A PROSPECTIVE, RANDOMIZED COMPARISON OF THE EFFECTS OF THIOPENTAL AND PROPOFOL ON BISPECTRAL INDEX DURING CAESAREAN SECTION TILL DELIVERY OF NEWBORN

Arzu Mercan*, Hala El-Kerdawy*, Mohamed Khalil*, Hannan Al-Subaie**, Hassan Salem Bakhamees*

Abstract

Background: Since in caesarean operations skin incision to delivery time is very short, induction agent could be still effective on BIS level till the time of delivery. Therefore this study was designed to analyze the effect on maintaining adequate bispectral index levels till delivery of neonate of propofol and thiopental as an induction agent for caesarean section.

Methods: Eighty two patients undergoing caesarean section were allocated into two groups. In the group T anesthesia induction was performed with thiopental (5 mg/kg) and in the group P with propofol (2.5 mg/kg). Anesthesia was maintained with sevoflurane. Heart rates, blood pressures and BIS values during significant events of surgery and anesthesia till delivery, durations of surgery, induction to skin incision and to delivery and Apgar scores were recorded. For statistical analysis T-test was used for comparison of means of independent samples.

Results: The groups were comparable with respect to age, weight and gestational age. The patients in the group P had significantly lower levels of bispectral index values during uterus incision; 40.6 vs. 59.5 ($p = 0.019$) and delivery; 41 vs. 62.9 ($p = 0.018$).

Conclusion: Anesthesia induction with propofol in a dose of 2.5 mg/kg maintains lower levels of heart rate, blood pressure and BIS till delivery when compared with thiopental in a dose of 5 mg/kg.

There is no financial support taken from any kind of company or person. There are no financial relationships between authors and commercial interests with a vested interest in the outcome of study.

Key words: caesarean; sevoflurane; induction; bispectral index; propofol; thiopental.

Introduction

The bispectral index (BIS) is widely used to monitor the depth of anesthesia and values lower than 60 indicate a low probability of intraoperative awareness[1-7]. Most researchers focus on the period after the delivery of neonate and they studied the BIS levels as an indicator of adequate depth of anesthesia[8,9]. For the last decade BIS guided maintenance of anesthesia instead of having a target anesthetic concentration is advocated to prevent anesthesia awareness while allowing decreased anesthetic usage especially in the population having high risk of awareness

* Consultant of Anesthesiology, Saad Specialist Hospital, Department of Anesthesiology.
** Consultant of Obstetrics and Gynecology, Saad Specialist Hospital, Department of Obstetrics and Gynaecology.
Correspondence to: Dr. Arzu Mercan, Department of Anesthesiology, Saad Specialist Hospital, P.O. Box 30353, Al-Khobar, 31952, Kingdom of Saudi Arabia, Tel: 00 966 03 801 2218. E-mail: arzumercan66@hotmail.com.

and most importantly decreasing the morbidity and mortality related with surgery[10-13]. Considering that in caesarean operations skin incision to delivery time is a short period of time, till the time of delivery induction agent could be still effective on BIS level which in turn let one to use lower inhalational anesthetics. Effect on the BIS levels till delivery of the anesthetic induction agent has not yet been studied. Although thiopental is known to be the drug of choice for anesthesia induction of caesarean section operations[14], propofol has also been used for the same purpose[15-17]. Therefore this prospective, randomized study was designed to test the hypothesis that induction agent for caesarean section could be effective on maintaining adequate BIS levels till the delivery of neonate. With this purpose the effect of propofol and thiopental as an induction agent for caesarean section on maintaining adequate BIS levels till the delivery was compared.

Materials and Methods

The prospective, randomized, clinical study was performed between January 2009 and December 2009 at Saad Specialist Hospital, Saudi Arabia. After the Ethics Committee of the hospital had given approval and the patients had given written informed consent, 82 nulliparous parturients were recruited to the study. All the participants were in physical status class I-II according to the American Society of Anesthesiologists guidelines at full term who requested general anesthesia for their elective caesarean section. Following premedication with ranitidine at 50 mg and metocloropromide at 20 mg intravenously in the holding area the patients were assigned randomly to one of the two treatment groups by one of the authors (MK), using a computer-generated randomization table. The treatments were differentiated by the induction agent (thiopental or propofol).

