Pre-delivery Conscious Sedation with Intravenous Low Dose Thiopental Na Bolus during Spinal Anesthesia for Cesarean Section

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ABSTRACT

Background: Nowadays, according to the large number of cesarean sections under spinal anesthesia, finding a simple and safe pre-delivery sedation technique which provides satisfaction for mothers with no over sedation and amnesia seems to be necessary. However, there is not enough evidence about the best choice of drug for this purpose. In the present study we aimed in evaluating the clinical effects of different concentrations (0.25, 0.5, 0.75mg/kg) of thiopental Na bolus for the mother’s satisfaction in cesarean section under spinal anesthesia.

Methods: Two hundred and forty term singleton pregnant women with normal ASA physical status were scheduled for an elective term cesarean delivery under spinal anesthesia and allocated into four groups. Groups I, II, III received 0.25, 0.5, 0.75mg/kg/IV of Thiopental Na respectively and group IV as the control group received 1.5cc of sterile water,1 min after spinal anesthesia. The level of consciousness with observer assessment of alertness/sedation score (OAA/S) and mother’s satisfaction was considered as primary outcomes.

Results: The level of mothers’ satisfaction in group II was significantly higher than other groups without any over sedation (P<0.001) and no adverse effect on their verbal contact was observed and they could easily communicate. All women could remember their infants. All babies were healthy with no complications and the Apgar scores were the same in all studied groups.

Conclusion: Based on the results of the present study and with comparison of different concentrations and side effects indicates pre-delivery conscious sedation with 0.5 mg/kg/IV of Thiopental Na could be a safe and appropriate technique for sedation in cesarean sections surgery under spinal anesthesia.

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Today, the subarachnoid block is a single highly accepted technique for cesarean section (CS). Moreover, the rate of maternal mortality has been found to be lower in mothers receiving regional anesthesia [1] but, due to the stressful environment of the operation room, the majority of pregnant women prefer general anesthesia for being unconscious during the surgery. Also complaints about the nausea and vomiting due to hypotension occurring right after spinal anesthesia and restlessness or lower limb discomfort during the surgery and even sometimes suffering from pain in their legs, made patients not to choose this type of anesthesia for the second delivery. Thus, performing spinal anesthesia is often limited by the patients who want to remain awake during surgery [2]. The purpose of sedation in spinal anesthesia is to alleviate patients’
anxiety, give them more satisfaction with anesthesia and to
prevent their body movement. An ideal sedative drug
results in an acceptable decrease in awareness during the
procedure, without any side effect [3-4]. Any sedation
protocol within cesarean section under spinal anesthesia
could soothe mothers and give them more satisfaction.
But, at present time there is no real consensus of sedation
protocol for cesarean section under spinal anesthesia [3].
A good sedation protocol for this purpose should be safe
and effective and, in addition to mothers’ sedation within
the surgery, it would keep the mother airway open.
Moreover, it should not disturb the fetus oxygenation,
Apgar score and umbilical cord pH.

Conscious sedation is a minimally depressed level of
consciousness providing an independent and constant
breathing for patients and it makes them able to respond
appropriately to physical stimulation and verbal
command using mere pharmacologic or non-
pharmacologic method or a combination of both [5]. Due
to some probable adverse neonatal outcomes associated
with sedative drugs administered for spinal anesthesia
during cesarean section such as Ketamin, Midazolam,
Diazepam, Propofol, and fentanyl [6-8], they have been
mostly used after baby’s birth. The infant low Apgar
score and mother hallucination have been reported as the
negative effects of Ketamine used before delivery [9].
However, most post-spinal anesthesia complications and
mother’s discomforts occur at the first moments after
spinal anesthesia before delivery. So far, a few studies
carried out in order to find a safe pre-delivery drug with
low side effects for maternal sedation in cesarean section
[8,10].

Thiopental Na is an ultra-short-acting barbiturate
and has been commonly injected intravenously at the dose
of 4-5mg/Kg in the induction phase of general anesthesia for
cesarean section [11], without any adverse effect on
neonatal Apgar score. It has been used at a sub anesthetic
dosage for sedation in different surgeries and diagnostic
or therapeutic processes [5,13]. With these
considerations, in this study we aimed to find out: 1) the
effectiveness of low dose Thiopental Na as a sedative
drug, by assessing mother’s satisfaction and 2) the lowest
dose of Thiopental Na that provides the highest
satisfaction with safety for both mother and the infant.

