Extubation Time after Target-Controlled Infusion of Propofol Guided by Clinical Signs only versus Bispectral Index and Clinical Signs in Patients Undergoing Spine Surgery: A Randomized Open Labeled Study

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Objective: *To compare using bispectral index (BIS)-guided with clinical signs-guided for TCI propofol on extubation time.*
Material and Method: *All patients received total intravenous anesthesia that included TCI of propofol (3-7 mcg/dL; Schnider model) and continuous intravenous fentanyl infusion. The patients were randomly divided into two groups, Non-BIS group and BIS group. The dose of propofol was adjusted according to clinical signs in the non-BIS group, while BIS (target 40 to 60) was used in the BIS group. The assessed outcomes were extubation time and total propofol dose.*
Results: *Thirty-four patients were analyzed; 17 patients in each group with mean ages were 48.0±12.1 (non-BIS) vs. 50.1±11.6 (BIS) years, (p = 0.61). There were no significant differences between groups in patient demographics, and the most common diagnosis was spinal cord tumor. The two groups did not significantly differ in extubation time [16.6±8.9 (non-BIS) vs.16.3±9.7 (BIS) minutes, p = 0.91] or total propofol consumption [2,340±839 (non BIS) vs. 2,146±742 (BIS) mg, p = 0.48]. There were no significant differences between groups in other intraoperative parameters such as fentanyl dose, major movement, blood loss, and operative time.*
Conclusion: *In spine surgery, BIS monitor added up to clinical signs monitoring has little value and it has no significant effects to patients' extubation time.*

Keywords: *Propofol, Target controlled infusion (TCI), Bispectral index (BIS), Extubation time*

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Total intravenous anesthesia (TIVA) is often used during spine surgery with the use of electrophysiological monitoring. This is frequently accomplished using infusions of propofol and an opioid (e.g. fentanyl). Propofol has short duration, can be rapidly cleared from the body, and minimally interferes with neurophysiologic monitoring[1,2].

Effect-site (Cet) target controlled infusion (TCI) gains much popularity nowadays[3-5]. It administers intravenous drug continuously to the desirable effect or target. TCI uses patients' data to calculate and infuse drug to the desired target[6]. The needed data for TCI propofol (Schnider model) include body weight, height, age and sex. However, TCI propofol can cause overdose or suboptimal dose that leads to unsatisfied outcomes such as delayed awakening or patient movement during the procedure. Anesthetic depth can be adjusted during surgical procedures with clinical signs and/or Bispectral index (BIS). BIS is widely used to monitor depth of anesthesia and to titrate the dose of propofol and may decrease anesthetic related complications[7-10].

The aim of this study was to compare the extubation time between patients receiving general anesthesia with BIS-guided and clinical signs-guided (non-BIS).

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Material and Method

This randomized controlled study was approved by the Institutional Review Board (Si 168/2014) approval and written informed consent was obtained, 40 patients were randomized into 2 groups. Randomization was performed in blocks of 4 by computer-generated numbers. The random sequence were placed inside concealed envelopes, which were

opened before anesthetic induction.

Inclusion criteria were patients aged 18 to 80 years old, ASA physical status I-III, scheduled for elective spinal surgery under general anesthesia, cooperative, no sedatives or any pain killer within 24 hours prior to surgery. Exclusion criteria included patients with unstable hemodynamic, allergic to propofol, received other medications which might affect to electroencephalography (EEG) such as antiepileptic drugs, liver diseases, BMI more than 30 kg/m^2, and who had complete cord injury.

Before induction, the patient was given acetate Ringer solution 7 mL/kg and standard monitoring were applied to all patients. In Non-BIS group, the patients received fentanyl 1 mcg/kg and then fentanyl infusion 1 mcg/kg/hr and TCI propofol target 3 to 7 mcg/mL (Schnider model, Fresenius KabiInjectomat TIVA Agilia®) until asleep then atracurium 0.5 mg/kg was given to facilitate endotracheal intubation. The patients were ventilated with fresh gas flow 2 L/min (air: oxygen = 1:1). In non-BIS group, the TCI propofol levels were adjusted according to clinical signs (blood pressure, heart rate, and movement). Movement during the operation was defined as major movement if the operation needed temporarily stopped or minor movement if it did not disturb the operation. If there was major or minor movement or increase heart rate and blood pressure, fentanyl 0.5 mcg/kg was given and the TCI propofol level would be increased incrementally 0.5 to 1.0 mcg/mL (maximum 7.0 mcg/mL). If hypertension persisted or last after 10 minutes of above treatments, the nicardipine or diltiazem was given. If hypotension occurred, it was treated simultaneously by fluid loading, vasopressors and decreasing TCI propofol level but kept the TCI level $\geq$3.0 mcg/mL (Fig. 1).

