ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Effects of Sedation on Spinal Anesthesia-induced Maternal Hypotension in Preoperatively Anxious Parturients Underwent Urgent Category-1 Cesarean Section: A Historical Cohort Study

Preoperatif Anksiyetesi olup Acil Kategori-1 Sezaryen Cerrahisi Geçiren Gebelerde, Sedasyonun Spinal Anestezinin Sebep Olduğu Maternal Hipotansiyon Üzerine Etkileri: Tarihi Bir Kohort Çalışma

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ABSTRACT Objective: This study was designed to investigate the effect of sedation on maternal hypotension in preoperatively anxious parturients underwent urgent category-1 Cesarean section (C/S) under spinal anesthesia (SA). **Material and Methods:** After ethics committee approval, data of 1824 parturients underwent C/S were reviewed from the surgical database and patient charts. Parturients with high preoperative anxiety scores (VAS-A)≥70) underwent C/S under SA with thiopental 2 mg/kg (if necessary additional 50 mg) sedation until reaching Ramsay sedation score≥3 (Group S, n=49), and without any other type of sedation (Group NS, n=53) were included in the study. All parturients received SA with hyperbaric bupivacaine 0.5% 2.5 mL. Hemodynamic parameters and maximum systolic arterial pressure (SAP) reductions (%) from the baseline were recorded. Maternal hypotension (SAP≥30% decrease or <100 mmHg) and bradycardia (heart rate <55 beats/min) incidences, required ephedrine (5mg IV bolus) and atropine (0.5 mg IV bolus) doses, and newborn Apgar scores were also analyzed. **Results:** Fifty-nine parturients' data (Group S: 29 and Group NS: 30) were analyzed. The maximum SAP reductions were 23±12.8% and 30.8±16.1% in Groups S and NS, respectively (p=0,044). Hypotension was observed in 5 (17,2%) parturients of Group S and 15 (50%) of Group NS (p=0.012, 95% CI 0,14-0,82; relative risk=0,344). Ephedrine requirement was 17±4,4 mg and 25±7,4 mg in Groups S and NS, respectively (p=0,04). Incidence of bradycardia, required atropine dose and newborn Apgar scores were similar in both groups (p>0,05). **Conclusions:** The maximum SAP reduction, hypotension incidence and required ephedrine doses were lower in thiopental sedation used preoperatively anxious parturients who underwent category-1 C/S under SA.

Keywords: Cesarean section; anxiety; anesthesia, spinal; conscious sedation; thiopental

ÖZET Amaç: Bu çalışma, preoperatif dönemde anksiyöz olup spinal anestezi (SA) altında acil kategori-1 sezaryen (C/S) operasyonu geçiren gebelerde, sedasyonun hipotansiyona etkisini araştırmak için planlanmıştır. **Gereç ve Yöntemler:** Etik kurul onayı alındıktan sonra, C/S operasyonu geçiren 1824 gebenin verileri cerrahi arşiv ve hasta dosyaları aracılığıyla incelendi. Preoperatif anksiyete skoru (VAS-A)≥70) yüksek olup SA altında C/S geçiren gebelerden Ramsay sedasyon skoru ≥3 olacak şekilde tiyopental 2 mg/kg (gereğinde 50 mg ek doz) uygulanan hastalar (Grup S, n=49) ve herhangi bir sedasyon uygulanmayan hastalar (Grup NS, n=53) çalışmaya dahil edildi. Tüm gebelere, 2,5mL %0,5'lik hiperbarik bupivakain ile SA uygulandı. Hemodinamik parametreler ve bazale göre sistolik arteryal basınçtaki (SAB) maksimum düşüşler (%) kaydedildi. Maternal hipotansiyon (SAB'ın ≥%30 düşmesi veya <100 mmHg olması) ve bradikardi (kalp hızı <55 atım/dk) insidansları, efedrin gereksinimi (5 mg IV bolus), atropin gereksinimi (0,5 mg IV bolus) ve yenidoğan Apgar skorları da analiz edildi. **Bulgular:** Elli dokuz hastanın (Grup S: 29 ve Grup NS: 30) verisi analiz edildi. SAB'taki maksimum düşüşler, Grup S ve NS'te sırasıyla %23±12 ve %30,8±16,1 idi (p=0,044). Hipotansiyon, Grup S'te 5 (%17,2) hastada ve Grup NS'te 15 (%50) hastada görüldü (p=0,012, 95% CI 0,14-0,82; rölatif risk=0,344). Efedrin gereksinimi Grup S ve NS'te sırasıyla 17±4,4 mg ve 25±7,4 mg idi (p=0,04). Bradikardi insidansı, atropin gereksinimi ve yenidoğan Apgar Skorları açısından iki grup birbirine benzerdi (p>0,05). **Sonuç:** Bazale göre SAB'taki maksimum düşüş, hipotansiyon insidansı ve ihtiyaç duyulan efedrin dozları, preoperatif dönemde anksiyöz olup tiyopental sedasyonu uygulanarak SA altında kategori-1 C/S geçiren gebelerde daha düşüktür.

