A comparative study of desflurane inhalation and propofol TCI regimen for temporal lobectomy: Early recovery, cognitive functions and costs

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Background : A number of the anesthesia regimens are used in craniotomy. Rapid emergence is one of the important goals in Neuroanesthesia. In this study, we compared desflurane inhalation and propofol TCI regimen in patients undergoing craniotomy for temporal lobectomy regarding recovery profiles including time of recovery, cognitive function, postoperative pain, post-operative nausea and vomiting (PONV). In addition, we compared the costs between the two regimens.

Objective : To study effects of desflurane inhalation regimen and propofol TCI in patients undergoing elective craniotomy for temporal lobectomy. Recovery profiles, post-operative complications and treatments and overall costs between two group are compared.

Design : Randomized double-blind prospective study

Setting : Neurosurgery and Neuroanesthesia unit at King Chulalongkorn Memorial Hospital.

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Materials and Method: Forty-two patients were randomly assigned into group D with desflurane inhalation and group P with propofol TCI. Anesthetic depth was controlled by bispectral index (BIS). Time to awakening, cognitive function using Mini-Mental Status Exam (MMSE-Thai version), pain score and PONV were documented. Clinical symptoms and recovery profiles of all patients were followed up until 24 hours postoperatively.

Results: Time from discontinuing anesthesia to eyes opening was faster in group D than group P (5.20 ± 2.91 vs. 8.90 ± 4.64 min). However, times to extubation and orientation were similar. There were no statistically significant differences in Post-Anesthesia Recovery Scores (PARS), discharge times or MMSE scores between the two groups. More significant number of patients suffered from PONV in group D than group P (45% vs. 4%). Pain scores and shivering needed to be treated; 24-hour MMSE scores were not different. However, overall costs were significantly higher in group P than group D (2924.88 vs. 1474.34 Thai Baht).

Conclusion: Patients in both groups showed similar emergence and recovery profiles. However, the costs of propofol TCI regimen were significantly higher than that of desflurane inhalation group.

Keywords: Recovery profile, postoperative cognitive dysfunction, anesthetic cost, neurosurgery, Mini-mental status exam.
การศึกษาเปรียบเทียบการฟื้นตัวและหน้าที่ด้านการรับรู้การเข้าใจ (cognitive function) ภายหลังการให้ยาระงับความรู้สึกด้วยยาดมสลบ desflurane กับ propofol ในผู้ป่วยผ่าตัดสมองส่วน temporal และค่าใช้จ่าย

เหตุผลของการทำวิจัย:
จุดมุ่งหมายหนึ่งของการให้ยาระงับความรู้สึกในการผ่าตัดสมองคือผู้ป่วยฟื้นตัวจากฤทธิ์ยาอย่างรวดเร็วและมีหน้าที่ด้านการรับรู้การเข้าใจดีพร้อมสำหรับการตรวจทางระบบประสาท แนวทางให้การให้ยาระงับความรู้สึกมีอยู่หลากหลาย หากแต่การพิจารณาประสิทธิผลและความคุมค่าการเป็นสิ่งสำคัญในประเทศไทย

วัตถุประสงค์:
เพื่อศึกษาการฟื้นตัวจากการให้ยาระงับความรู้สึกในการผ่าตัดสมองส่วน temporal ในผู้ป่วยโรคหลอก ได้แก่ผู้ป่วย desflurane และ propofol โดยพิจารณาความรู้สึกและคุณภาพของการฟื้นตัว หน้าที่ด้านการรับรู้การเข้าใจ แสดงเจตนาและราคา

รูปแบบการทำวิจัย:
การศึกษาวิจัยแบบไปข้างหน้า โดยมีกลุ่มเปรียบเทียบ

สถานที่ทำการศึกษา:
โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย

ตัวอย่างและวิธีการศึกษา:
ศึกษาในกลุ่มผู้ป่วยผ่าตัดสมองส่วน temporal จำนวน 42 รายที่เข้ารับการผ่าตัดสมองส่วน temporal ได้รับการสุ่มให้ได้รับการระงับความรู้สึกด้วย desflurane หรือ propofol เข้าทางหลอดเลือดดำ โดยมีการควบคุมบริหารยาียาระบบความรู้สึก ปริมาณยาหน้ากล้ามเนื้อ และยาแก้ปวดให้ไม่แตกต่างกัน มีการติดตามความลึกของอาการระงับความรู้สึก โดยการใช้ระบบ bi-spectral index (BIS)