The exclusion criteria were: any previous anesthesia received before the current surgery, parturient with preterm or multiple gestations, fetal distress, and any requirement to administer a drug that was not in the study protocol.

Medications for induction were given via covered syringes by the same anesthetist (MK) who did the randomization. He left the operating theatre right after the induction. All other authors were blinded to the randomization and the induction agents. One of the authors (HE) other than the in charge one who was unaware of any medication given observed the monitor and recorded the precise time of the specific surgical events staying over the surgical side of the screen at all times. The third anesthetist (AM) was in charge of the patient.

Routine monitoring devices (5-lead electrocardiogram, non-invasive blood pressure, and pulse oxymetry-Dräger Infinity Delta XL) were applied. Level of muscle blockade was monitored by using train-of-four stimulation of the ulnar nerve (Dräger, model Infinity Trident). EEG data were acquired continuously and recorded by using BIS monitor (Aspect Medical Systems produced to be used with appropriate Dräger devices, Norwood USA) with its recommended electrode. The BIS electrodes were placed properly according to the manufacturer's recommendation.

Baseline values of hemodynamic variables and BIS were obtained. Following urinary catheterization and surgical draping of the patient, rapid sequence induction with preoxygenation was performed with 5 mg/kg thiopental and 1-1.5 mg/kg succinylcholine in the group T (n = 42), and 2.5 mg/kg propofol and 1-1.5 mg/kg succinylcholine in the group P (n = 40). The doses were calculated on the basis of prepregnancy weight of the patients. An expiratory concentration of sevoflurane of 1% was maintained with a Zeus Anesthesia workstation (Dräger Medical, Lübeck, Germany) in auto control mode with nitrous oxide 50% in oxygen (O_2) till delivery. Controlled ventilation was used to maintain the end-tidal pressure of carbon dioxide ($ETCO_2$) between 32 and 35 mmHg. The patients were monitored throughout anesthesia with respect to their heart rate, $ETCO_2$, percentage of oxygen saturation, inspiratory and expiratory concentrations of the anesthetic agent, and body temperature. Muscle relaxation was obtained with atracurium with an initial bolus of 20 mg and additional boluses as necessary. After delivery 20 IU of oxytocine is given with ongoing intravenous fluid as infusion to avoid any adverse effects. Whenever heart rate or blood pressure higher than 20% of baseline value was detected after delivery of newborn, 1 μg/kg fentanyl was given as an intravenous bolus. Ringer's Lactated solution at

a constant rate of 999 mL/hour was given through the surgery. In case of intraoperative hypotension, 20% decrease in blood pressure from baseline value; ephedrine in boluses of 5 mg were given. Immediately after skin closure, anesthetic gases were ceased and system was flushed with flush function of the anesthesia machine. Muscle blockade had been reversed if Train of Four ratio was between 0.3 and 0.7 with neostigmin and glycopyrrolate. Controlled ventilation of 100% O_2 at 6 L/min was maintained. Patients were extubated with the return of cough reflex followed by spontaneous regular breathing, facial grimacing and purposeful movements; they were followed in the recovery unit until the modified Aldrete score was 9-10.

Values of BIS, non-invasive blood pressure and heart rate were recorded at the following times: before anesthesia induction, after endotracheal intubation, at skin and uterine incision, at neonatal delivery, and at 5 minutes after delivery. One of the authors (HE) recorded the precise time of the specific surgical events staying over the surgical side of the screen at all times. At the end of operation the same anesthetist (HE) recorded heart rate, blood pressure and BIS values from the computerized recordings printed out from the monitor (Dräger Infinity Delta XL) matching their specific timing. Other values recorded manually included neonatal Apgar scores for 1st and 5th minute, ephedrine requirement, estimated blood loss, time for skin incision and delivery after induction, operation duration.