To the best of our knowledge, this study is the first
clinical trial assessing sedation with Thiopental Na
during spinal anesthesia for CS.

**Methods**

**Trial design**

This balanced randomized double-blind, placebo-
controlled trial study was performed at Arash Hospital,
Tehran, Iran, from July to August 2014. Informed
consent was obtained from all participants before any
study-related tests and the study protocol was approved
by Institutional Review Board and Ethics Committee of
the Tehran University of Medical Sciences. Also the
study was registered in Iranian Registry of clinical Trial
(www.irct.ir) by the number of IRCT2014011116162N1.

**Participants**

Inclusion criteria were: normal history of pregnancy,
ASA physical status I, II and primly parity. Pre-anesthetic
assessments were performed.

Patients with bleeding disturbance, gross abnormality
in vertebral column, infection in the injection site, liver
or kidney diseases, hypertension, preeclampsia and using
anticoagulant were excluded from the study.

**Randomization**

Assignment to therapy or placebo was performed using
computer-generated randomization scheme with 1:1:1:1
allocation in random blocks of 6. Randomization
procedure was performed by the clinical trial
epidemiologist, who kept the codes until completion
of the study. Participants, care providers and those assessing
the outcomes were blinded.

**Intervention**

The baseline blood pressure, heart rate, and SaO2
(saturation of O2 in arterial blood) were measured. The
intravenous cannula was opened and then the patient was
pre-loaded with serum Ringer’s 10 ml/kg +100 ml within
20-30 minutes. The spinal block was done with a 25G
Quincke (B. Braun Germany) spinal needle in the L3-L4
interspaced in sitting position with 0.5% solution of
Bupivacaine 15 mg (Marcain spinal heavy 0.5%; Astra
Zeneca, Istanbul, Turkey). Then mother was turned to
supine position and a pillow was placed under the head.
After 1 min, 0.25, 0.5, 0.75mg/kg/IV of Thiopental Na
was injected to groups I, II, III respectively and 1.5CC of
sterile water as placebo was injected in group IV. All
injection volumes were increased to 1.5CC by adding
sterile water. After measuring mothers’ satisfaction, If
mothers suffered from discomfort, 2mg of Midazolam as
anxiolytic drug was injected via intravenous line after
delivery. Hypotension after spinal anesthesia was defined
as systemic blood pressure lower than 90 mmHg or less
than 30% of basal line and, it was managed with 10 mg
of Ephedrine which increased gradually up to 50 mg.
Bradycardia (HR<60 beat/min) was treated with 0.5mg
of atropine which was repeated for 3 times.

**Outcomes**

The level of consciousness and mother’s satisfaction
were considered as primary outcomes. Level of
consciousness was measured continuously from 30
second after thiopantal injection of up to 10 min with
observer assessment of alertness/sedation score (OAA/S)
(Table 1) [14]. The scores of mother’s satisfaction was
measured using the maternal satisfaction score shown in
(Table 2) [3]. We considered score 0-1-2 for each
parameter and categorized patient’s score as follow:
highly satisfied between 8-10 score, fairly satisfied
between 5-7 score, and not satisfied with the score of below 5.

Blood pressure, Gag reflex, SaO2, end tidal CO2 (EtCO2), heart rate, memory, Apgar score and cord pH were measured as secondary outcomes and controlled by an observer from the beginning of the surgery up to leaving the recovery room.

