A Comparison Between Thiopental Sodium and Propofol for Induction of Anesthesia in Elective Cesarean Section Using Bispectral Index and Isolated Forearm Technique: A Randomized, Double-Blind Study

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Objective: Although regional anesthesia is the most frequently used method for selected surgical approaches, general anesthesia (GA) is still common. Awareness and recall of events are among the main hazards during GA, particularly in Caesarean Section (C/S). In this study, we decided to compare depth of anesthesia, that was measured by Bispectral index (BIS) and isolated forearm technique (IFT) in GA, induced by propofol vs. thiopental for elective C/S. We also aimed to determine the incidence of postoperative recall using these two anesthetic medications.

Methods: Ninety parturient were allocated to receive either thiopental (group T) or propofol (group P) with blocking on a 1:1 ratio. All patients underwent standard GA. BIS and IFT were used to monitor depth of anesthesia at different predetermined perioperative events. All patients were evaluated for recall of the events.

Results: No patient recalled the perioperative events during the follow up period. BIS scores were significantly lower in group P compared with group T after induction of GA until discontinuation of volatile anesthetics (p < 0.001). IFT values were significantly higher in thiopental group in time interval of induction to skin incision comparing to propofol group (p < 0.050).

Conclusion: The current study suggests regarding better effect of propofol on decreasing of awareness during anesthesia and surgery, it seems to be better to use propofol in cases where we are forced to use GA in cesarean section.

Keywords: caesarean section, bispectral index, isolated forearm technique, anesthesia, recall

Introduction

Although regional anesthesia is the most frequently used method for selected surgical approaches, general anesthesia (GA) is still an immediate and rapid technique for emergency operations and unfeasible or forbidden deliveries or because of patients’ desire.¹² Recall of events during GA is too important,³⁴ particularly in caesarean section (C/S), while sedative premedication is contraindicated and low doses of nitrous oxide and volatile agents are administered.⁵ This increases the risk of awareness.⁶ Such awareness with recall may cause severe postoperative psychological squeal, including post-traumatic stress...
disorder, anxiety, neurosis, nightmares and fear of hospitals. Therefore, selecting the appropriate anesthetic medications is an essential aspect of GA in C/S to decrease the incidence of awareness.3,4

Various methods such as bispectral index (BIS) and isolated forearm technique (IFT) were applied to monitor depth of anesthesia.7 BIS monitor, calculated from the processed electroencephalogram, has adequate sensitivity and specificity for monitoring depth of anesthesia.8,11 However, IFT is the gold standard test for detecting wakefulness during GA.12 Other methods have lower sensitivity and specificity to monitor depth of anesthesia.6,13

Sodium thiopental and propofol are routinely used and suggested as safe drugs for mother and fetus.14,15 Previous studies assessed depth of anesthesia while administering these two drugs during in C/S as monitored by BIS or auditory evoked potential. Some suggested that thiopental provided inadequate depth of anesthesia, but these two drugs have never been compared using both BIS and IFT for monitoring yet.

In the study of Zand et al.,17 it was shown that lower than previously recommended values of BIS are needed to avoid higher IFT scores during laryngoscopy, intubation, and skin incision with thiopental.

So the aim of this study was to investigate the effects of propofol and thiopental sodium on the depth of anesthesia in elective C/S under GA using both BIS and IFT. We also tested the hypothesis that administering propofol would decrease the risk of awareness compared with thiopental.

Methods

In this double-blind controlled trial, approved by the Medical Ethics Committee of Shiraz University of Medical Sciences and registered in Iranian Registry of Clinical Trials (IRCT No. 2016082819470N44), all pregnant women with American Society of Anesthesiologist physical status I, II score, in Ghadir Mother and Child Hospital affiliated to Shiraz University of Medical Sciences, Shiraz, Iran, were screened for eligibility criteria from November 2016 to March 2017.