Anahtar Kelimeler: Sezaryen; anksiyete; anestezi, spinal; bilinçli sedasyon; tiyopental

Spinal anesthesia (SA) is an alternative to general anesthesia (GA) that is used for parturients underwent category-1 Cesarean section (C/S). The most common adverse effect of SA is maternal hypotension, and its incidence varies between 1.9% and 71% depending on different definitions.[1-4] It is important in the obstetric population because of compromising the welfare of both mother and fetus.[5] Many factors, including local anesthetic dose, patient positioning, fluid pre-loading and/or co-loading, baseline vascular tone and prophylactic or therapeutic vasopressor use, have a role in the occurrence of maternal hypotension.[6] Although use of higher local anesthetic dose is recommended for early onset of SA in urgent C/S procedures, this may result in higher hypotension incidence.[1]

Mainly, the mechanisms of maternal hypotension after SA are vascular resistance decrease due to sympathetic blockade and cardiac output decrease due to blood pooling in blocked body parts.[7-9] Patients with higher preoperative sympathetic activation have been shown to be subjected to more remarkable hypotension after SA, and increased anxiety results in generalized sympathetic activation.[7,10-12] Recently, significant effect of preoperative anxiety on maternal hypotension after SA has been reported.[13]

This study was designed to investigate the effect of thiopental sedation on maternal hypotension in preoperatively anxious parturients underwent category-1 C/S under SA. Our primary endpoint was to compare the maximum systolic arterial pressure (SAP) reductions (%) from the baseline in Groups S and NS. Secondary endpoints were maternal hypotension and bradycardia incidences, required ephedrine and atropine doses, incidences of nausea and vomiting, and also newborn Apgar scores at 1st and 5th min.

This study is registered on "ClinicalTrials.gov (NCT02732197)" and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (Strobe) guidelines.[14]

MATERIAL AND METHODS

PARTURIENT DATA SELECTION

After institutional ethics committee approval, data of 1824 parturients, who underwent C/S at our Training and Research Hospital between August 2014 and February 2015, were identified from the Clinic of Obstetrics and Gynecology database. Urgent category-1 (immediate threat to the life of the woman or fetus) parturients with American Society of Anesthesiologists (ASA) physical status I-II, aged between 18 and 35 years, term (≥37 weeks) singleton pregnancy, body mass index (BMI) <40 kg m^{-2}, height >150 cm or <180 cm, high preoperative anxiety scores (visual analogue scale for anxiety (VAS-A) ≥70) underwent C/S under SA were included in the analysis. Exclusion criteria were preoperative prehydration, placenta previa or accreta, diagnosis of chronic or pregnancy-induced hypertension, urgent category ≥2, having GA and SA with sedation other than thiopental.

PERIOPERATIVE CARE AND PERFORMANCE OF SA

Standard monitoring including noninvasive blood pressure, electrocardiography and pulse oximetry were applied to all parturients in the operating room. They received peripheral 18 G intravenous (IV) cannula, and then rapid 1000 mL Ringer's lactate cohydration. Spinal anesthesia was performed at the level of L3-4 intervertebral space using a 25 G spinal Quincke needle (Egemen International, Izmir, TR) and hyperbaric bupivacaine 0.5% 2.5 mL, with the patient in the sitting position by the same experienced anesthesia team.

After the procedure, all parturients were given supine 15 degrees left lateral (uterine displacement) and 10 degrees reverse Trendelenburg position. Supplemental oxygen was administered routinely. Category-1 C/S parturients were divided into Group S and Group NS according to their data. Parturients in Group S were the ones, who received IV thiopental 2 mg/kg and if necessary additional 50 mg immediately after SA, until reaching at least Ramsay sedation score of 3 (1: patient anxious, agitated or restless, 6: patient with no response to light glabella tap or loud auditory stimulus.). Par-

turients in Group NS did not receive any sedative agent after the SA performance.