Power analysis was carried out using the software G*Power 3.0® (Institute of Experimental Psychology, Heinrich-Heine-University, Dusseldorf, Germany), when power (1-β) is 95%, α error probability is 0.05, and the effect size 0.82, the total sample size required was calculated to 66. The statistical analysis was performed using a statistical software package (SPSS 9.01®, SPSS INC. Chicago, IL, USA) and $p < 0.05$ was accepted as statistically significant. All data were recorded as the mean ± standard deviation (SD). T-test was used for comparison of means of independent samples.

Results

The study population comprised 82 partruients who were aged 21-43 years and all were included in the analysis.

The groups were comparable with respect to age, weight and gestational age (Table 1). Induction to skin incision time and to delivery time, duration of surgery, Apgar scores in 1st and 5th minutes, estimated blood loss during the surgery were all comparable in both groups (Table 2). The mean total fentanyl requirement (84 ± 36 μg in group T and 91 ± 33 μg in group P) was similar in both groups. The mean duration of recovery stay in both groups (28 ± 6 minutes in group T and 31 ± 5 minutes in group P) was also statistically comparable.

Table 1
Demographic data of the patients. (Mean ± SD).

	Group T (n = 42)	Group P (n = 40)
Age (years)	30.8 ± 5.1	32.6 ± 4.3
Weight (kilograms)	79 ± 10.5	83.8 ± 10.8
Gestation (weeks)	38.6 ± 0.8	37.5 ± 1.4

Table 2
Surgical data of the patients and mean APGAR scores of the newborns according to the groups (Mean ± SD).

	Group T (n = 42)	Group P (n = 40)
Induction-to-skin incision time (sec)	78.2 ± 16.3	84.4 ± 14.2
Induction-to-uterus incision time (min)	2.9 ± 0.9	3.1 ± 1
Induction-to-delivery time (min)	3.4 ± 1	3.7 ± 0.7
Duration of surgery (min)	38 ± 6	37.1 ± 5
Estimated blood loss (mL)	525 ± 100	480 ± 101
1 min APGAR	8.5 ± 0.5	8.4 ± 0.6
5 min APGAR	9.5 ± 0.5	9.9 ± 0.1

sec: seconds, min: minutes, mL: millilitres

No intra- or postoperative complications were encountered.

Heart rate, systolic blood pressure and BIS values during the significant events of surgery and anesthesia till delivery of neonate were illustrated in Figs. 1, 2

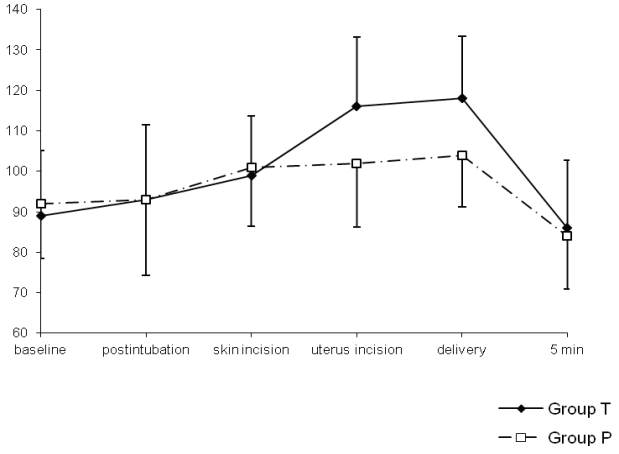
and 3 respectively. The mean values of heart rate and systolic blood pressure were significantly lower in the group P than the group T both during uterus incision and delivery. The mean heart rate levels during uterus incision were 102 ± 17 in the group P and 116 ± 18 in the group T; p = 0.031 and they were 104 ± 12 during delivery in the group P and 118 ± 14 in the group T; p = 0.038. The mean systolic blood pressure values during uterus incision were 126 ± 10 in the group P and 144 ± 11 in the group T; p = 0.024 and they were 128 ± 9 during delivery in the group P and 151 ± 12 in the group T; p = 0.022. The patients in group P had significantly lower levels of BIS values than the patients in group T during uterine incision; 40.6 ± 20 vs. 59.5 ± 25 (p = 0.019) and during delivery; 41 ± 20 vs. 62.9 ± 26 (p = 0.018). While 8 patients (19.4%) in the group T had BIS values between 60 and 65, none in the group P did (p = 0.024). None of the groups had a patient with a BIS value higher than 65.