คนกลุ่มศึกษาทำการประเมินระยะเวลาตั้งแต่หลักรายระบบความรู้สึกหลักที่ผ่านไปถึงระดับความรู้สึกดี ระดับความรู้สึกดี ระดับหน้าที่การรับรู้การเข้าใจ ความปวด อาการคลื่นไส้อาเจียน และอาการรักษาที่ได้รับโดยเริ่มตั้งแต่หลังการผ่าตัดทันทีไปจนกระทั่งครบ 24 ชั่วโมง
ผลการศึกษา:
ระยะเวลาตั้งแต่หยุดยาระงับความรู้สึกจนกระทั่งผู้ป่วยลืมตาเองสั้นกว่าอย่างมีนัยสำคัญทางสถิติในกลุ่มยาสลบ desflurane (5.20 ± 2.91 และ 8.90 ± 4.64 นาที) และเวลาที่ใช้เพื่อออกจากช่วยหายใจและกลุ่มปุ่มรั้วน เวลา สถานที่นั่นไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติเมื่อเปรียบเทียบระหว่างการพัฒนาในห้องฟื้น ระยะเวลาที่อยู่ในห้องฟื้น หรือระดับหน้าที่การรับรู้การเข้าใจเมื่อประเมินโดยแบบทดสอบ Mini-Mental Status Exam (MMSE) ผู้ป่วยที่ได้รับยา propofol เข้าทางหลอดเลือดด้านต่าง มีอัตราการเกิดภาวะคลื่นไส้อาเจียนหลังการผ่าตัดยาวนานกว่าผู้ป่วยที่ได้รับยา desflurane (ร้อยละ 4 และร้อยละ 41) หากแต่เวลาตั้งแต่ค่าน้ำยา ค่าความชื้นประกอบด้วยความรู้สึก ยามกับปกติ และการรับรู้ในการดูแลแข้งขาตั้งท่าที่มีภาวะคลื่นไส้อาเจียนหลังการผ่าตัดมีค่าที่สูงกว่าในกลุ่มที่ได้รับยา propofol (2924.88 และ 1474.34 บาท)

สรุป:
ผู้ป่วยผ่าตัดสมองส่วน temporal ที่ได้รับการระงับความรู้สึกด้วยยาสลบ desflurane หรือยา propofol เข้าทางหลอดเลือดด้านต่าง มีความเรารในการพัฒนาและหน้าที่การรับรู้สึกการเข้าใจไม่แตกต่างกัน แต่มีความชื้นอยู่สูงกว่าในกลุ่ม propofol

คำสำคัญ:
การผ่าตัดสมองส่วน temporal, MMSE, หน้าที่การรับรู้การเข้าใจ, ราคา.
With emerging new technology and anesthetic drugs, there are varieties of the regimen used in neurosurgical anesthesia. As for intracranial surgery neither intravenous nor inhalation regimen has been used and extensively compared. Nonetheless, no conclusive result on a better patient outcome has been reported.\(^{(1,2)}\)

The ideal properties of anesthetic agents for neurosurgery include the following: maintenance of blood flow/metabolic coupling, having the least effect on autoregulation, having neither increase in cerebral blood volume nor intracranial pressure, neuroprotection and anticonvulsive potential. Furthermore, rapid recovery is needed for evaluation of the neurological signs which indicates the patient welfare. Therefore, rapid emergence and least sedated awakening is one of the important goals in neuroanesthesia.\(^{(3)}\)

With the development of computer-assisted target-controlled infusion (TCI), Propofol has become popular for general anesthesia and in neurosurgery procedures. It has a favorable pharmacokinetic profile that has been reported to enable rapid emergence and awakening.\(^{(4)}\) However, both propofol and TCI technology are expensive and may increase costs considerably.\(^{(6)}\)

The newer volatile anesthetic agents (e.g. desflurane and sevoflurane) have a low blood-gas solubility coefficient, allowing rapid induction and rapid recovery from anesthesia similar to propofol.\(^{(6,4)}\) However, there are few studies that compared the cost of propofol-based TCI anesthesia with and inhaled anesthetic agent especially desflurane. Despite the effect on intracranial pressure of higher dose of desflurane (> 1.0 MAC) reported either in animal or human studies\(^{(9,10)}\), the extremely rapid recovery property made this drug interesting and valuable in neurosurgical procedure.