Surgery was allowed to start when the sensory block level was confirmed to be at least at T4 level bilaterally by hot-cold and pinprick tests, and performed by the same surgical team.

RECORDED FOLLOW-UP PARAMETERS AND INTERVENTIONS

Preoperatively, VAS-A scores (0: not anxious, 100: extremely anxious) of all parturients were noted. Maternal SAP, diastolic arterial pressure (DAP) and heart rate (HR) values were recorded preoperatively (baseline (0 min)) as well as at every 2 minutes until the end of surgery. All measurements had been taken in the supine position with the left uterine displacement. Hypotension was defined as a decrease in SAP >30% from baseline or an absolute value <100 mmHg. It was treated promptly with ephedrine 5 mg IV boluses with 2 min intervals until SAP returned to a value of >100 mmHg. A bolus of IV 0.5 mg atropine was given if bradycardia (HR <55 beats /min) occurred.

Durations of SA performance (the time period between the spinal needle insertion and withdrawal), skin incision (the time period between the spinal needle withdrawal and skin incision for C/S) and Cesarean delivery of the neonate (the time period between the spinal needle withdrawal and delivery) were obtained from the records. After delivery of the neonate, slow IV infusion of oxytocin 20 U diluted in 1000 mL was a routine. Durations of both anesthesia (defined as the time period between the spinal needle insertion and when the patient left the operating room after surgery) and surgery (defined as the time period between the incision and the dressings) were documented.

Incidences of maternal nausea and vomiting during the Cesarean delivery, and newborn Apgar scores (0-3: severely depressed, 4-6: moderately depressed, 7-10: excellent condition) were recorded.

All routinely collected perioperative data were obtained from both the Department of Obstetrics and Gynecology database and patients' anesthesia charts.

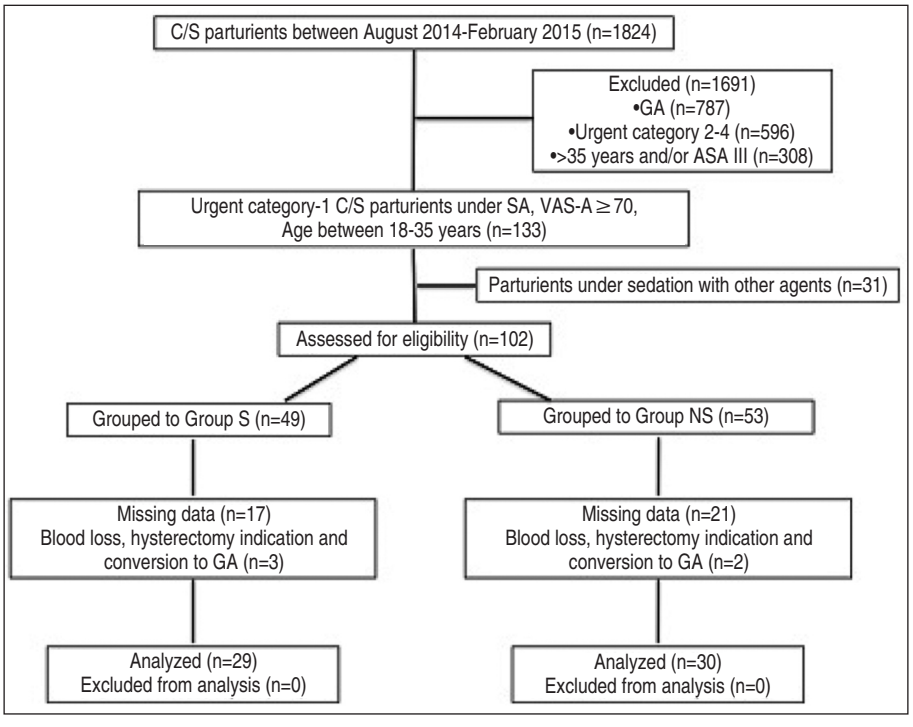

FIGURE 1: Strengthening the Reporting of Observational Studies in Epidemiology (Strobe) diagram of Groups S and NS. C/S: Cesarean Section, GA: General anesthesia, SA: Spinal anesthesia, ASA: American Society of Anesthesiologists, VAS-A: Visual analogue scale for anxiety, Group S: Parturients received IV thiopental for sedation, Group NS: Parturients did not receive any sedative agent.