No ephedrine required during surgery.

Discussion

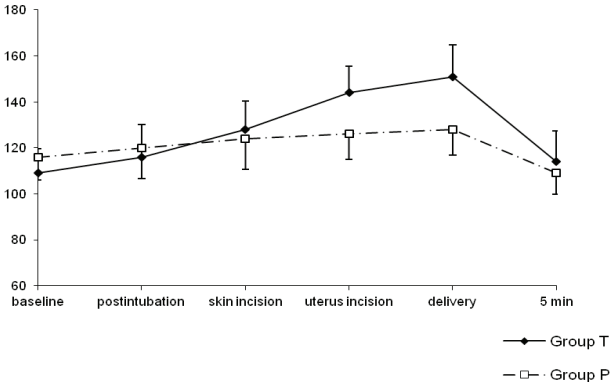
The results of this study revealed that induction agent for caesarean section could be effective on maintaining adequate BIS levels till the delivery of neonate. Furthermore propofol was more effective to keep BIS levels till delivery of newborn lower than thiopental when it was used as an induction agent.

Fig. 1
Mean heart rate levels of the patients during significant events of surgery according to the groups.



*p = 0.031, §p = 0.024
min: minutes
HR: heart rate

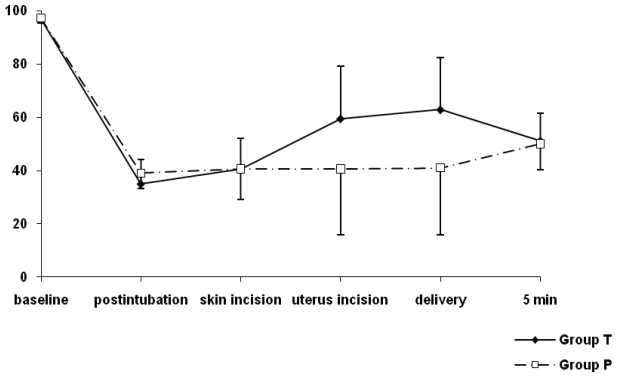
Fig. 2
Mean systolic pressure levels of the patients during significant events of surgery according to the groups.



*p = 0.024, §p = 0.022
min: minutes
SBP: systolic blood pressure

It has been a common practice to administer 0.5 minimum alveolar concentration of a volatile anesthetic in 50% nitrous oxide and introducing opioid after the delivery of neonate during general anesthesia for caesarean section[18-19]. However there is evidence suggesting that 0.5 MAC of volatile anesthetics is not enough in providing adequate anesthesia depth[8]. Chin et al have shown that the use of 1.0% Sevoflurane does not consistently provide adequate BIS values whereas 1.5% Sevoflurane does[8]. Since sevoflurane was reported to affect uterine tonus in a dose related manner[20] in this study sevoflurane was used as Chin et al did[8]. Induction agent might be effective to obtain enough BIS levels till the time of delivery as it is a very short period of time. Many induction agents are being used for caesarean section operations such as thiopental, propofol, ketamine[14-17] and there has not yet been any study published comparing their effect on BIS values before the delivery of newborn. Ok and co-workers have published that BIS value was raised to range of 69 and 72 during delivery when the induction was performed with thiopental[9]. They had their induction to delivery time around 3.6 minutes[9] which is close to the induction to delivery time that was 3.4 minutes encountered in the current study (Table 2). While BIS levels at the time of uterine incision and delivery were 60 or over 60 in the Group T, it was lower than 60 at all times in the Group P (Fig. 3). It is

Fig. 3
Mean BIS levels of the patients during significant events of surgery according to the groups.