The cost of each regimen is one of the important issues that were discussed before choosing the regimen of choice. In previous studies, the recovery profiles and the costs only in abdominal and ENT surgery have been compared.\(^{(11,12)}\)

Because of the lack of information, we conducted a prospective randomized study to compare the effects of different anesthetic regimens on recovery and costs in neurosurgical patients. In this study, we used temporal lobectomy as a model of supra-tentorial, intracranial normotensive, intermediate length (<4 hours) neurosurgical procedure.

**Materials and Method**

This study has been approved by the ethics committee and written informed consents of subjects were obtained before the study. The study population included 18 - 65 years old, ASA physical I-II patients undergoing elective craniotomy with temporal lobectomy for the treatment of epilepsy. Patients with history of delayed emergence, alcohol or drug abuse, psychiatric drugs used, previous anesthesia within one month, increased intracranial pressure, allergy to anesthetic drugs, morbid obesity and inability to perform a Mini-Mental Status Exam (MMSE) test were excluded.

The day before surgery, the Mini-Mental Status Exam (MMSE)-Thai version 2002 was performed. MMSE is a screening test to quantitatively assess cognitive deterioration by questions on orientation, memory, attention, verbal recall and
learning, and visual-constructive ability. The maximum score is 30 points; scores <23 indicate cognitive impairment and decrease of > 2 was defined as a decline in cognitive function. (13)

Using a closed envelope system, patients were allocated randomly to receive either a total intravenous propofol anesthesia (P group; n = 21) or an anesthetic regimen using desflurane (D group; n = 20). No premedication was given. Induction of anesthesia was achieved with fentanyl 1 - 2 mcg/kg and propofol 2 mg/kg intravenously. The patients were ventilated with 6 L/min fresh gas flow of oxygen, propofol and desflurane for maintenance depth of anesthesia throughout the operation having been commenced at this point. Endotracheal tube intubation was facilitated by cis-atracurium 0.15 mg/kg.

In the maintenance period, patient had controlled ventilation with 50% nitrous oxide in oxygen with total flow 1 L/min. Group P received propofol TCI infusion with target plasma concentration up to 6 mcg /kg. In group D, anesthesia was maintained by desflurane up to 1.5 MAC. To achieve similar depth of anesthesia, BIS monitoring was used with adjusting value between 40 and 60 intraoperatively. Increase in BIS level>60 were treated by increasing, firstly, the propofol and secondly with fentanyl 1 - 2 mcg/kg/ dose in group P and firstly desflurane concentration and secondly with fentanyl bolus dose in group D. Continuous intravenous infusion of Cis-atracurium at the dose of 1 - 1.5 mcg/kg/min was used to maintain the Train-of-four (TOF) ratio 0 - 1/4. Controlled ventilation was performed by the control of continuous capnometry (end-tidal CO2 30 - 35 mmHg). Hypotension was corrected with either fluid administration or small boluses of ephedrine.

Intraoperative events including hypotension, hypertension, tachycardia, bradycardia, brain swelling, seizure and surgical condition evaluated by the surgeon were recorded.

At the end of surgery, Cis-atracurium infusion was stopped after dura closure. After finishing the skin closure, propofol or desflurane were discontinued and the patient was ventilated with 100% oxygen at a fresh gas flow of 6 L/min. Reversals of neuromuscular blockade with neostigmine 2.5 mg and atropine 1.2 mg were given to all patients. The times from discontinuing anesthetics to extubation were recorded as well as obeying commands such as eye opening, hand squeezing and orientation to stating name and date of birth (assessed at 60-120 second intervals). All patients were transferred to PACU. Medication in the PACU included analgesic, antiemetic or anti-shivering drugs. Pain was documented using visual analog scale (0 - 10), PONV and other adverse side effects were also noticed. Post-operative analgesia was pethidine 1 mg/kg/dose given every 15 minute if VAS>3/10. Ondansetron 4 mg intravenously was given to treat PONV.

