

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

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ARTICLE INFO

Article history:

Received 06 May 2019

Revised 28 May 2019

Accepted 12 June 2019

Keywords:

Sedation;

Thiopental Na;

Spinal anesthesia;

Cesarean section;

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'

The authors declare no conflicts of interest.

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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 (Marcaïn 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 an 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

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

Table 2- Levels of Mother's satisfaction

Parameter	*Score		
	2	1	0
Nausea/Vomiting	No Nausea	Nausea	Vomiting
Chest Pain	No pain	Heaviness	Pain
Restlessness	Calm quiet	Apprehended	Restless
Limb Discomfort	No	Mild	Severe
Shivering	No	Mild	Severe

*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

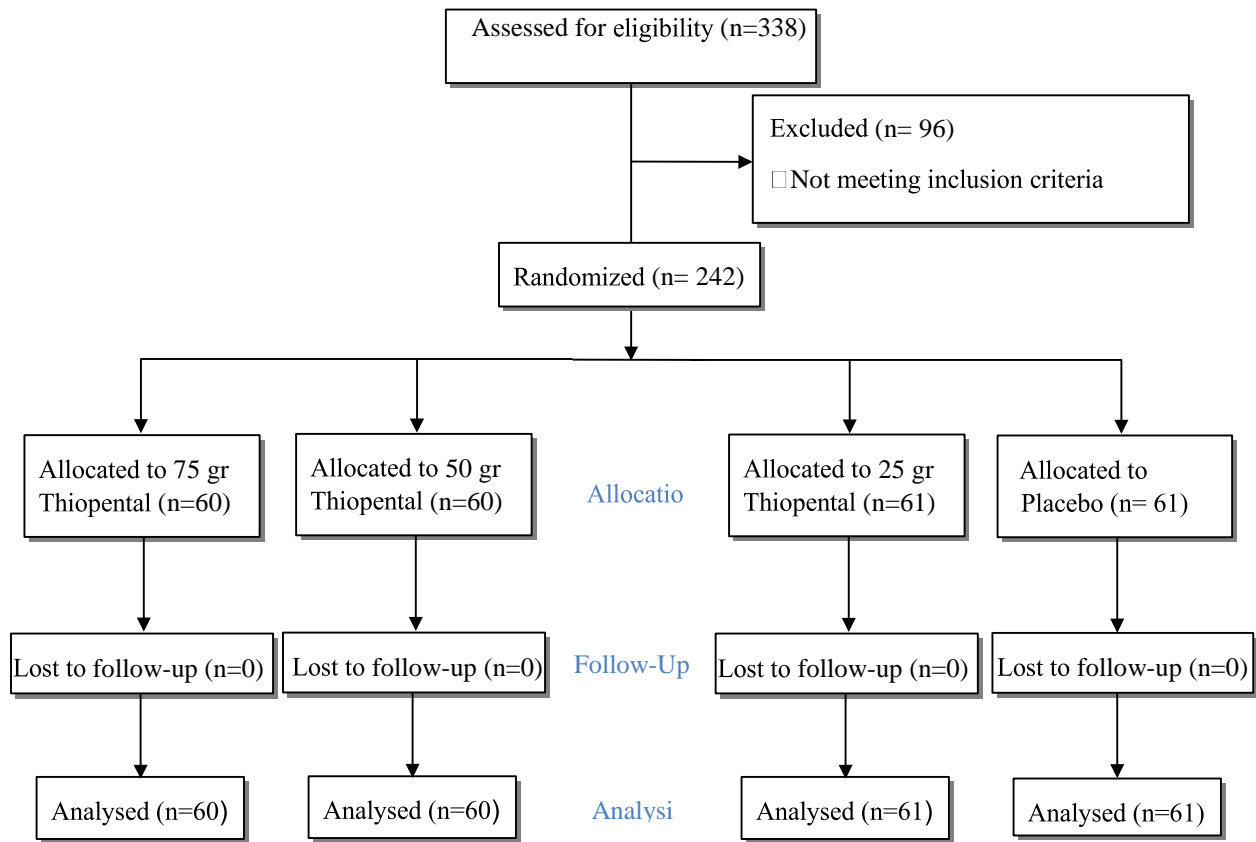


Figure 2- Means of satisfaction score in patients in four study groups after treatment

