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Comparison of Different Fentanyl Doses in Spinal Anesthesia for Cesarean Delivery

Sezaryen Doğum için Spinal Anestezide Farklı Fentanil Dozların Karşılaştırılması

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ÖZ

Amaç: Bu çalışmada sezaryen doğum için spinal anestezide bupivakain yanısıra 10 veya 25 mcg fentanilin spinal bloğun klinik etkinliği ve özelliklerini karşılaştırmayı amaçladık. Maternal ve neonatal hemodinamik üzerindeki etkilerini de ek olarak değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Amerikan Anestezistler Derneği (ASA) Skoru I-II olan, elektif sezaryen için spinal anestezi uygulanan, 18-45 yaş arası gebe kadınlar çalışmaya dahil edildi. Doğumda yaş, ağırlık, boy, gebelik haftaları. Hastalar üç gruba ayrıldı: Sadece hiperbarik bupivakain alan hastalar Grup I, hiperbarik bupivakain artı 10 mcg fentanil alan hastalar Grup II ve hiperbarik bupivakain artı 25 mcg fentanil alan hastalar Grup III olarak sınıflandırıldı. Hemodinamik verilerin yanı sıra blok özellikleri de kayıtlardan alındı. Ayrıca yenidoğanın kalp atım hızı, 5-10 ve 10. dakikada SpO2 okumaları ve 1- ve 5- dakikalık Apgar skorları kaydedildi.

Bulgular: Demografik özellikler üç grup arasında benzerdi. T10 dermatomunda duyu bloğunun başlaması için ortalama süre ve Modifiye Bromage skalası 3 için ortalama süre Grup III'de diğer iki gruba göre anlamlı olarak daha kısaydı (p <0,05). İlk analjezik gereksinim süresi Grup II ve III'te Grup I'e göre daha uzun bulundu (p = 0,05). Üç dakikada SBP ve DBP değerleri her üç grupta da anlamlı olarak azaldı (p <0,05). Bununla birlikte, üç grup arasındaki fark anlamlı değildi. Bir ve 5 dakikalık Apgar skorları gruplar arasında benzerdi. 5- ve 10 dakikalık kalp atım hızları ve yenidoğanların doyma hızları gruplar arasında farklılık göstermedi. Ameliyat sonrası baş ağrısı, kaşıntı, bulantı, kusma ve idrar retansiyonu görülme sıklığı da gruplar arasında benzerdi.

Sonuç: Anestezi başlangıcını kısaltır, intraoperatif analjezi kalitesini arttırır, duyusal blok süresini uzatır ve postoperatif ağrının başlamasını geciktirir, çünkü intratekal fentanil kullanılmasını öneririz.

Anahtar Kelimeler: Spinal anestezi, Fentanil, Sezaryen doğum, Bupivakain

ABSTRACT

Objective: We aimed to compare the clinical efficacy and characteristics of bupivacaine spinal block when combined with either 10 or 25 mcg fentanyl in spinal anesthesia for Cesarean delivery. We also sought to evaluate its effects on maternal and neonatal hemodynamics.

Methods: American Society of Anesthesiologists (ASA) Score I-II pregnant women aged 18-45 years who received spinal anesthesia for elective Cesarean section were included in the study. Age, weight, height, weeks of gestation at delivery. Patients were divided into three groups: Patients who received hyperbaric bupivacaine alone were classified as Group I, those who received hyperbaric bupivacaine plus 10 mcg fentanyl were classified as Group II and those who received hyperbaric bupivacaine plus 25 mcg fentanyl were classified as Group III. Block characteristics, as well as hemodynamic data, were retrieved from records. Additionally, heart rate, SpO2 readings at 5- and 10- minute and 1- and 5- minute Apgar scores of the newborn were noted.