One hour after extubation, the anesthesiologist staff who did not know patient’s grouping evaluated the patient’s orientation to time, place, and person and performed a MMSE test. When the patients showed stable hemodynamics, no complications from the surgical field and the Post Anesthesia Recovery Score (PARS) was more than 11, they were then discharged from PACU. Twenty-four hour post-operatively, the patients were visited by an independent anesthesiologist; a MMSE test was re-performed and adverse effects of anesthesia were evaluated.
The cost in our study was focused on variable anesthetic cost limited to drugs’ cost, as mentioned below. The fixed cost including cost of oxygen, nitrous oxide, staff (physicians, nurses, and nurse-assistants), medical devices and disposables were not calculated.

The cost of anesthesia analyses included cost of intraoperative drugs and drug used in PACU to treat pain, PONV or shivering. Using the selling price of our hospital (Appendix), the cost of intravenous drugs, excluding propofol, included all vials opened for the patients, regardless of whether their entire contents were used.

The cost was divided into intraoperative and postoperative costs. The intraoperative cost was including the price of propofol, desflurane, cis-atracurium, and fentanyl. The details of cost calculations of propofol and desflurane were indicated below. As for the postoperative cost, we included the price of anti-emetics, analgesics, and anti-shivering drugs (Table 1).

The cost of propofol was calculated by multiplying the milligrams of propofol administered during surgery by the cost of 1 mg of propofol. The cost of desflurane was measured by using the classic formula:

\[ \text{Cost of desflurane} = \frac{PFMTCD}{2412D} \]

Where \( P \) is the delivered concentration (%), \( F \) is fresh gas flow (1 L/min), \( M \) is desflurane molecular weight, \( T \) is time (min), \( C \) is cost of 1 mL and \( D \) is the density of desflurane.

**Sample Size Calculation**

An a priori power analysis base on previously published data suggested that a minimum sample size of 17 patients per group would be required to detect a 10% difference in time of recovery among the anesthetic groups with a power of 90% at the \( P <0.05 \) level of significance. \(^{(1)}\)

**Statistics**

SPSS version 17.0 (SPSS Inc., Chicago, Illinois) was used for statistical analysis. Data are shown as mean and standard deviation (SD) or median and range. Demographic and peri-operative data were compared using either the student’s \( t \)-test or the Mann-Whitney \( U \) test as proper. The comparison of MMSE scores between the groups and time points were analyzed using Kruskal-Wallis One Way ANOVA on ranks, and subsequent multiple comparisons were done using Dunn’s Method due to unequal variance. The incidences including PONV, shivering, pain and all other complications were calculated using Fisher’s exact test.

**Results**

Twenty-one patients were included in each anesthesia group. One patient in group D had immediate re-operation due to post-operative surgical bleeding, and hence was excluded from the study. Both groups were similar in demographics and doses of anesthetic drugs (Table 1). However, there are statistical differences regarding the duration of anesthesia and the volume of solution administered. The anesthetic time was longer in group D and patients in this group received more intraoperative fluid administration. No cardiovascular or neurological event occurred.
The time from discontinuing anesthesia to eye opening was significantly faster in group D (5.20 ± 2.91 min) than in group P (8.90 ± 4.64 min). As for other recovery time points including times from discontinuing anesthesia to extubation, and to stating own name, birth date and phone number, there were trend to be more faster in group D. However, the differences were not statistically significant between the groups (Figure 1).

Time in PACU was similar in both groups. The PARS scores at arrival in PACU was 13 in group D and 12 in group P and increased at the time to discharge from PACU without statistical differences. In group D, significantly more patients suffered from PONV compared with group P (45% vs. 4%). No statistical significance in number of patients requiring analgesic or anti-shivering treatment.