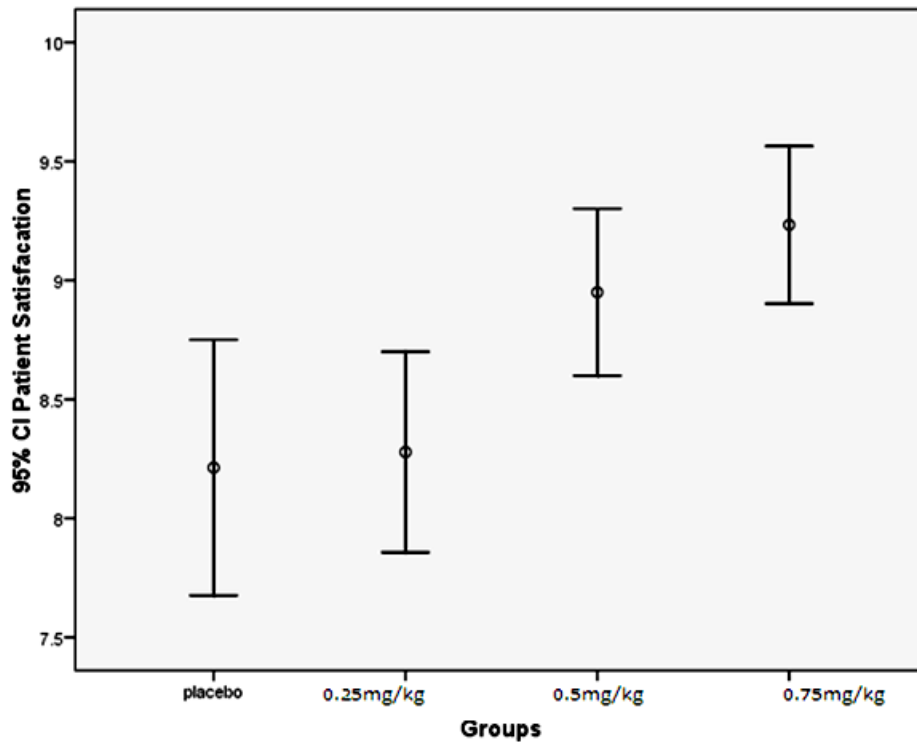


Figure 3- Means of sedation score in patients in four study groups after treatment