Results: Demographic properties were similar among the three groups. Mean time to onset of sensory block at T10 dermatome and mean time to Modified Bromage scale 3 was significantly shorter in Group III compared to the other two groups (p<0,05). The first analgesic requirement time was found to be longer in Group II and III compared to Group I (p= 0,05). SBP and DBP values at 3-minute were significantly decreased in all three groups (p<0,05). The difference in-between the three groups, however, was not significant. One- and 5-minute Apgar scores were similar among groups. 5- and 10-minute heart rates and saturation rates of the newborns did not differ among groups. The incidence of postoperative headache, pruritus, nausea, vomiting and urinary retention was also similar among the groups.

Conclusion: We recommend the use of intrathecal fentanyl because it shortens the onset time of anesthesia, increases the quality of intraoperative analgesia, prolongs the duration of sensorial block and delays the onset of postoperative pain.

Keywords: Spinal anesthesia, Fentanyl, Cesarean delivery, Bupivacaine

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INTRODUCTION

Owing to its rapid onset of action and short-duration of procedure, spinal anesthesia is the most frequently used technique for Cesarean delivery (1). The combination of intrathecal opioids with low dose local anesthetics for spinal anesthesia provides greater hemodynamic stability and more efficient anesthesia without pushing the block level higher (2). Intrathecal fentanyl shortens the onset of anesthesia, improves the quality of intraoperative analgesia, prolongs the duration of sensorial block and delays the onset of postoperative pain (3).

The most commonly used local anesthetic and opioid in spinal anesthesia for Cesarean section are intrathecal hyperbaric bupivacaine and fentanyl, respectively. Intrathecal hyperbaric bupivacaine is a potent local anesthetic with slow onset (5- 8 minutes) and long duration of action (1.5-2 hours). The use of this anesthetic reduces the incidence of intraoperative visceral pain related to the traction of peritoneum and retraction of intraperitoneal organs during Cesarean delivery (4).

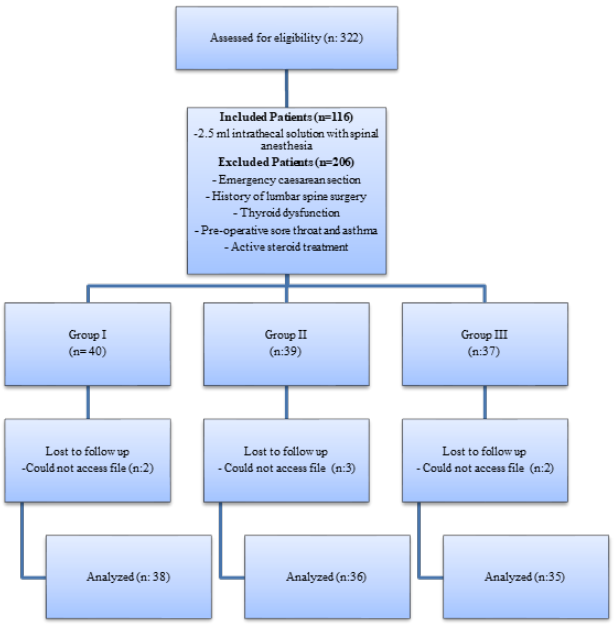
Fentanyl is a potent synthetic opioid derivative with rapid onset, short duration of action and early postoperative analgesic effect (5). The combination of low-dose opioids reduces the need for high-dose local anesthetics and, hence, the incidence of local anesthesia-related side effects accelerates the onset of anesthesia and improves the quality of intraoperative and postoperative analgesia (6).

The aim of this study was to compare the clinical efficacy and characteristics of bupivacaine spinal block when combined with either 10 or 25 mcg fentanyl. We also sought to evaluate its effects on maternal and neonatal hemodynamics.