Without showing any significant difference between the two groups, MMSE scores decreased significantly from baseline in both groups at an hour after extubation (Figure 2). At one hour postoperative time point, the data showed a trend of increasing cognitive dysfunction (MMSE score < 23) in group P (5 of 21 patients) compared to group D (2 of 20 patients). However, there was no statistical significance (p-value = 0.25). After 24-hours after discharge from PACU, almost all of the patients had regained their MMSE score above 23, except one
The scores returned to the pre-operative values at 24-hours time point (Figure 2).

**Figure 1.** Recovery time after discontinuing anesthetic agents (mean ± SD).

There were a statistically significant faster time from discontinuing anesthetic agents to eye opening in Group D (5.2 ± 2.91 min) in comparison with Group P (8.9 ± 4.64 min), (P <0.05).

**Figure 2.** Mini Mental Status Examination (MMSE) Score in Median (range).

There were significantly decrements of the score from preoperative level in both group (P<0.05) as of 25.5 (24-27) and 26(23.25-27) in Group D and Group P, respectively. The MMSE score were return to baseline level at 24-hr post-operation.
Overall drugs costs including intraoperative drug(s) used in PACU were higher in the group P than in group D. Group P’s overall cost per case was 1,243.10 baht (1.65 times) more expensive than group D. The major fraction of anesthetic cost of either group was anesthetic agent, 66.35% and 83.37% of total cost in Group D and Group P, respectively. In Group D, the anesthetic agent cost included propofol for induction, 18% and desflurane for maintenance, 48.35%. On the other hand, group P anesthetic agent was solely from propofol (Table 2). In addition, there was a considerable amount of discarded leftover propofol, $82.3 \pm 21.53$ mg in group D and $88.76 \pm 61.02$ mg in group P.

Antiemetic drug costs were significantly higher in group D. There was 8.27% of the total anesthetic cost (157 baht per case) in group D while there was 0.53% of total cost (16.6 baht per case) in group P (Table 2).

### Table 2. Cost of anesthesia in Thai Baht (mean ± SD)

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<tr>
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<th>Desflurane (n = 20)</th>
<th>Propofol (n = 21)</th>
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<tr>
<td><strong>Mean ± SD</strong></td>
<td><strong>Percentage</strong></td>
<td><strong>Mean ± SD</strong></td>
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<tr>
<td><strong>Overall costs</strong></td>
<td>1897.57 ± 237.78</td>
<td>100</td>
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<tr>
<td><strong>Intraoperative</strong></td>
<td></td>
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<tr>
<td><strong>Desflurane</strong></td>
<td>917.45 ± 299.07</td>
<td>48.35</td>
</tr>
<tr>
<td><strong>Propofol</strong></td>
<td>348</td>
<td>18</td>
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<tr>
<td><strong>Cis-atracurium</strong></td>
<td>427.2 ± 89.50</td>
<td>22.51</td>
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<tr>
<td><strong>Fentanyl</strong></td>
<td>42.35 ± 12</td>
<td>2.23</td>
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<tr>
<td><strong>Postoperative</strong></td>
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<tr>
<td><strong>Antiemetics</strong></td>
<td>157 ±178</td>
<td>8.27</td>
</tr>
<tr>
<td><strong>Analgesics</strong></td>
<td>5.2 ± 2.62</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Shivering</strong></td>
<td>0.33 ± 1.45</td>
<td>0.02</td>
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Discussion

In this study, both anesthetic regimens proved successful in term of fast recovery in all patients and absence from serious complication. In the past few years, a number of researches have been performed comparing propofol infusion with the inhalation of desflurane, sevoflurane and desflurane. Some supposed that propofol may improve cognitive outcome with faster recovery. However, other studies including meta-analysis showed faster emergence using desflurane than propofol. Our results showing faster time to eye-opening in group D. There was a trend of faster recovery times including to extubation and time at which patient be able to stating own name, birthday and phone number after discontinuing anesthetic drugs in group D. But we, as well as other investigators, have not been able to demonstrate any statistical significance. In term of clinical relevance, these results showed inconclusive benefit of desflurane over propofol regimen.