Inclusion criteria covered all the patients aged 18 and above with elective C/S and met eligible criteria for GA. Patients were excluded if they had any previous history of awareness during GA, anticipated difficult airway, psychiatric disorders, neuromuscular disease, opium addiction or multiple drug allergies, bradycardia, heart block, multiple gestation, preterm labor, fetal distress, hypertension, and administration of MgSO4.

In the preoperative examination, all of the patients were informed about the protocol of the study and each eligible patient signed the written informed consent.

Patients were randomly assigned to receive 5.0 mg/kg of Sodium thiopental (group T, n = 45) or 2.5 mg/kg of propofol (group P, n = 45) to induce rapid sequence anesthesia. Both groups received 2.0 mg/kg of succinylcholine, then cricoid pressure and tracheal intubation were performed. A senior resident who was not involved in the administration of drugs or observation of the patients, prepared the medications based on the randomization table.

The patients were monitored with end-tidal carbon dioxide and BIS in addition to the routine monitoring (electrocardiogram, non-invasive blood pressure, peripheral oxygen saturation). Anesthesia was maintained with N2O 50% and O2 50% and sevoflurane 2%, and continued with N2O 50%, O2 50%, and sevoflurane 1.2% after new born delivery. Midazolam 0.03 mg/kg, morphine 0.10 mg/kg and Cisatracurium 0.04 mg/kg were administered after umbilical cord clamping for muscle relaxation. Sevoflurane administration was stopped at the start of skin closure.

A blood pressure cuff tourniquet was secured on the dominant arm and inflated to 200 mmHg immediately before induction. After induction, a recorded message was played by the earphones every 1 min which asked the patient to move her fingers of the dominant hand. Arm activity was scored as no movement (0), non-specific movement (e.g., fine movements of fingers) (1), or firm clenching/flexing movement. We divided the patients into two groups according to their IFT responses on the basis of a revised IFT scoring system which divided patients into responders (score 2), and non-responders (score 0 or 1). In this new scoring system, the patients with IFT = 1 (non-specific movements) are considered as non-responders for the following reasons: (1) they believe that depth of anesthesia is either adequate or inadequate, and thus a third state does not exist; and (2) non-specific movement cannot be considered as a meaningful indicator of wakefulness.15

After applying tourniquet on the right arm, following laryngoscopy and intubation, regular intravenous induction was injected, then, the tourniquet was inflated about 50–100 mmHg greater than systolic blood pressure, before administration of muscle re-
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laxant. This inflated tourniquet obstructed systemic circulation and muscle relaxants affect. Muscle relaxant was injected and ventilation with oxygen and isoflurane was applied for patients.\textsuperscript{18,19} The cuff tourniquet was deflated after 20 min but was re-inflated before administering any further boluses of neuromuscular blocking drugs.

The BIS monitor (Aspect Medical Systems Inc., Norwood, MA, USA) was connected to the Aspect BIS sensor, which had been placed on the forehead as recommended by the manufacturers. BIS values were recorded for 16 perioperative events: (1) baseline level, (2) induction of anesthesia, (3) laryngoscopy, (4) intubation, (5) skin incision, (6) opening the peritoneum, (7) uterine incision, (8) uterine retraction, (9) childbirth, (10) uterine closure, (11) closure of fascia and muscle, (12) subcutaneous closures, (13) volatile discontinuation, (14) start of skin closure, (15) eye opening, (16) extubation. End tidal sevoflurane was measured by gas analyzer in all patients.

For IFT scores 4 separate periods were used for analysis, including the baseline (1 event), induction to skin incision (4 events), opening of peritoneum to delivery (4 events) and uterine closure to extubation (7 events). In each period the accumulation of data was considered in a way that the summation of responders and non-responders (each one separately) in two groups for the period 1 should be 45, for period 2 and 3 should be 180 and finally for the period 4 should be 315.

All patients were interviewed for recall at 3 points of 12, 24, and 72 h postoperatively using a standardized set of postoperative questions.\textsuperscript{18} This included inquiring for the recall of any unpleasant dreams during intubation or surgery as well as explicit memory recall for operative events.