ENDPOINTS

Our primary endpoint was to compare the maximum SAP reductions (%) from the baseline in Groups S and NS. Secondary endpoints were maternal hypotension and bradycardia incidences, required ephedrine and atropine doses, nausea and vomiting incidences, and also newborn Apgar scores at 1st and 5th minutes.

STATISTICAL ANALYSIS

A pilot study was performed to determine the number of required parturients for the study. We calculated a mean (SD) 34% (9.1) reduction in SAP after SA for urgent category-1 C/S delivery in 20 parturients. In each group, 28 parturients would be required to identify a 20% difference between the groups for the change of SAP with respect to baseline, with a power of 80% and a P-value of 0.05. We analyzed data using an unpaired Student's t-test, the Mann-Whitney U test and Fischer's exact test, as appropriate. P-value less than 0.05 was considered to be statistically significant. All statistical analysis were performed using SPSS 22.0.0.0 for WINDOWS (SPSS Inc., Chicago, IL, USA).

RESULTS

Of 1824 parturients, data of 102 were eligible for the study. Forty-nine parturients were grouped to Group S and 53 were grouped to Group NS. Forty-three parturients' data were excluded, 38 were (17 from Group S and 21 from Group NS) incomplete and 5 patients' surgery was changed from C/S to hysterectomy. Fifty-nine parturients, who underwent urgent category-1 C/S under SA with complete data, were included in the study for analysis. Twenty-nine parturients were in Group S and 30 in Group NS as per their recorded sedation data (Figure 1).

As shown in Table 1, characteristics of parturients, anesthesia and surgery were similar between the groups. Perioperative parturient and newborn follow-up values were presented in Table 2. In Group S, 2 parturients had a Ramsay sedation score of 2 following IV thiopental administration and received additional 50 mg. In the same group, Ramsey sedation score of 4 was obtained in 2 different parturients and none had respiratory depression. There were 25 parturients with a Ramsay sedation score of 3 in Group S.

Maximum SAP reduction was significantly lower in Group S (23±12.8%) when compared with Group NS (30.8±16.1%) (P=0.044; Figure 2). Arterial blood pressure and HR follow-ups during C/S were shown in Figure 3 and 4, respectively. Hypotension was observed in 20 of the 59 parturients included in the study, of whom 5 (17.2%) were in Group S and 15 (50%) in Group NS (P=0.012, 95% CI 0.14 to 0.82; relative risk: 0.344) (Table 2).

TABLE 1: Parturient, anesthesia and surgery characteristics. Data are presented as mean±standard deviation (SD) (Student's t-test).

	Group S (n=29)	Group NS (n=30)	P
Age (yr)	28,4±6,5	28±4,4	0,778
Weight (kg)	77,5±8,1	76,5±12,4	0,693
Height (cm)	160,5±2,8	161,6±5,0	0,328
Gestational age (weeks)	37,8±2,3	37±2,4	0,173
Gravida	3,9±1,9	3,2±1,7	0,264
Parity	2,4±2,1	1,8±1,3	0,221
Duration of spinal anesthesia performance (sec)	13,9±3,0	15,1±5,7	0,704
Duration of skin incision (sec)	178,0±51	158±46	0,149
Duration of Cesarean delivery of the neonate (sec)	298,8±41	284±79	0,386
Surgery duration (min)	27,4±5,7	24,6±4,6	0,248
Anesthesia duration (min)	30,2±5,6	27,7±4,5	0,293

Group S: Parturients received IV thiopenthal for sedation; Group NS: Parturients did not receive any sedative agent

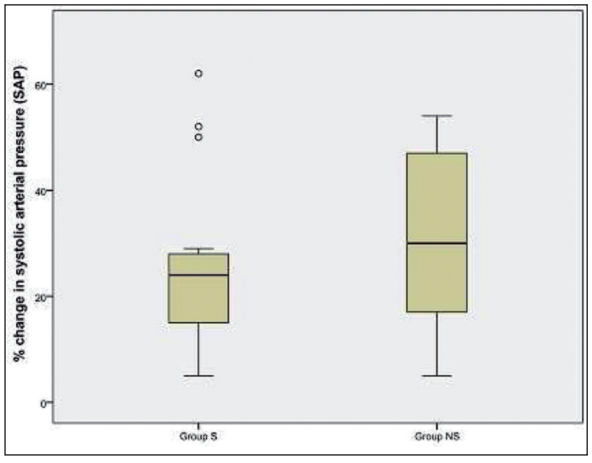

FIGURE 2: Comparison of mean maximum systolic arterial pressure reductions (%) from the baseline values in Group S and Group NS. Error bars indicate the standard error of the mean.