MATERIAL AND METHODS

After we obtained ethical approval from The Ethics Committee of Ankara, Turkey Etlik Zubeyde Hanim Maternity and Gynecology Training and Research Hospital (No: 2018/7, 04.04.2018), we reviewed records of ASA I-II pregnant women aged 18-45 years who received spinal anesthesia for elective Cesarean section, between January 2016-December 2016. Eligibility of 322 files was evaluated. Patients who underwent an emergency cesarean section, those with a history of lumbar spine surgery, patients with thyroid dysfunction and those with pre-operative sore throat and asthma, patients on active steroid treatment, and those who received endotracheal intubation were excluded from the study. A total of 116 patients who received a total of intrathecal 2.5 ml solution were included in the study and were stratified into three groups (Figure 1). Accordingly, patients who received 2.5 ml (12.5 mg) 0.5% hyperbaric bupivacaine alone were classified as Group I, those who received 2 ml (10 mg) 0.5% hyperbaric bupivacaine plus 0.3 ml saline plus 0.2 ml (10 µg) fentanyl were classified as Group II and those who received 2 ml (10 mg) 0.5% hyperbaric bupivacaine plus 0.5 ml (25 µg) fentanyl were classified as Group III. A total of 109 patients were included in the study because the file information of 7 patients in 3 groups could not be reached (Figure 1).

Figure 1: Flow diagram of patient distribution. Group I: Hyperbaric bupivacaine only group, Group II: Hyperbaric bupivacaine plus 10 mcg fentanyl, Group III: Hyperbaric bupivacaine plus 25 mcg fentanyl.



Patients undergoing spinal anesthesia in our clinic are routinely placed in the 10 to 15-degrees left lateral decubitus position to reduce aorta-caval pressure. They receive 4 lt / min O2 through a face mask and are closely monitored using non-invasive blood pressure, electrocardiography (ECG) and oxygen saturation (SpO2). All patients receive intravenous (IV) ringer lactate solution at the rate of 15 ml/kg/minute, 15 min before the spinal block. Afterward, the interspaces of L3-4 or L4-5 are identified and the skin is prepared with an appropriate antiseptic solution. Spinal anesthesia is performed with a 25-G pencil-point spinal needle. During the procedure 8 ml/kg/hour IV ringer lactate solution is administered. During the first 10 minutes, sensorial and motor block is assessed every minute until complete block is established, which was defined as obtaining similar data on three consecutive assessment.

Time to onset of sensory block at T10 (thoracic 10) dermatome and time to complete motor block (Modified Bromage scale: 0=no motor block, 1=Able to flex knees, but unable to flex the hip, 2=Unable to flex knees, but with free movement of feet, 3=Unable to move any of the lower extremity joints) were recorded (6). The degree of motor block, total ephedrine and atropine dose used were also recorded. Surgery commenced following the establishment of sensory block at T4 using the pinprick test. The time of skin and uterus incision, time of umbilical cord clamping, as well as the duration of surgery were noted. Blood pressure was measured at baseline, following spinal anesthesia, at 5-minute and thereafter at 5-minute intervals. Hypotension was defined as a mean blood pressure less than 90 mm Hg or a decrease of 20% or more from the baseline. Hypotension was treated with rapid fluid infusion and IV bolus of ephedrine 10 mg. Ephedrine treatment was repeated every 2-minute if hypotension persisted or recurred. If hypotension still persisted on two consecutive blood pressure measurements, IV bolus of ephedrine 10 mg was repeated. The number of hypotension episodes was recorded. We defined bradycardia as a heart rate of less than 45 beats per minute (BPM) and treated with 0.01 mg/kg I.V. atropine. After delivery of the neonate and clamping of the umbilical cord, i.v. oxytocin 5 i.u. was given.

Hemodynamic parameters, time to regression of motor block and time to the first request for analgesia were documented. The need for analgesia was assessed using the visual analog scale (VAS) and patients with a score higher than 4 were treated with intramuscular 75 mg diclofenac sodium. We also documented the weight, sex, 1- and 5-minute Apgar scores, 5- and 10-minute SpO2 and heart rate values of neonates. Neonates who required free flow oxygen support due to cyanosis were also noted. The presence of adverse effects such as nausea, vomiting, pruritus, and headache occurring in the first 24h was documented from patients' notes.