*p = 0.019, §p = 0.018
min: minutes

known that propofol has a significantly rapid recovery than thiopental[21,22]. However, in this study a longer effect as an induction agent on maintaining adequate BIS level than thiopental to cover uterine incision and delivery has been obtained (Fig. 3). This may be related to the antanalgesic effect of thiopental[23]. However there is no blood level measurement of the induction agents in this study it is difficult to put forward any mechanism, it is known that barbiturates actually decrease the pain threshold causing antanalgesic effect at low blood levels such as with small induction doses of thiopental or after emergence from thiopental anesthesia when its blood levels are low[23]. Clinically, patients awake from single dose of thiopental 5 to 10 minutes after administration[23]. During uterus incision and delivery blood thiopental levels may be low enough to cause antanalgesic effect. During pregnancy it is well known that volume of blood and plasma increases relatively higher than other components[24]. It is also known that there are changes related with the hemodynamic variables; cardiac output, systemic vascular resistance, heart rate and blood pressure by advancing pregnancy[24]. Those changes may affect one drug's initial distribution or its redistribution half life more than the other causing this result.

Anesthesia awareness has been studied previously and it has been already accepted that BIS values lower than 60 decreases the incidence of awareness[4,11,12]. Since the focus of this study was the effect of induction agents on BIS values Therefore patients in this study were not questioned about awareness after surgery. Furthermore that could initiate different questions about recall or awareness which might be originating from different stages of anesthesia other than the study period. As previously mentioned the focus was the period till delivery after induction in this study. According to the results of this study, propofol for anesthesia induction of caesarean deliveries appeared to be the better option when the BIS levels till the delivery of newborn concerned. Studies with different designs and other available induction agents for caesarean section procedures may improve the adequacy of anesthesia till delivery.

As a conclusion; induction agent chosen, propofol or thiopental, for the anesthesia induction of caesarean section seem to affect the bispectral index levels obtained till the time of delivery; anesthesia induction with propofol in a dose of 2.5 mg/kg maintains lower levels of bispectral index along with heart rate and systolic blood pressure till delivery than thiopental in a dose of 5 mg/kg.