Primary outcome was the depth of anesthesia which was measured by IFT and BIS was evaluated as a supplementary outcome.

The participants were equally randomized into two groups by block randomization. Determination of whether a patient would be allocated to thiopental group (T) or propofol (P) was made by reference to the randomization table by a senior resident who induced anesthesia but was not involved in the study. Other physicians, patients and data analyst were kept blinded to the allocation. Before induction, the patients practiced to squeeze the investigator’s fingers twice to command. The sample size was calculated to be 45 subjects in each study group based on the obtained results of similar study,\textsuperscript{20} with a two-sided 5% significant level and a power of 80%. Demographic data were presented as mean ± standard deviation for continuous data. Chi square and independent t-test were used to compare BIS and IFT scores in two groups. Repeated measures analysis of variance test was applied to compare end tidal sevoflurane concentrations in two groups. Statistical analyses were performed using statistical package for the social sciences, version 19.0 (SPSS, Inc., Chicago, IL, USA). All graphs were prepared in Microsoft Excel, version 14.0 for Windows.

Results

Out of 129 patients who were screened for recruitment, 39 patients were excluded and 90 eligible participants were enrolled the study (Fig. 1).

There was no statistically significant difference between the groups with regard to age, weight, duration of GA and APGAR scores in newborns (p > 0.050) (Table 1).

No patient recalled the perioperative events during 12, 24, and 72 h of follow up. BIS scores were not significantly different at the baseline levels and at the two final perioperative events, i.e., eye opening and extubation. However, eye opening and extubation were significantly lower in propofol group at other 14 predetermined perioperative events compared with thiopental group (Table 2). Mean BIS scores in patients receiving thiopental and propofol were 55.32 and 48.87, respectively.

IFT values were significantly higher in thiopental group in time interval of induction to skin incision comparing to propofol group. There was no statistically significant difference between the groups in the remaining events (Table 3).

Regarding to the end tidal sevoflurane concentration, the difference between the two groups at the end of the surgery was not significant (p = 0.35) (Fig. 2).

Discussion

Our study demonstrated that although the concentrations of inhalation agents were comparable in both groups, our study demonstrated that the propofol when used as an induction agent provided lower BIS value throughout the surgery compared with that following the administration of thiopental. Furthermore, IFT scores were significantly lower immediately be-
Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.
BIS: Bispectral index.

Table 1. Demographic features and baseline clinical data

<table>
<thead>
<tr>
<th></th>
<th>T (n = 45) Mean ± SD</th>
<th>P (n = 45) Mean ± SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.40 ± 52.70</td>
<td>31.50 ± 11.10</td>
<td>0.550</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.80 ± 24.52</td>
<td>81.10 ± 11.72</td>
<td>0.990</td>
</tr>
<tr>
<td>Duration of GA (min)</td>
<td>63.80 ± 63.02</td>
<td>62.70 ± 11.94</td>
<td>0.350</td>
</tr>
<tr>
<td>APGAR (1 min)</td>
<td>8.00 ± 91.29</td>
<td>8.00 ± 84.37</td>
<td>0.340</td>
</tr>
<tr>
<td>APGAR (5 min)</td>
<td>10</td>
<td>10</td>
<td>1.000</td>
</tr>
</tbody>
</table>

T: thiopental group; P: propofol group; SD: standard deviation; GA: general anesthesia.
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Table 2. Bispectral index values at 16 predetermined operative events