In BIS group, the same induction, intubation and ventilation were applied but the TCI propofol level

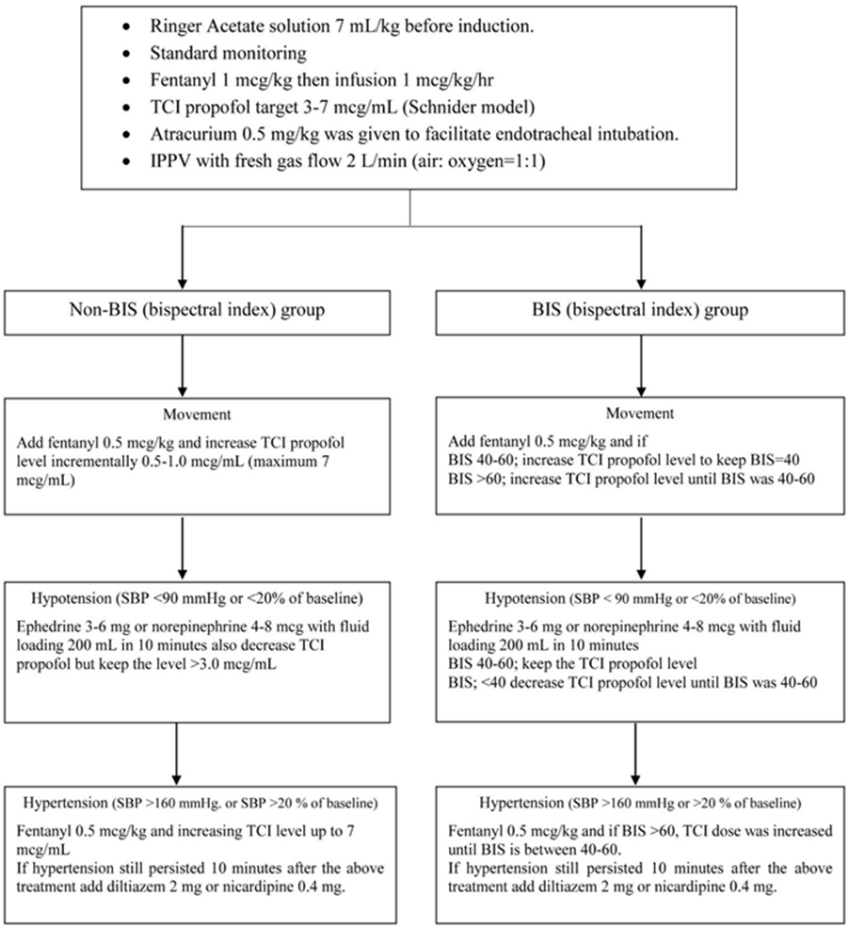

Fig. 1 The study protocol .

was adjusted in order to keep BIS between 40-60 using (BIS™, Covidien). Movement, hypotension or hypertension were treated according to the protocol (Fig. 1).

At starting wound closure, the fentanyl infusion was stopped. In Non-BIS group the propofol TCI levels were lower to 1 to 3 mcg/mL and stopped at the end of the operation. In BIS group, the propofol TCI levels were adjusted to keep BIS around 60 and also stopped at the end of the operation. Then the patient was turned to supine, BIS sensor and monitor was removed. Then the other anesthesiologist, who was blinded to the patient's group, would take care the patient during emergence and extubation.

Times from discontinue TCI propofol to extubation (extubation time), resume adequate spontaneous ventilation, eye opening to command, purposeful responses to verbal command, and recall name and age were recorded. In addition, data were collected on demographics, intraoperative complications, hemodynamic parameters, estimated blood loss, total fentanyl dose and total propofol dose.