The varying results of previous studies may due to the differences of anesthetic protocols, the diversity of study population and type of surgery. Most of them were performed in short procedure such as laparoscopic Cholecystectomy, ENT surgery and peripheral orthopedics surgery. Thus, the neurosurgical patient was a primary selection in this study because rapid emergence and least sedated awakening is one of the goals of anesthesia in this group and also there is lack of information.

Another factor that may affect the recovery quality is depth of anesthesia. Moreover, BIS guided technique has been reported to decrease excessive anesthetic drug consumption compared to the conventional method. Thus, we use BIS-monitoring for guiding administration of anesthetics instead of using clinical signs alone.

One concern of using desflurane for neurosurgical patient is the cerebral vasodilatory property of this drug. Increase in cerebral blood flow and intracranial pressure resulted from vasodilatory effect of desflurane in dose response manner have been reported. Therefore, the applicable use of desflurane in brain surgery has been doubtable in brain surgery in spite of its rapid recovery property. However, there are some reports indicating that 1 MAC of desflurane has no effect on ICP even in preoperative increased ICP patients. Nevertheless, the use of desflurane in neurosurgical procedure should be cautiously monitored with vigilance. In our study, anesthetic drugs were given by BIS guided with maximum limit of 1 MAC of desflurane. With this technique, the depth of anesthesia was strictly controlled with less excessive desflurane has been used, in other word, lesser effect on the ICP with adequate depth of anesthesia. None of the patients in group D required supplement fentanyl to control either depth of anesthesia or hypertension. This result indicated that BIS guided desflurane regimen would be one of alternative practices to propofol infusion in neurosurgical anesthesia.

A of quality of recovery can be measured in term of postoperative psychological dysfunction including difficulties in learning and recall, verbal capabilities, concentration and attention. In spite of modern anesthetics drugs, general anesthesia and major surgery still associated with this complication. Tools and timing to detect postoperative cognitive impairment have not been standardized. In this study, we used the Mini-Mental Status Exam (MMSE)
because of high validity and reliability. The MMSE Thai version is a tool to evaluate cognitive function in Thai patients, recommended by the Royal College of Psychiatrists of Thailand. We found only a temporary decline at one hour after anesthesia without difference between two groups.

After that, at 24-hours postoperatively, there was no difference in cognitive function compared with the baseline value. However, the patients in group P (5 from 21 patients) trend to have more cognitive dysfunction (MMSE score < 23) than group D (2 from 20 patients). In addition, because of complexities and cooperative dependency of the test, one patient in group D having been indicated as significantly decrease cognitive function without any other sign of neurological deficit and complication. The MMSE score remains at 9/30 after one-hour postoperative and 24-hour postoperative time point. All investigators and surgeon agreed with the wellness of this patient and this might indicate the weakness of MMSE scoring system for testing postoperative recovery profile.

The lower incidence of postoperative nausea and vomiting (PONV) in group P is in agreement with numerous previous studies. In spite of more PONV in group D, there were no differences between both groups in duration of stay and time to discharge from PACU. In this study, the cost of medication using in PACU is less than 10% of overall cost in either group, nonetheless, the clinical impact of vomiting on increasing ICP after surgery hasn’t been identified and calculated for the cost.

Selection of anesthetic agents should base not only on safety and efficacy, but also economic profiles. This present study shows overall drug costs including intraoperative drug and drugs used in PACU, were significantly higher in group P. Previous studies demonstrated that TCI technique increases the amount of drug injected compared with manual infusions. Furthermore, a considerable amount of propofol is wasted in the TCI machine. In contrast, desflurane has low blood-gas solubility this allows a fast recovery period similar to propofol. Furthermore, low-flow inhalation anesthesia creates no waste. In fact, this study showed no significantly difference of discarded propofol which was left over in each case from a 200 mg-vial (Table 3). However, further investigation about the cost of anesthesia should consider to design in cost-effectiveness analysis. The depreciation of equipment (i.e. vaporizer or TCI driver), costs of medical devices and nursing workload should be calculated.

Conclusion

A BIS-guided desflurane regimen provided a fast recovery period compared to propofol-TCI regimen. Cognitive function was similar in both groups. However, propofol-TCI technique cost was much higher than desflurane.

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