References

1. Sigl JC, Chamoun NG: An introduction to bispectral analysis for the EEG. *J Clin Mont*; 1994, 10(6):392-404.
2. Glass PSA, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P: Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane and alfentanil in healthy volunteers. *Anesthesiology*; 1997, 86(4):836-47.
3. Kearse LA, Rosow C, Zaslavsky A, Connors P, Dershwitz M, Denman W: Bispectral analysis of electroencephalogram predicts conscious processing of information during propofol sedation and hypnosis. *Anesthesiology*; 1998, 88(1):25-34.
4. Avidan MS, Zhang L, Burnside BA, Finkel KJ, Searleman AC, Selvidge JA, Saager L, Turner MS, Rao S, Bottros M, Hantler C, Jacobsohn E, Evers AS: Anesthesia awareness and bispectral index. *N Engl J Med*; 2008, 358(11):1097-1108.
5. Robins K, Lyons G: Intraoperative awareness during general anesthesia for caesarean section. *Anesth Analg*; 2009, 109(3):886-890.
6. Yeo SN, Lo WK: Bispectral index in assessment of adequacy of general anaesthesia for lower segment caesarean section. *Anaesth Intensive Care*; 2002, 30(1):36-40.
7. Chin KJ, Yeo SW: Bispectral index values at sevoflurane concentrations of 1% and 1.5% in lower segment cesarean delivery. *Anesth Analg*; 2004, 98(4):1140-1144.
8. Chin KJ, Yeo SW: A BIS guided study of sevoflurane requirements for adequate depth of anaesthesia in caesarean section. *Anaesthesia;* 2004, 59(11):1064-1068.
9. Ok SJ, Kim WY, Lee YS, Kim KG, Shin HW, Chang MS, Kim JH, Park YC: The effects of midazolam on the bispectral index after fetal expulsion in caesarean section under general anaesthesia with sevoflurane. *J Int Med Res*; 2009, 37(1):154-162.
10. Myles PS, Leslie K, Mcneil J, Forbes A, Chan MT: Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. *Lancet;* 2004, 363(9423):1757-1763.
11. Punjasawadwong Y, Boonjeungmonkol N, Phongchiewboon A: Bispectral index for improving anaesthetic delivery and postoperative recovery. *Cochrane Database Syst Rev*; 2007, 17(4):CD003843.
12. Recart A, Gasanova I, White PF, Thomas T, Ogunnaike B, Hamza M, Wang A: The effect of cerebral monitoring on recovery after general anesthesia: a comparison of the auditory evoked potential and bispectral index devices with standard clinical practice. *Anesth Analg*; 2003, 97(6):1667-1674.
13. Leslie K, Myles PS, Forbes A, Chan MTV: The Effect of Bispectral Index Monitoring on Long-Term Survival in the B-Aware Trial. *Anesth Analg*; 2010, 110(3):816-822.
14. Birnbach DJ, Browne IM: Anesthesia for Obstetrics. In: Fleisher LA, Johns RA, Savarese JJ, Kronish JPW, Young WL ed. Miller's Anesthesia. 6th ed. Elsevier Churchill Livingstone, 2005; vol. 2: pp. 23-26.
15. Yau G, Gin T, Ewart MC, Kotur CF, Leung RK, Oh TE: Propofol for induction and maintenance of anaesthesia at caesarean section. A comparison with thiopentone/enflurane. *Anaesthesia*; 1991, 46(1):20-23.
16. Celleno D, Capogna G, Emanuelli M, Varrassi G, Costantino P, Sebastiani M: Which induction drug for caesarean section? A comparison of thiopenthol sodium, propofol, and midazolam. *J Clin Anesth*; 1993, 5(4):284-288.
17. Wanna O, Werawatganon T, Piriyakitphaiboon S, Taesiri B: A comparison of propofol and ketamine as induction agents for caesarean section. *J Med Assoc Thai*; 2004, 87(7):774-779.
18. Abboud TK, D'Onofrio L, Reyes A, Mosaad P, Zhu J, Mantilla M, Gangolly J, Crowell D, Cheung M, Afrasiabi A, Khoo N, Davidson J, Steffens Z, Zaki N: Isoflurane or halothane for caesarean section: comparative maternal and neonatal effects. *Acta Anaesthesiol Scand*; 1989, 33(7):578-581.
19. Gambling DR, Sharma SK, White PF, Van Beveren T, Bala AS, Gouldson R: Use of sevoflurane during elective caesarean birth: a comparison with isoflurane and spinal anaesthesia. *Anesth Analg*; 1995, 81(1):90-95.
20. Yoo KY, Lee JC, Yoon MH, Shin MHO, Kim YH, Song TB, Lee JU: The effects of volatile anesthetics on spontaneous contractility of isolated human pregnant uterine muscle: A comparison among sevoflurane, desflurane, isoflurane and halothane. *Anesth Analg;* 2006,103(2):443–447.
21. Doze VA, Shafer A, White PF: Propofol-nitrous oxide versus thiopental-isoflurane-nitrous oxide for general anaesthesia. *Anesthesiology*; 1988, 69(1):63-71.
22. Heath PJ, Kennedy DJ, Ogg TW, Dunling C, Gilks WR: Which intravenous induction agent for day surgery? A comparison of propofol, thipentone, methohexitone and etomidate. *Anaesthesia*; 1988, 43(5):365-368.
23. Reves JG, Glass PSA, Lubarsky DA, Mcevoy MD: Intravenous nonopioid anesthetics. Miller's Anesthesia In: Fleisher LA, Johns RA, Savarese JJ, Kronish JPW, Young WL ed. Miller's Anesthesia. 6th ed.; vol. 1, pp. 331-332.
24. Taslimi MM, El-Sayed Y, Carvalho B, Cohen SE: Cesarean section-lower segment and classic. In: Jaffe RA, Samuels SI ed. Anesthesiologist's Manuel of Surgical Procedures. 3rd ed. Lippincott Williams and Wilkins 2004; p. 661.