All statistical analyses were carried out using SPSS for Windows, version 21.0 (SPSS Inc., Chicago, IL, USA). Results are expressed as the mean ± SD. A t-test and Mann-Whitney U test were used for comparison of quantitative variants. Qualitative variants were compared using a chi-square test. A $p<0.05$ was considered statistically significant.

RESULTS

Groups were similar in regard to age, weight, height, the number of Cesarean section deliveries, ASA classification, weeks of gestation at delivery ($p> 0.05$) (Table 1).

Table 1. Demographic data

	Group I n= 38	Group II n= 36	Group III n=35	*P*
Age (year)	29.89 ±5.53	30.08±5.59	29.68±6.84	*0.962*
Weight (kg)	75.07±7.28	77.47±10.69	80.31±10.69	*0.073*
Height (cm)	159.44±3.86	162.08±7.08	161.60±5.16	*0.092*
Gestational age (wk)	39.11±0.98	39.03±0.97	39.03±0,95	*0.91*
Hb (gr/dl)	11.37±1.31	11.23±1.60	11.32±1.73	*0.924*
Mcv (%)	85.88±7.56	85.55±8.79	87.86±8.34	*0.33*

The duration of surgery, time from skin incision to uterine incision, and from uterine incision to cord clamping were also similar among the groups (Table 2).

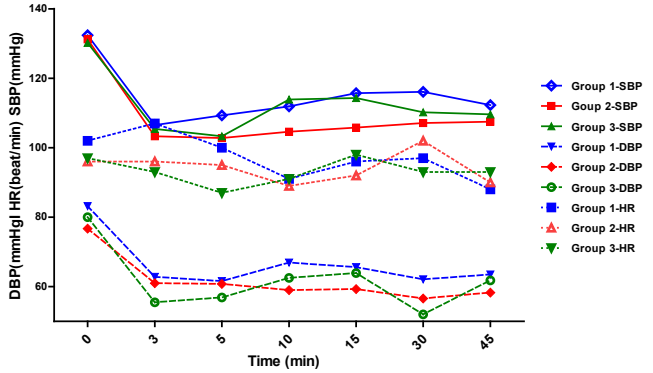
Table 2: Block characteristics

	Group I n= 38	Group II n= 36	Group III n=35	*P*
Duration of surgery (min)	34.15±8.47	33.58±10.25	35.11±9.81	*0.63*
Skin incision–uterine incision (min)	3.5 (1-9)	3.5 (1-9)	4 (1-10)	*>0.05*
Uterine incision–Delivery time (min)	1 (0-2)	1 (0-2)	1 (0-2)	*>0.05*
Duration of motor block Bromage 3 (min)	4 (2-5)[a]	4(2-4)[b]	3 (2-4)[c]	*a-b:0.002* *a-c<0.001* *b-c:0.084*

Time to T10 sensory block (min)	4 (2-5)[a]	3 (1-6)[b]	3 (2-4)[c]	*a-b:0.856* *b-c:0.011* *a-c:0.000*
Time to resolution of motor blockade (min)	179.47±43.86	183.61±47.27	193.42±43.65	*>0.05*
Time to first analgesic request (min)	200 (130-260)[a]	210 (140-300)[b]	240 (150-330)[c]	*a-b:0.098* *a-c:0.02* *b-c:0.15*
Ephedrine dose (mg)	6.84±7.01	6.97±8.19	7.42±8.16	*0.81*

Time to onset of sensory block at T10, as well as time to Grade 3 motor block was shorter in Group III compared to the other two groups (p= 0.001, p <0.001; respectively) (Table 2). Mean time to first request for analgesia was 200 (130-260) minute in Group I, 210 (140-300) minute in Group II, and 240 (150-330) minute in Group III (p<0,05) (Table 2). Mean time to complete regression of motor block was 179,47±43,86 minute in Group I, 183,61±47,27 minute in Group II, and 193,42±43,65 minute in Group III (p>0,05) (Table 2). All groups had similar baseline SBP, DBP, and HR values. Three-minute SBP and DBP values were significantly lower than baseline values (p<0,05) but the level of decrease was similar among groups (p>0.05) (Figure 2).