Table 1 - Consciousness with observer assessment of alertness/ sedation score

<table>
<thead>
<tr>
<th>Observation</th>
<th>Score level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responds readily to name spoken in normal tone</td>
<td>5</td>
</tr>
<tr>
<td>Lethargic response to name spoken in normal tone</td>
<td>4</td>
</tr>
<tr>
<td>Responds only after name is called loudly and/or repeatedly</td>
<td>3</td>
</tr>
<tr>
<td>Responds only after mild prodding or shaking</td>
<td>2</td>
</tr>
<tr>
<td>Does not respond to mild prodding or shaking</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2- Levels of Mother’s satisfaction

<table>
<thead>
<tr>
<th>Parameter</th>
<th>*Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>No Nausea</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>No pain</td>
</tr>
<tr>
<td>Restlessness</td>
<td>Calm quiet</td>
</tr>
<tr>
<td>Limb Discomfort</td>
<td>No</td>
</tr>
<tr>
<td>Shivering</td>
<td>No</td>
</tr>
</tbody>
</table>

*The scores of mothers satisfaction were set as highly satisfied (8< score >10), fairly satisfied (5< score >7), and not satisfied (score < 5)

Sample size

Sample size calculation was based on detecting a minimum difference of one regarding to the mean values of primary outcome (satisfaction score) between treatment groups. Such a difference can be detected at the 0.05 level of statistical significance with 80% power with a sample size of 242 patients allocated to four groups.

Statistical analysis

The intent-to-treat (ITT) was used in primary and secondary efficacy analyses. Patients and study characteristics expressed as mean± (SD) or percentages as appropriate. The Chi square and Student's t tests were used to compare differences between control and intervention groups at baseline. An analysis of covariance (ANCOVA) was used to compare primary and secondary outcomes with the age, BMI and parity as the covariates, and included treatment as fixed effect in the model, with Duncan multiple range test approach as adjustment for multiple comparisons. All tests were 2-sided and the difference between study groups was considered significant when the P value was <0.05. Data were analyzed using Statistical Package for the Social Science version 18 (SPSS, Chicago, IL, USA).

Results

Between July and August, 2014, three hundred and thirty-eight volunteers were screened for inclusion in the study. Ninety-six subjects were removed from the study after the first interview and were excluded. Two hundred and forty-two women were randomly allocated treatment and one placebo group. (Figure1) shows the trial profile. The four groups were similar with regards to demographics and baseline characteristics (Table 3).

The patients’ score regarding satisfaction and sedation after treatment among four study groups is shown in (Table 4). There were significant differences between groups regarding satisfaction score (F3, 235=5.84, p=0.001). A post hoc test showed that the patients treated with 0.75 mg/kg (group III) had significantly higher satisfaction score compared to other groups except group II (0.50mg). In contrast, there were no significant differences between placebo (group IV) and both of group I (0.25mg) and group II (0.50mg) (Figure 2).
Figure 1 - Flowchart showing participants and groups disposition

Assessed for eligibility (n=338)

- Excluded (n=96)
  - Not meeting inclusion criteria

Randomized (n=242)

- Allocated to 75 gr Thiopental (n=60)
- Allocated to 50 gr Thiopental (n=60)
- Allocated to 25 gr Thiopental (n=61)
- Allocated to Placebo (n=61)

- Lost to follow-up (n=0)
- Lost to follow-up (n=0)
- Lost to follow-up (n=0)
- Lost to follow-up (n=0)

- Analysed (n=60)
- Analysed (n=60)
- Analysed (n=61)
- Analysed (n=61)

Figure 2 - Means of satisfaction score in patients in four study groups after treatment
Figure 3- Means of sedation score in patients in four study groups after treatment