Statistical analysis

The sample size was calculated based on our pilot study (5 patients for each group). The mean $\pm$ SD of extubation time in Non-BIS and BIS groups were 20$\pm$10 minutes and 10$\pm$10 minutes, respectively. When type I error = 0.05, 2-sided and type II error = 0.2, 17 patients were needed for each group. We included 20 patients in each group for unexpected protocol violation.

The qualitative data were presented as number and percentage. The parametric quantitative data were presented as mean and standard deviation. Comparison between groups was analyzed by using Chi-square test or Fisher exact test for qualitative data and unpaired t-test for parametric quantitative data. All statistical analysis was performed using PASW Statistics for Windows, 18.0. Chicago: SPSS Inc. The $p<0.05$ was considered statistically significant.

Results

During a 24-month period, 49 patients were potentially eligible for the study, but 9 patients were excluded because of BMI >30 kg/m^2 (4), age 80 or more years old (3), history of liver diseases (1), and received antiepileptic drug (1). Only 40 patients met the inclusion criteria (Fig. 2). Three patients in each group discontinued from the study because they had multiple

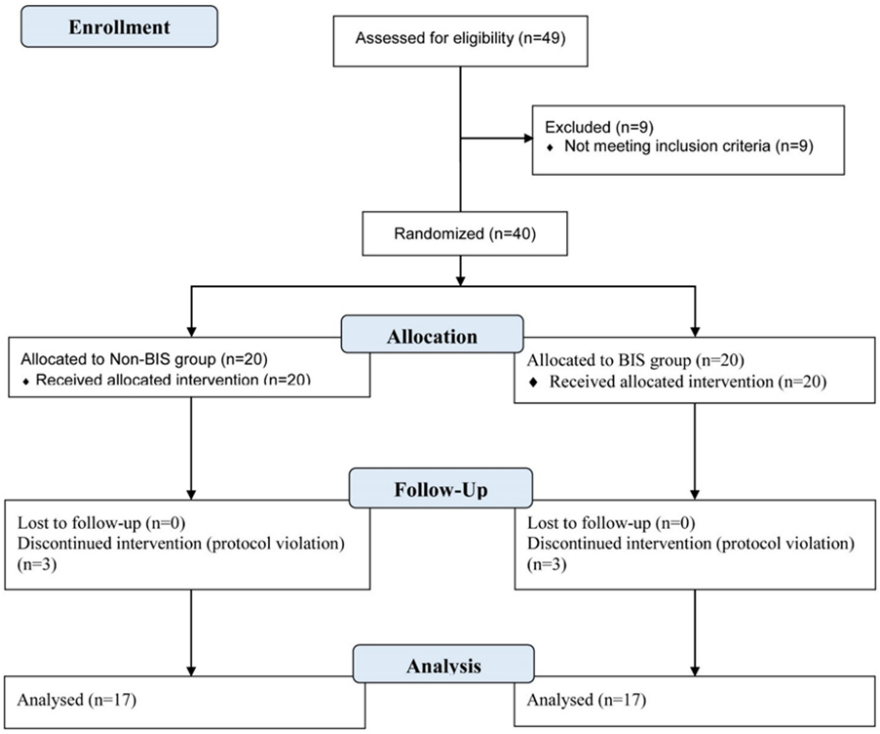

Fig. 2 Consort flow.

major movements and caused the operation to be temporarily stopped and the anesthesiologists in charge had to manage these patients with extra drugs which were not allowed according to the study protocol and finally 34 patients were analyzed. There were no differences in demographic data. The mean ages were 48.0±12.1 (non BIS) vs. 50.1±11.6 (BIS) years (p = 0.61). The body weight were 60.4±8.1 (non BIS) vs. 62.8±11.8 (BIS) kg (p = 0.58). The most common diagnosis is spinal cord tumor. The underlying diseases (diabetes mellitus, hypertension) were not different (Table 1).

There were no differences in major and minor movement, total fentanyl used, estimated blood loss, urine output, fluid administered, duration of anesthesia and operative time (Table 2). The hemodynamic parameters were well controlled in both groups. No abnormal SSEP and MEP signals occurred during this study.