Ephedrine requirement (17±4.4 mg) was significantly lower in Group S compared with Group NS (25±7.4 mg) (P=0.040; Table 2). Incidence of maternal bradycardia, required atropine dose, nausea and vomiting were comparable in both groups. Newborn Apgar scores at 1st and 5th minutes were also similar in groups (Table 2).

None of the patients experienced SA failure or any other complication.

DISCUSSION

This present study showed that thiopental sedation after SA offers hemodynamic stability in preoperatively anxious parturients while undergoing urgent category-1 C/S. Thiopental sedation lowered the maximum SAP reduction, incidence of hypotension occurrence and ephedrine requirement in parturients without effecting newborn Apgar scores.

Cesarean section procedure under SA was reported to be associated with extreme anxiety effecting maternal satisfaction due to its adverse effects, anesthesia process and postoperative recovery.[15-17] For this reason, relieving anxiety and minimizing side effects may provide gladsome C/S and childbirth.[15]

The relationship between anxiety and increased sympathetic activity has been shown in previous studies investigating heart variability and

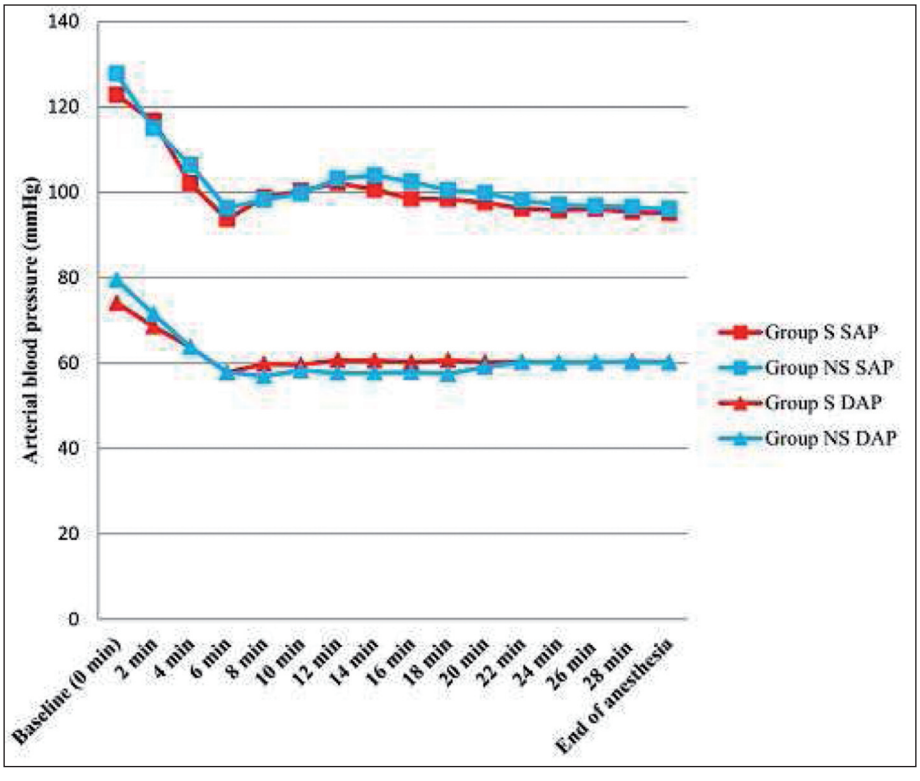

FIGURE 3: Baseline (0 min) and perioperative systolic (SAP) and diastolic (DAP) arterial pressure follow-ups in Groups S and NS. Group S: Parturients received IV thiopental for sedation, Group NS: Parturients did not receive any sedative agent.