<table>
<thead>
<tr>
<th>Events</th>
<th>T (n = 45) Mean ± SD</th>
<th>P (n = 45) Mean ± SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. baseline</td>
<td>97.98 ± 0.15</td>
<td>97.84 ± 0.52</td>
<td>0.161</td>
</tr>
<tr>
<td>2. induction</td>
<td>54.30 ± 8.70</td>
<td>49.00 ± 9.50</td>
<td>0.039</td>
</tr>
<tr>
<td>3. laryngoscopy</td>
<td>45.60 ± 8.80</td>
<td>38.40 ± 4.70</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>4. intubation</td>
<td>46.20 ± 9.20</td>
<td>37.70 ± 4.50</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>5. skin incision</td>
<td>47.30 ± 8.60</td>
<td>37.40 ± 6.90</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6. peritoneal incision</td>
<td>48.10 ± 8.20</td>
<td>36.20 ± 6.40</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>7. uterine incision</td>
<td>47.08 ± 9.40</td>
<td>36.04 ± 5.80</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>8. uterine retraction</td>
<td>46.67 ± 9.20</td>
<td>37.55 ± 6.60</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>9. delivery</td>
<td>47.13 ± 9.50</td>
<td>38.06 ± 6.30</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>10. closure of uterus</td>
<td>40.40 ± 7.60</td>
<td>33.40 ± 3.70</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>11. muscle and fascia closure</td>
<td>43.30 ± 8.02</td>
<td>36.20 ± 5.40</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>12. subcutaneous closure</td>
<td>45.90 ± 9.40</td>
<td>39.70 ± 7.30</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>13. volatile discontinue</td>
<td>60.40 ± 7.70</td>
<td>55.60 ± 6.70</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>14. start of skin closure</td>
<td>47.80 ± 9.30</td>
<td>40.70 ± 7.70</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>15. eye opening</td>
<td>81.40 ± 4.07</td>
<td>82.40 ± 2.90</td>
<td>0.301</td>
</tr>
<tr>
<td>16. extubation</td>
<td>85.10 ± 3.80</td>
<td>85.40 ± 2.90</td>
<td>0.800</td>
</tr>
</tbody>
</table>

T: thiopental group; P: propofol group; SD: standard deviation.

Table 3. Isolated forearm technique categories, responder and non-responder, in two groups

<table>
<thead>
<tr>
<th>Events</th>
<th>T Non-responders</th>
<th>Responders</th>
<th>P Non-responders</th>
<th>Responders</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0</td>
<td>45</td>
<td>0</td>
<td>45</td>
<td>1</td>
</tr>
<tr>
<td>Induction to skin incision</td>
<td>156</td>
<td>24</td>
<td>121</td>
<td>59</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Peritoneum opening to the birth</td>
<td>178</td>
<td>2</td>
<td>176</td>
<td>4</td>
<td>0.4109</td>
</tr>
<tr>
<td>Uterus closure to the extubation</td>
<td>311</td>
<td>4</td>
<td>308</td>
<td>7</td>
<td>0.3619</td>
</tr>
</tbody>
</table>

T: thiopental group; P: propofol group. 1 = responder and 0 = non-responder.

fore skin incision in propofol group compared with that in thiopental group. Our finding suggested that when elective C/S was anticipated, the use of propofol may avoid the risk of awareness immediately after skin incision.

IFT was used for studying awareness during GA in C/S by Çakırtken et al. for the first time.¹⁶ The trial conducted by Zand et al. suggested that IFT is more reliable for monitoring the depth of anesthesia during GA for C/S compared with BIS,¹⁷ but some other studies revealed that the IFT is inadequate for the evaluating awareness.¹⁶

The study conducted by Rampil showed that BIS is useful in some situations and it has been approved by the Food and Drug Administration.²¹ Therefore, we used both BIS and IFT to achieve more reliability for monitoring the depth of anesthesia.

In our trial, BIS and IFT scores were significantly lower after induction of anesthesia in propofol group compared with thiopental group. This is consis-
tent with the study of Çakırtken et al. which showed that BIS score from induction to infant delivery for propofol was lower compared to thiopental and both drugs didn’t have any negative effect on 1–5 min APGAR scores, cord blood gas and postoperative visual analogue scale scores. Thus, the concluded that propofol is superior to thiopental for suppressing the hemodynamic response to intubation and gives better anesthesia depth beside fast recovery.