The extubation time did not differ between two groups [16.6±8.9 (non BIS) vs.16.3±9.7 (BIS) minutes, p = 0.91]. As shown in Table 4, time from the end of the TCI propofol infusion to adequate breathing,

Table 1. Patient characteristics

	Non-BIS (n = 17)	BIS (n = 17)	*p*-value
Age (yr)	48.0±12.1	50.1±11.6	0.61
Gender: male	7 (41.2)	6 (35.3)	0.72
Weight (kg)	60.4±8.1	62.8±11.8	0.58
Height (cm)	159.5±7.4	160.8±9.4	0.66
ASA physical status I: II	6 (35.3): 11 (64.7)	4 (23.5): 13 (76.4)	0.71
Underlying diseases			
DM	3 (17.6)	0 (0)	0.23
HT	5 (29.4)	6 (35.3)	0.71
DLD	3 (17.6)	3 (17.6)	1.00
Others	4 (23.5)	4 (23.5)	1.00
Diagnosis			
Spinal cord tumor	9 (52.4)	6 (32.3)	
Spinal stenosis	2 (11.6)	5 (29.4)	
Spondylolisthesis	3 (17.6)	1 (5.8)	
Herniated nucleus pulposus	2 (11.6)	3 (17.6)	
Others	1 (5.8)	2 (11.6)	

Data presented as mean ± SD or n (%)
ASA = The American Society of Anesthesiologists Physical Status classification

Table 2. Intraoperative data

	Non-BIS (n = 17)	BIS (n = 17)	*p*-value
Number of major movement			0.53
1	4 (23.5)	2 (11.8)	
2	3 (17.6)	5 (29.4)	
≥3	1 (5.8)	1 (5.8)	
Total fentanyl (mcg)	304±138	295±116	0.84
Blood loss (mL)	380±342	312±254	0.52
Crystalloid (mL)	1,726±874	1,738±903	0.97
Urine output (mL)	512±341	502±447	0.94
Anesthetic time (min)	272±80	283±104	0.73
Operative time (min)	201±67	207±92	0.83

Data presented as mean ± SD or n (%)
Major movement = movement that caused the operation to be temporarily stopped until the propofol TCI dose was increased and fentanyl was given

Table 3. TCI propofol levels (mcg/mL) and total consumption

	Non-BIS (n = 17)	BIS (n = 17)	BIS level	*p*-value	Mean differences	95% CI of differences
Average	4.6±0.8	3.83±0.8	39.3±4.9	0.02	0.75	0.20, 1.30
1st hr	4.6±0.5 (n = 17)	4.4±0.6 (n = 17)	39.7±10.3	0.48	0.13	-0.24, 0.51
2nd hr	4.9±1.0 (n = 17)	4.2±0.9 (n = 17)	36.4±5.94	0.04	0.70	0.04, 1.35
3rd hr	5.1±1.0 (n = 16)	4.03±1.08 (n = 16)	35.5±8.3	<0.01	1.03	0.27, 1.78
4th hr	5.0±1.1 (n = 12)	3.30±1.03 (n = 12)	40.1±10.9	<0.01	1.65	0.76, 2.55
5th hr	3.4±2.0 (n = 9)	3.01±1.0 (n = 9)	41.6±9.6	0.62	.34	-1.20, 1.94
6th hr	2.4±1.2 (n = 2)	2.3±1.6 (n = 7)	56.6±15.6	0.97	.04	-2.82, 2.90
Total (mg)	2,340±839	2,146±742		0.48	193.6	36.2, 747.5

Data presented as mean ± SD

Table 4. Awakening times (mins)

Emergence time	Non-BIS (n = 17)	BIS (n = 17)	*p*-value	Mean differences	95% CI of differences
Adequate breathing	9.8±5.5	10.9±8.1	0.64	-1.1	-5.9, 3.7
Eye opening	15.9±13.0	12.4±7.5	0.34	3.6	-3.9, 10.9
Responses to command	16.0±13.4	12.7±9.0	0.41	3.2	-4.7, 11.2
Extubation	16.6±8.9	16.3±9.7	0.91	0.3	-6.2, 6.9
Recall name and age	22.7±14.2	21.5±10.8	0.79	1.1	-7.6, 10.0

Data present as mean ± SD

eyes opening, responses to command, and recall names and ages were not different in both groups. Target concentration of propofol after first hour of operation and overall average concentration were slightly lower in BIS group (Table 3). However, the total propofol usages were not significantly different between the two groups [2,340±839 (non BIS) vs. 2,146±742 (BIS) mg, $p = 0.48$]. Average bispectral index was 39±4.9 (min = 33, max = 50) (Table 3). No postoperative neurological complications were found in both groups.