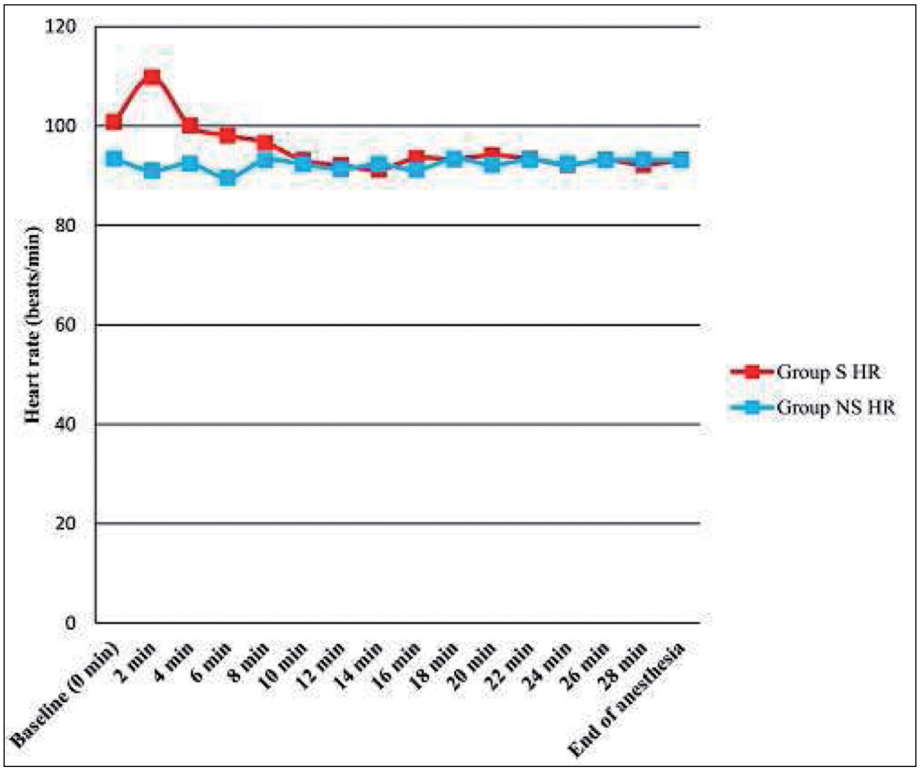

FIGURE 4: Baseline (0 min) and perioperative heart rate (HR) follow-ups in Groups S and NS. Group S: Parturients received IV thiopental for sedation, Group NS: Parturients did not receive any sedative agent.

postural blood pressure changes.[18-20] Furthermore; various indicators of sympathetic activation including maternal baseline HR, maternal HR variability and maternal postural arterial pressure changes were studied, and the relationship between the increased sympathetic activity and hypotension developed after SA was demonstrated.[10,11,21]

Recently, Orbach-Zinger et al. reported their observation of greater hypotension and vasopressor use in the parturients with high preoperative anxiety undergoing C/S following SA.[13] In this present study, we enrolled only the parturients with high VAS-A scores, and our findings as approximately 30% reduction in SAP of non-sedated group was similar to their high anxiety group. At this point, as they emphasized the importance of alleviating the anxiety; in our sedated group, we demonstrated the beneficial effects of thiopental sedation on controlled decrease of both the maximum SAP reduction from the baseline and hypotension incidence in preoperatively anxious parturients. As expected, we also found lower ephedrine requirement in the same group.

TABLE 2: Perioperative parturient and newborn follow-up values. Data are presented as mean±standard deviation (SD) (Student's t-test), median [min-max] (Mann-Whitney U test) and n (%) (Fisher's exact test).

	Group S (n=29)	Group NS (n=30)	P
Baseline SAP (mmHg)	122,8±17,9	127,8±14,6	0,253
Baseline HR (beats min-1)	100,8±12,2	93±20,3	0,079
Baseline VAS-A (0-100)	90 [70-100]	80 [70-100]	0,812
Incidence of hypotension	5 (17,2%)	15 (50%)	0,012*
Ephedrine requirement (mg)	17±4,4	25±7,4	0,040
Incidence of bradycardia	0 (0)	3 (10%)	0,237
Atropine requirement (mg)	0±0	0.5±0	0,070
Thiopental consumption (mg)	153.3±12,6	N/A	N/A
Incidence of nausea	4 (13.8%)	10 (33.3%)	0,125
Incidence of vomiting	1 (3.4%)	5 (16.6%)	0,194
Apgar 1st min (0-10)	7 [0-10]	7 [0-10]	0,912
Apgar 5th min (0-10)	8 [0-10]	8 [0-10]	0,864

*p=0,012. 95% CI 0,14 to 0,82, relative risk 0,344.
Group S: Parturients received IV thiopenthal for sedation; Group NS: Parturients did not receive any sedative agent; SAP: Systolic arterial pressure; HR: Heart rate; VAS-A: Visual analogue scale for anxiety

Regarding the relationship between HR, arterial blood pressure and SA; Frölich et al. demonstrated maternal baseline HR as a possible predictive factor for obstetric patients' hypotension after SA.[11] In contrast, HR and required atropine dose follow-ups did not show us any association in our study.