![Figure 3](image_url)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group (Placebo) (n=61)</th>
<th>Group I (25mg) (n=61)</th>
<th>Group II (50mg) (n=60)</th>
<th>Group III (75 mg) (n=60)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>27.57 ± (4.89)</td>
<td>26.98 ± (5.4)</td>
<td>27.1 ± (4.84)</td>
<td>26.91 ± (4.31)</td>
<td>0.87</td>
</tr>
<tr>
<td>BMI</td>
<td>29.5 ± (4.63)</td>
<td>31.03 ± (3.93)</td>
<td>31.66 ± (4.13)</td>
<td>29.62 ± (3.98)</td>
<td>0.87</td>
</tr>
<tr>
<td>Parity</td>
<td>1.4 ± (0.58)</td>
<td>1.34 ± (0.57)</td>
<td>1.41 ± (0.59)</td>
<td>1.35± (0.7)</td>
<td>0.35</td>
</tr>
<tr>
<td>Hypotension Yes</td>
<td>47 (77)</td>
<td>54 (88.5)</td>
<td>42 (70)</td>
<td>43 (71.7)</td>
<td>0.067</td>
</tr>
<tr>
<td>Hypotension No</td>
<td>14 (23)</td>
<td>7 (11.5)</td>
<td>18 (30)</td>
<td>17 (28.3)</td>
<td></td>
</tr>
<tr>
<td>Gag R Yes</td>
<td>61 (100)</td>
<td>61 (100)</td>
<td>59(98.3)</td>
<td>58 (96.7)</td>
<td>0.28</td>
</tr>
<tr>
<td>Gag R No</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1.7)</td>
<td>2 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Respiratory function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPO2&gt; 94%</td>
<td>59 (98.3)</td>
<td>61 (100)</td>
<td>60 (100)</td>
<td>57 (95)</td>
<td>0.002</td>
</tr>
<tr>
<td>SPO2&lt;94%</td>
<td>1 (1.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (5)</td>
<td></td>
</tr>
<tr>
<td>Bradycardia Yes</td>
<td>26 (42.6)</td>
<td>17 (27.9)</td>
<td>24 (40)</td>
<td>17 (28.3)</td>
<td>0.19</td>
</tr>
<tr>
<td>Bradycardia No</td>
<td>35 (57.4)</td>
<td>44 (72.1)</td>
<td>36 (60)</td>
<td>43 (71.7)</td>
<td></td>
</tr>
<tr>
<td>Remembering the infant Yes</td>
<td>61 (100)</td>
<td>60 (98.4)</td>
<td>58 (96.7)</td>
<td>60 (100)</td>
<td>0.29</td>
</tr>
</tbody>
</table>
Also sedation scores were different between groups (F3, 235=16.78, p<0.001). Patients in placebo group remarkably had higher score compared with other groups except group I (0.25 mg). There was significant difference between group I (0.25mg) and group II (0.50mg). But there was no significant difference between group II (0.50mg) and group III (0.75mg) (Figure 3).

As we can see in (Table 3), all babies were healthy without any complication and the Apgar scores were significantly similar in four groups (p=0.52). A few patients suffered from nausea and vomiting within or after the procedure (8, 2, 4 and 5 patients in placebo and I, II, III groups respectively, p=0.68). Frequency of impaired gag reflex was very low and only one patient in group II and two patients in group III were affected which was not obviously significant (p= 0.28). There were some episodes of respiratory depression (Spo2<94%) in three patients in group III and one patient in group IV which was not statistically significant (p = 0.002) and, all were treated by verbal stimulation at the time of the surgery. There was just one patient with apnea in group II who was treated by positive pressure ventilation. All women could remember their infants. No significant changes (p>0.05) were observed in other variables such as hypotension, bradycardia, cord pH and Etco2 between four groups during operation (Table 3).

**Discussion**

Today, spinal anesthesia is preferred over general anesthesia for CS. Many efforts have been made to modify this procedure in order to make it more interesting to mothers and to minimize side effects.
This study was conducted to find an appropriate conscious sedation method for spinal anesthesia that is safe for women undergoing caesarian section and for their newborns. In this regard, as thiopental Na has been administered in other operations [5,12-13] as a safe sedative agent, a single bolus of thiopental Na was administered one minute after spinal anesthesia to induce conscious sedation and enhance the mothers’ satisfaction. On the other hand, since there were concerns about over sedation in mothers, three different doses of thiopental were administered to determine the most effective dose that provided the highest satisfaction beside being safe (no deep sedation). The results of the present study demonstrated that mothers’ satisfaction improved by conscious sedation with 0.5 and 0.75 mg/kg of thiopental Na (group II and III). This result was noticeably better than previous studies in which mothers were highly satisfied with low doses of diazepam and pethidine as sedative drugs for cesarean section [1]. Comparison of the results revealed that the ideal sedation scores of III and IV were also observed in groups II and III that received 0.5 and 0.75 mg/kg thiopental Na. Admittedly, post hoc test indicated a significant difference in the satisfaction and sedation score among four groups except group III and IV. We demonstrated that higher dose of thiopental (0.5 and 0.75 mg/kg) improved the mothers’ satisfaction significantly with no over sedation and other side effects and administering higher dose of drugs was accompanied by a higher incidence of side effects such as over sedation and dizziness. The authors suggest the use of 0.5 mg/kg thiopental Na to improve the mother’s satisfaction and lower side effects. Therefore, this study proved that a single dose of 0.5 mg/kg thiopental Na was an appropriate and safe dose to sedate mothers during spinal anesthesia.