Discussion

Delayed awakening is an occasional problem occurring after prolonged intravenous anesthesia with propofol which leads to longer time in operating room or PACU and increases postoperative pulmonary complications[11,12]. So techniques and optimal propofol dose adjustment are crucial.

Bispectral index (BIS) is widely used to monitor depth of anesthesia. BIS satisfactorily correlates with cerebral cortex-acting drugs, such as propofol, midazolam, and sevoflurane. It can reliably evaluate the anesthetic depth and predict the changes in consciousness during and after an operation[9,10]. However, in Thailand, middle income country, the relatively high cost (1,800 baht or 50 US dollar for the sensor and the equipment) of BIS limits its usage.

From our study, TCI propofol levels after first hour and average propofol levels were slightly lower in BIS group compared with non-BIS group. However, the total propofol doses were comparable (2,340±839 vs. 2,146±742 mg, $p = 0.48$) so the awakening times by all definitions were not different. The average anesthetic time was more than four hours in both groups (272±80 vs. 283±104 minutes, $p = 0.73$) which led to considerably prolonged extubation time in both groups (16.6± 8.9 vs. 16.3±9.7 minutes, $p = 0.91$).

Guo et al. studied BIS for monitoring anesthetic depth in patients with severe burns underwent wound debridement receiving target-controlled infusion of remifentanil and propofol and they found that in BIS group the eye opening time was considerably shorter (7.9±0.6 vs. 8.4±0.7 minutes, $p<0.01$) but half a minute shorter is not clinically significant[13].

Arya et al studied propofol dose for induction of anesthesia guiding by BIS or clinical signs. Both techniques had no differences in propofol doses, they

concluded that clinical signs can be used, without BIS, to guide drug dosage and adjust appropriate depth of anesthesia during induction[14]. However, the study studied only induction period which is different from our study that used BIS and non-BIS for entire operation.

Karwacki et al studied the effect of BIS on anaesthetic requirements in TCI propofol for lumbar microdiscectomy and concluded that BIS decreased propofol and fentanyl dose and one minute faster in recevery time[7]. In this study, the operation was minor and operative time was shorter compared with our study which led to the different results.

In our study, our BIS target was 40 to 60 which was associated with some major movements (41%) and the anesthesiologists in charge kept BIS around 40 (average was 39±4.9) or sometimes lower according to patients' movement. So in BIS group, they used both BIS and clinical signs for propofol dose adjustment. With or without BIS, the anesthesiologists in charge avoided to decrease propofol dose until nearly the end of the operation for fear of inadvertent movement since there was no neuromuscular blocking agent used during anesthetic maintenance. Some anesthesiologists added some extra drugs or doses violation from our protocol, in that cases, these patients were excluded. The average BIS level was slightly lower from study's intention. Li et al studied BIS level in non-paralyzed patient under anesthesia and concluded that BIS level of 30 to 40 is appropriate and can prevent muscle movement during anesthesia[15].

From Cochrane database of systematic reviews, most studies, BIS was used to guide doses of manually controlled propofol infusion. The overall recovery time profiles were a few minutes shorter and did not affect the time for being discharged from the hospital[10]. There were few studies used BIS to guide TCI propofol doses for the whole operation. Most of these studies used BIS for both groups and compared TCI and manually controlled infusion techniques or compared with different population or different procedures[7,16-18]. Our study is the first one that compares clinical signs with BIS guided TCI propofol usage in patients undergoing complex spines surgery with the use of neurophysiologic monitoring. We found that clinical signs including patients' movement were valuable for TCI dose adjustment.

Our study has some limitations. Firstly, in BIS group, the average BIS levels were lower from study's intention because of patients' movements so the TCI levels were increased and the BIS levels were temporarily lower than 40. Secondly the anesthesiologists during induction and maintenance were not blinded to study group and this might affect their decision for drug titration or unintended bias. Finally, during study period (25 months), some anesthesiologists gained clinical experiences from taking care of this kind of spine patients and they could better use clinical signs for drug adjustment.

Further researches should focus on how to reduce movement during operation and the BIS target might need to be lower than this study.