It was shown that thiopental had greater electroencephalographic (EEG) activity than propofol following endotracheal intubation. Based on the target control infusion method using the relative dosages of these two hypnotic drugs required for reaching the definite endpoints, it was revealed that for induction of anesthesia, propofol was around 1.5–2.0 times more potent than thiopental. In the study of Grounds et al. after bolus doses of propofol and thiopental and by means of the failure “to open eyes on command” technique representing the loss of awareness, propofol showed 1.6 times higher potency than thiopental. The theoretic drug concentration of the propofol at the effect site (Ce) shows higher potency of this drug around 7–8 times than thiopental. On the other hand, thiopental concentration quickly reaches the peak level in effect-site and then its distribution started from central nervous system (CNS) to blood compartment which quickly decreases its concentration at effect site compared to other hypnotic drug doses. Therefore, in view of this point that EEG shows the concentration of hypnotic drug at the site of effect, the EEG rises with thiopental after intubation could be a reflection of its clearance from CNS.

It was studied by Veselis et al. whether propofol and thiopental influence on different areas of brain despite the similar drug effects. The significant finding was that, in spite of very comparable actions, the pattern of blood flow distribution in the brain is affected by these two drugs in a variety of ways. These dissimilarities at the effect site might be useful in locating the nonsedative effects of propofol, such as an anesthetic site. We suppose that propofol has a greater amnestic effect than thiopental and these differences in effect site may also lead to different BIS scores between the two anesthetics.

This is consistent with the finding of Mercan and El-Kerdawy who compared propofol and thiopental for GA in C/S measuring BIS. They concluded that propofol could provide lower BIS score, heart rate and blood pressure. However, they used clinical signs such as blood pressure and heart rate as indicators of wakefulness and these measures are nonspecific for evaluation of depth of anesthesia. Also, Siafaka et al. reported propofol as a suitable alternative to thiopental as an induction agent for obstetric anesthesia.

BIS score was significantly lower at the time interval between anesthesia induction and discontinuation of volatile agents in propofol group compared with thiopental but there was not statistically significant difference in IFT response between the two groups. This might be due to the decreased serum drug concentrations after anesthesia induction and on top of that, we need more reductions in BIS score to obtain meaningful changes in IFT score. This is also supposed to be related to decreased stimulations at the interval between newborn delivery and skin closure. However, this study for the first time is using IFT score showing better anesthesia indexes in C/S patients going under GA.

Although many patients showed signs of wakefulness and responding in the current study, none of them had evidence of explicit recall. This finding is also confirmed by other studies showing no recall of events or experiences during surgery by these drugs. This might be due to the anesthesia that often extended quickly before recording the experience in explicit memory, or because the patients were undergoing high concentrations of hypnotic drugs during the orders.

There are some limitations in our study. First, we checked hand movements at specific discrete time
points instead of assessing responses continuously; thus, we cannot exclude consciousness between these time points. Second, we simply played an audio tape to patients through closed headphones and did not speak directly with them, so we were only able to observe hand movement if it occurred and could not clearly determine whether this was contiguous with a command through the headphones. Third, the lack of recall for events occurring after delivery might be also attributed to the use of midazolam and morphine after delivery among our patients. Also, we didn’t use peripheral nerve stimulator to ensure that neuromuscular integrity was maintained under the tourniquet. Therefore, further studies with bigger sample size are warranted in this area.

In conclusion, this study suggests that more attention could be paid to propofol and regarding its better effect on decreasing of awareness during anesthesia and surgery, it seems to be better to use propofol in cases where we are forced to use GA in cesarean section, although more and large scale studies are warranted to provide proving results.

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Conflicts of Interest

None.

Authors’ Contribution

Mohammad-Reza Hadavi participated in the study conception, proposal writing, data collection

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and the article draft. Maryam Beihaghi was contributed in the study conception, proposal writing, manuscript revision and article draft. Farid Zand participated in study design, data analysis and the article draft. Golnar Sabetian was contributed in proposal preparation, data collection, analysis and the final draft. Simin Azemati participated in the data collection and the article draft. Elham Asadpour participated in manuscript preparation, article writing and editing and final draft.

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