The safety of the drug for newborns was another concern of the present study. Since higher doses of thiopental Na are the choice for general anesthesia induction in CS [11], the safety of this drug for the fetus has been confirmed. However, in order to evaluate the safety of this type of sedation in newborns, the Apgar score was measured one minute after birth. The results indicated that thiopental Na at a dose of 0.75 mg/kg was safe for newborns. Therefore, this dose of thiopental Na can be administered for sedation in CS before delivery to improve the mothers’ satisfaction. This is while most sedative drugs are injected after birth during CS.

Breathing was monitored in mothers under sedation through checking SPO2 and EtCO2 in this study. Mild oxygen desaturation (SaO2<94%) was observed in 5% of the patients in group III and the safety of our sedation protocol was remarkably better than a study by Saha et al in which 13.3% of the cases had mild oxygen desaturation [3] and a study by Riavis et al that found 10% of cases had transient oxygen desaturation [15]. Although a transient fall in SPO2 up to 90% has no significant effect on tissue oxygenation, less desaturation is more preferable for clinicians and the results of this study indicated that thiopental Na could prevent desaturation during spinal anesthesia.

Sedation was assessed 30 seconds after drug administration for two reasons: 1- approximately 50% of thiopental is non-ionized at physiologic pH, which accounts partly for the rapid accumulation of thiopental in the cerebrospinal fluid (CSF) after IV administration, and 2- an effective factor in the speed of drug penetration into the blood-brain barrier is the plasma drug concentration, which causes a concentration gradient. Two primary determinants of the plasma concentration are the dose administered and the rate (speed) of administration. Clinically, patients awaken 5 to 10 minutes after administering a single dose of thiopental, as the drug is redistributed from highly perfused CNS tissues to well-perfused lean tissues; therefore, we monitored the sedation score for up to 10 min.

The OAAS score was selected for the assessment of sedation levels rather than using other scales suggested by previous studies that require patient stimulation for each assessment [16]. An OAAS score of 3 or 4 were the main objective of the present study [17], which was found in 38.3% and 18.33% of the subjects in group III, respectively. This finding was comparable to the results of other studies like a study by Nishiyama et al in which propofol infusion was used for sedation during spinal anesthesia [18]. The authors suggested that the maintenance infusion dose of propofol to keep the OAAS score at 3 or 4 was about 2.5 mg/kg/h, and about 60% of the patients had a score of 4 and 35% had a score of 3 in their study. Although our results indicated lower efficacy, the use of propofol before delivery for cesarean section is still controversial.

In addition, maternal recall of infant birth was considered as it is one of the foremost rewards of regional anesthesia. Maternal responses to our two simple questions revealed that the sedation technique practiced in this assay was not associated with maternal amnesia and most mothers in all three groups expressed more pleasant recalls of the infant birth. These findings were consistent with the results of a study conducted by Frolic et al [7].

Our findings regarding the stability of the hemodynamic status after using thiopental Na were in accordance with the results of studies by Patki et al and Sen el et al in which midazolam and propofol as sedative drugs did not alter the baseline cardiovascular variables [8,17].

To the best of our knowledge, this study is the first clinical study that suggests that thiopental Na is a safe and useful drug for sedation in mothers undergoing spinal anesthesia during CS. Therefore, it is not possible to compare the results with other trials. Thus, further studies
are needed to determine the safest and the most effective dose of thiopental Na.

**Conclusion**

Pre-operative well-being of patients depends on several factors, the most important of which is patients’ mental status and attitude towards the whole procedure. According to this evaluation, Thiopental Na as the most commonly used sedative agent in our department for cesarean sections leads to mild–moderate levels of sedation (conscious sedation), maternal satisfaction, no hemodynamic disturbance and no adverse neonatal effects.

**References**