Conclusion

BIS monitor added up to clinical signs monitoring has no significant effects to patients' extubation time. For experienced anesthesiologists, BIS adds little value for adjusting dose of TCI propofol for spine surgery.

What is already known about this topic?

BIS is successfully used to guide doses of propofol infusion with a few minutes shorter in recovery from anesthesia.

What this study adds?

Clinical signs such as vital signs and patients' movement can be used for adjusting dose of target controlled infusion of propofol.

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Trial registration

ClinicalTrials.gov: NCT 02174913.

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Potential conflicts of interest

None.

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เวลาถอดท่อหายใจของผู้ป่วยหลังการผ่าตัดกระดูกสันหลังที่ได้รับยาระงับความรู้สึกโปรโปฟอล (propofol) หยดต่อเนื่องแบบกำหนดเป้าหมาย (target controlled infusion) เปรียบเทียบระหว่างการใช้อาการแสดงทางคลินิกกับดัชนีคลื่นไฟฟ้าสมอง (bispectral index): การศึกษาเปรียบเทียบแบบสุ่มเปิด

มานี รักษาเกียรติศักดิ์, นรินทร์ พลายละหาร, ภูริพงศ์ ทรงอาจ, วรรณฉัตร กระต่ายจันทร์

วัตถุประสงค์: การระงับความรู้สึกทางหลอดเลือดดำนิยมใช้สำหรับการผ่าตัดกระดูกสันหลังที่มีการใช้อุปกรณ์เฝ้าระวังทางระบบประสาทประกอบด้วยการให้ยาโปรโปฟอล (propofol) ทำให้หลับและยาแก้ปวดกลุ่มโอปิออยด์ ในปัจจุบันมีการใช้เครื่องควบคุมการให้ยาที่มีการกำหนดเป้าหมาย (target controlled infusion, TCI) การศึกษานี้ต้องการเปรียบเทียบการใช้ดัชนีคลื่นไฟฟ้าสมอง (bispectral index, BIS) กับการใช้อาการแสดงทางคลินิกในการปรับยาและการฟื้นตื่นจากยาระงับความรู้สึก

วัสดุและวิธีการ: ผู้ป่วยทุกรายได้รับการระงับความรู้สึกด้วยทางหลอดเลือดดำด้วย TCI propofol (3-7 ไมโครกรัม/กล., Schnider model) และยาแก้ปวดเฟนทานิลหยดต่อเนื่อง แบ่งผู้ป่วยเป็นสองกลุ่มแบบสุ่ม คือ กลุ่มที่ใช้ BIS กับกลุ่มที่ไม่ใช้ BIS ซึ่งการปรับยาใช้อาการแสดงทางคลินิกในกลุ่มใช้ BIS ปรับยาโดยมีเป้าหมายให้มีค่า BIS 40-60

ผลการศึกษา: มี 17 คนในแต่ละกลุ่ม มีค่าอายุเฉลี่ยที่ 48.0±12.1 (non-BIS) vs. 50.1±11.6 (BIS) ปี (p = 0.61) ไม่มีความแตกต่างกันในผู้ป่วยทั้งสองกลุ่มในแง่ของคุณลักษณะ การวินิจฉัยโรค การฟื้นตื่นและถอดท่อหายใจใช้เวลาไม่แตกต่างกัน [16.6±8.9 (non-BIS) vs. 16.3±9.7 (BIS) นาที, p = 0.91] ปริมาณยาโปรโปฟอลที่ใช้ไม่แตกต่างกัน [2,340±839 (non BIS) vs. 2,146±742 (BIS) มก., p = 0.48] ข้อมูลในด้านอื่น ๆ ไม่แตกต่างกัน ได้แก่ ปริมาณยาแก้ปวดเฟนทานิล การขยับตัวของผู้ป่วยระหว่างการผ่าตัด การเสียเลือด ระยะเวลาของการผ่าตัด เป็นต้น

สรุป: สำหรับวิสัญญีแพทย์ที่มีประสบการณ์ อาการแสดงทางคลินิกสามารถใช้ได้ดีเท่ากับดัชนีคลื่นไฟฟ้าสมอง สำหรับการปรับยาโปรโปฟอลที่มีการให้แบบหยดต่อเนื่องแบบกำหนดเป้าหมายสำหรับการผ่าตัดกระดูกสันหลัง