-up, the same trend was observed in trials with a 30-day follow-up period.</td>
</tr>
<tr>
<td></td>
<td>This association is consistent with previous systematic reviews, but provides quantitative evidence supporting a relationship between deep anesthesia and mortality.</td>
</tr>
</tbody>
</table>
Cost-effectiveness of bispectral index monitoring.
Klopman MA, Sebel PS.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Meta-analysis of 30 randomized trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arms</td>
<td>30 randomized trials analyzing the cost effectiveness of BIS™ monitoring technology</td>
</tr>
<tr>
<td>Objective</td>
<td>To draw a conclusion regarding the cost-effectiveness of using BIS™ monitoring technology with general anesthesia</td>
</tr>
<tr>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>Patients undergoing general anesthesia</td>
</tr>
<tr>
<td>BIS™ target range</td>
<td>Variable by trial</td>
</tr>
</tbody>
</table>

**Results**

- BIS™ monitoring technology has been shown in multiple prospective randomized studies to positively affect several important aspects of an anesthetic, including less use of hypnotic anesthetic drugs, decreased time to extubation, earlier orientation, decreased times to PACU discharge, and decreased intraoperative awareness.
- The benefits associated with use of the BIS™ monitoring technology are achieved for an additional cost of approximately $5 per anesthetic.
- BIS™ monitoring technology has been shown in randomized controlled trials to make a difference in many anesthetic outcomes and should be used routinely irrespective of cost.

**Conclusions**

- Two modeling studies previously estimated the cost-effectiveness of the BIS™ monitoring technology for preventing intraoperative awareness. Taking into account various assumptions, the cost of preventing a single case of awareness ranged $4,410–11,111.
- In a clinical study, the cost of preventing a single case of awareness in high-risk patients was determined to be $2,200.
- Taking into account the decreased use of anesthetic and decrease in PACU stays, one study found that BIS™ monitoring technology use resulted in a net cost of only $5.55 per use.
- A diagnostic guidance assessment review by NICE determined that BIS™ monitoring technology is cost effective during TIVA anesthetics because it provides an alternative to ETAC monitoring.

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