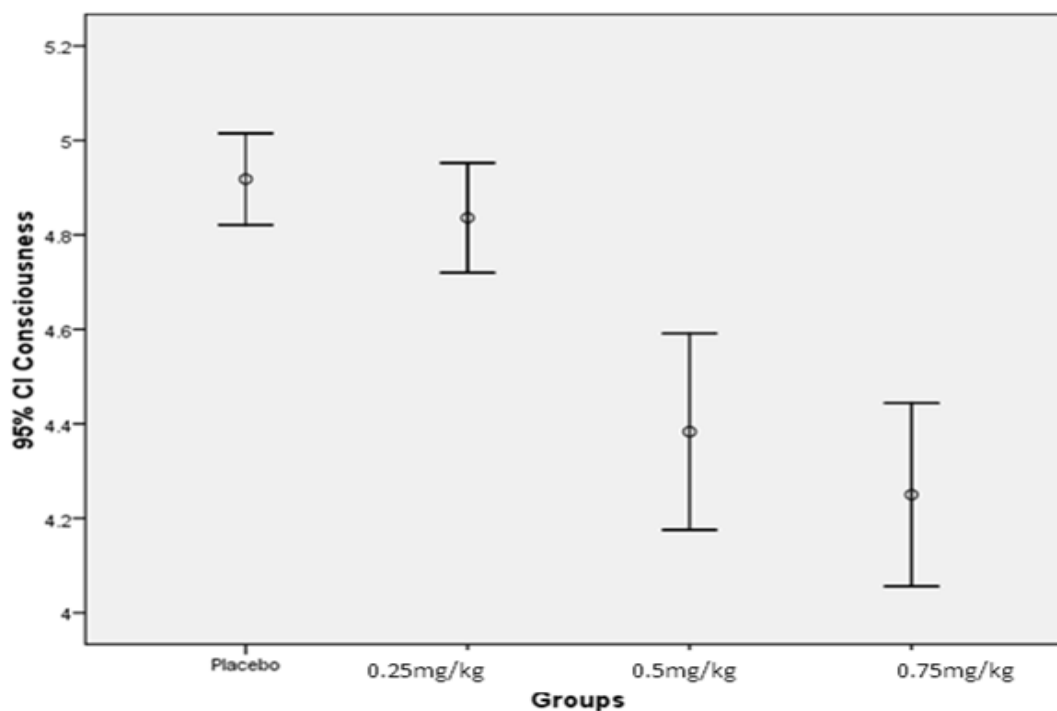


Table 3- Baseline demographics and disease characteristics of all participants

Variable	Group (Placebo) (n=61)	Group I (25mg) (n=61)	Group II (50mg) (n=60)	Group III (75 mg) (n=60)	P-value
Age	27.57 ± (4.89)	26.98 ± (5.4)	27.1 ± (4.84)	26.91 ± (4.31)	0.87
BMI	29.5 ± (4.63)	31.03 ± (3.93)	31.66 ± (4.13)	29.62 ± (3.98)	0.87
Parity	1.4 ± (0.58)	1.34 ± (0.57)	1.41 ± (0.59)	1.35 ± (0.7)	0.35
Hypotension					
Yes	47 (77)	54 (88.5)	42 (70)	43 (71.7)	0.067
No	14 (23)	7 (11.5)	18 (30)	17 (28.3)	
Gag R					
Yes	61 (100)	61 (100)	59 (98.3)	58 (96.7)	0.28
No	0 (0)	0 (0)	1 (1.7)	2 (3.3)	
Respiratory function					
SPO ₂ > 94%	59 (98.3)	61 (100)	60 (100)	57 (95)	0.002
SPO ₂ <94%	1 (1.7)	0 (0)	0 (0)	3 (5)	
Bradycardia					
Yes	26 (42.6)	17 (27.9)	24 (40)	17 (28.3)	0.19
No	35 (57.4)	44 (72.1)	36 (60)	43 (71.7)	
Remembering the infant					
Yes	61 (100)	60 (98.4)	58 (96.7)	60 (100)	0.29

No	0 (0)	1 (1.6)	2 (3.3)	0 (0)	
Apgar					
8-10	60 (98.4)	59 (96.7)	60 (100)	58 (96.7)	0.52
<8	1 (1.6)	2 (3.3)	0 (0)	2 (3.3)	
Midazolam					
Yes	53 (86.9)	47 (77)	45 (75)	39 (65)	0.046
No	8 (13.1)	14 (23)	15 (25)	21 (35)	
Cord PH_					
PH>7.3	60 (100)	60 (100)	60 (100)	59 (98.3)	0.39
PH<7.3	0 (0)	0 (0)	0 (0)	1 (1.7)	
EtCO2					
35-45 mmHg	60 (100)	60 (100)	59 (98.3)	60 (100)	0.39
>45mmHg	0 (0)	0 (0)	1 (1.7)	0 (0)	

Values are given as mean \pm SD or number (percentage) unless otherwise indicated

Table 4- patients' scores regarding to satisfaction and sedation among the four study groups

		Group (Placebo) (n=61)	Group I (0.25mg) (n=61)	Group II (0.50mg) (n=60)	Group III (0.75 mg) (n=60)	P-value
Satisfaction score	Not satisfied	9 (14.8)	5 (8.2)	2 (3.3)	3 (5)	p=0.001
	Fairly satisfied	7 (11.5)	11 (18)	6 (10)	1 (1.7)	
	Highly satisfied	45 (73.8)	45 (73.8)	52 (86.7)	56 (93.3)	
Sedation score	I	0 (0)	0 (0)	0 (0)	0 (0)	p<0.001
	II	0 (0)	0 (0)	1 (1.7)	0 (0)	
	III	2 (3.3)	2 (3.3)	9 (15)	11 (18.3)	
	IV	1 (1.6)	6 (9.8)	16 (26.7)	23 (38.3)	
	VI	58 (95.1)	53 (86.9)	34 (56.7)	26 (43.3)	