Previously, the positive effect of inhalation of nitrous oxide 50% on decreasing anxiety and pain in parturients under SA for C/S was reported.[17,22] In addition, sedation with either propofol or midazolam has been demonstrated to provide a high and comparable satisfaction during SA for C/S.[23] Thiopental was reported to be a safe and effective drug for sedation and premedication when rectally used in pediatric population.[24-26] There have also been some studies and case reports reporting the low dose thiopental effects in adults.[27-29] These were usually about ambulatory and emergency interventions such as short operations, diagnostic and therapeutic procedures and transportation. In this present study, we preferred to use low dose thiopental for sedation because of avoiding either the hypotensive effects of propofol or the lower neonatal Apgar and neurobehavioral scores of both midazolam and propofol.[30,31] In a previous study, the median effective doses (ED50s) for hypnosis and anesthesia were found to be 2,6-4 mg/kg in the pregnant women.[32] Therefore; we chose thiopental dose as 2 mg/kg and patients were followed until reaching at least Ramsay sedation score of 3.

On the other hand; SA-related sympathectomy and hypotension are the important factors which may influence the incidences of perioperative nausea and vomiting.[33,34] Samimi et al. showed no significant difference in the incidence of nausea and vomiting when subhypnotic doses of propofol or midazolam were used.[35] In contrast, Rasooli et al. found that subhypnotic doses of both agents effectively prevent peri- and postoperative nausea and vomiting in patients underwent C/S after SA.[36] Likewise, we found lower nausea and vomiting incidences in parturients during C/S, but this time by using IV thiopental.

Neonates born by C/S under SA were reported to be more acidemic compared with epidural anesthesia or GA. This may be explained either by consequence of maternal hypotension or -associated vasopressor use.[37,38] At this point, preventing hypotension would be an advantage for the neonates. It is known that thiopental can be detected in the umbilical venous blood in 30 sec and reaches its maximum within 2-3 min following its IV administration.[39] At delivery, umbilical vein/maternal vein ratio reaches almost.[1] However; if the induction thiopental dose is less than 4 mg/kg, the fetal brain will not be exposed to its high concentrations. With this dose umbilical artery levels are much lower than the umbilical venous levels.[40,41] Therefore; as anticipated, the preferred thiopental dose (2 mg/kg) in our study did not lower the Apgar scores of the newborns either at 1st or 5th minutes.

State-trait anxiety inventory (STAI), the hospital anxiety and depression scale (HAD), and VAS-A are the available scales for the assessment of preoperative anxiety. Previously, studies comparing the effectiveness and validity of these three scales found equivalent results in detecting preoperative anxiety.[42-45] In our study, VAS-A assessment scale was used as it would be a simple, rapidly applicable and a reliable method for urgent category-1 C/S performed parturients.

This present study had some limiting factors. First of all; this is a historical cohort study and the parturients were not randomized. Second; as parturients underwent urgent category-1 C/S procedures, neglecting preoperative hydration status, all were administered the same fluid management protocol and hypotension was treated only by IV ephedrine. Pelvic tilt, IV volume expansion and additional vasopressor use could have been alternative treatment methods or combined with ephedrine. However; the hypotension therapy restricted to ephedrine provided us to assess ephedrine requirement and to avoid cardiac arrythmia besides reactive hypertension.[46,47]

In conclusion, our results suggest that sedation with thiopental lowers the systolic arterial pressure reduction, hypotension incidence and associated-

ephedrine requirement in anxious parturients undergoing urgent category-1 C/S under spinal anesthesia. Furthermore; these positive maternal outcomes are supported with the high satisfying newborn Apgar scores.

Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

Cenk Sahan *helped design and conduct the study, review and analyze the data, and write the manuscript.* ***Emine Aysu Salviz*** *helped design the study, review and analyze the data, and write the manuscript.* ***Gulcin Hilal Alay*** *helped conduct the study, review and analyze the data.* ***Halide Erten Sahan*** *helped analyze the data and write the manuscript.* ***Volkan Anakli*** *helped analyze the data and write the manuscript.* ***Kamil Mehmet Tuğrul*** *helped analyze the data and write the manuscript.*

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