Values are given as frequency (percent)

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 ($Spo_2<94\%$) 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

- [1] Hawkins JL, Koonin LM, Palmer SK, Gibbs CP. Anesthesia-related deaths during obstetric delivery in the United States, 1979-1990. *Anesthesiology*. 1997; 86(2):277-84.
- [2] Sener EB, Guldogus F, Karakaya D, Baris S, Kocamanoglu S, Tur A. Comparison of neonatal effects of epidural and general anesthesia for cesarean section. *Gynecol Obstet Invest*. 2003; 55(1):41-5.
- [3] Saha DK, Rahman M, Sarkar PC, Banik D, Hudaak Q, Begum F. The effect of low dose pethidine and diazepam for sedation in Cesarean Section under Sub-Arachnoid Block on mothers' satisfaction. *Bangladesh Journal of Obstetrics & Gynaecology*. 2009; 24(1):10-3.
- [4] Pollock JE, Neal JM, Liu SS, Burkhead D, Polissar N. Sedation during spinal anesthesia. *Anesthesiology*. 2000; 93(3):728-34.
- [5] American Society of Anesthesiologists Task Force on S, Analgesia by N-A. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology*. 2002; 96(4):1004-17.
- [6] Shahriari A, Khooshideh M, Heidari MH. Prevention of nausea and vomiting in caesarean section under spinal anaesthesia with midazolam or metoclopramide? *J Pak Med Assoc*. 2009; 59(11):756-9.
- [7] Frölich MA, Burchfield DJ, Euliano T, Caton D. A single dose of fentanyl and midazolam prior to Cesarean section have no adverse neonatal effects. *Can J Anaesth*. 2006; 53(1):79-85.
- [8] Senel AC, Mergan F. Premedication with midazolam prior to caesarean section has no neonatal adverse effects. *Braz J Anesthesiol*. 2014; 64(1):16-21.
- [9] Sen S, Ozmert G, Aydin ON, Baran N, Caliskan E. The persisting analgesic effect of low-dose intravenous ketamine after spinal anaesthesia for caesarean section. *Eur J Anaesthesiol*. 2005; 22(7):518-23.
- [10] Cheng YJ, Wang YP, Fan SZ, Liu CC. Intravenous infusion of low dose propofol for conscious sedation in cesarean section before spinal anesthesia. *Acta Anaesthesiol Sin*. 1997; 35(2):79-84.
- [11] Birnbach DJ, Browne IM. *Anesthesia for obstetrics, Miller's anesthesia*. Philadelphia: Churchill-Livingstone; 2010.
- [12] Lee-Jayaram JJ, Green A, Siembieda J, Gracely EJ, Mull CC, Quintana E, et al. Ketamine/midazolam versus etomidate/fentanyl: procedural sedation for pediatric orthopedic reductions. *Pediatr Emerg Care*. 2010; 26(6):408-12.
- [13] Akhlaghpour S, Shabestari AA, Moghdam MS. Low dose of rectal thiopental sodium for pediatric sedation in spiral computed tomography study. *Pediatr Int*. 2007; 49(3):387-91.
- [14] Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, et al. Validity and Reliability of the Observer's: Assessment of Alertness/Sedation Scale: Study with: Intravenous Midazolam. *J Clin Psychopharmacol*. 1990; 10(4):244-51.
- [15] Riavis M, Laux-End R, Carvajal-Busslinger MI, Tschappeler H, Bianchetti MG. Sedation with intravenous benzodiazepine and ketamine for renal biopsies. *Pediatr Nephrol*. 1998; 12(2):147-8.
- [16] Nishiyama T. Propofol infusion for sedation during spinal anesthesia. *J Anesth*. 2007; 21(2):265-9.
- [17] Patki A, Shelgaonkar VC. A comparison of equisedative infusions of propofol and midazolam for conscious sedation during spinal anesthesia - a prospective randomized study. *J Anaesthesiol Clin Pharmacol*. 2011; 27(1):47-53.
- [18] Nishiyama T. Propofol infusion for sedation during spinal anesthesia. *J Anesth*. 2007; 21(2):265-9.