Figure 2. Maternal Hemodynamic Variables



* 15 minutes was lower in SBP group 2 (p: 0.026)
# 3 minutes HR was low in group 2 and group 3 (p: 0,036)
ð 30 minutes DBP was higher in group 1 (p: 0.005)

While 3-minute HR was similar between Group 2 and 3, it was significantly lower in both groups as compared to Group I (p= 0,036) (Figure 2). Change in MBP was similar among groups (p>0,05). One patient in Group I and three in Groups II and III required atropine infusion following spinal anesthesia. Mean ephedrine requirement did not significantly differ among groups (p=0,81); it was the highest in Group III (7,42±8,16 mg) followed by Group II (6,97±8,19 mg) and Group I (6,84±7,01mg).

One- and 5-minute Apgar scores were similar among groups. One-minute Apgar score was less than seven in one patient in Group I and in two patients in Group III. Among these, only one in Group III had a 5-minute Apgar score less than seven. Five- and 10-minute heart rates and saturation levels of the newborns did not differ among groups (Table 3). Following delivery seven of the newborns; three in Group III and two in Groups I and II, required free-flow oxygen delivery (p=0,816) (Table 3).

Table 3. Neonatal condition

	Group I n= 38	Group II n= 36	Group III n=35	*P*
Apgar Score				
1. min	8.55±0.82	8.41±0.80	8.42±1.44	*0.47*
5. min	9.42±0.59	9.52±0.60	9.40±1.14	*0.37*
Apgar score < 7 (n)				
1. min	1	0	2	*0.145*
5. min	0	0	1	*0.116*
5. min values of neonate				
Heart rate (bpm)	156.3±13.6	147.8±17.40	151.8±24.60	*0.059*
SpO_2 (%)	86.02±3.11	84.6±6.40	87.3±5.52	*0,11*
5. min values of neonate				
Heart rate (bpm)	157.07±9.47	148.11±12.32	151.57±16·83	*<0.05*
SpO_2 (%)	93.2±3.4	92.4±4.6	93.5±3.6	*0.55*
Requirement of respiratory support (n/%)	2 (5.3)	2 (5.6)	3 (8.6)	*0.816*

One patient in Group III developed nausea and vomiting. The rate of postoperative headache was similar among groups: two patients in Group I, three in Group II and one in Group III. One patient in Group I and two in Group II developed pruritus. Urinary retention was observed in two patients in Group I, in one patient in Group II and in two patients in Group III, with no significant difference among groups.

DISCUSSION

We found that the time to onset of sensory and motor block during spinal anesthesia consistently decreased with increasing concentrations of intrathecal fentanyl. We also found that sensory and motor block onset was faster in patients who received either fentanyl 25 mcg or 10 mg heavy bupivacaine. Furthermore, although the duration of motor block was similar among the groups, intrathecal fentanyl prolonged time to first request for analgesia. Although ephedrine requirement increased with the use of higher concentrations of intrathecal opioid, the decrease in MBP values was not clinically significant. Finally, APGAR scores, saturation and heart rate values did not significantly differ among the groups.

The optimal dose for local anesthetics and intrathecal opioids in patients undergoing spinal anesthesia for elective and emergency Cesarean section has yet to be determined (7). The dosage of opioids used in combination with local anesthetics affects the quality of sensory and motor blockade, the quality and duration of postoperative analgesia, and also the incidence of maternal and neonatal adverse effects. The rapid penetration of lipophilic opioids, such as fentanyl, into the neuronal tissues, provides a fast onset of action (8).

Gandam, et al compared the hemodynamics and duration of analgesia between patients who received a combination of 25 µg fentanyl and 7.5 mg (0.5%) of hyperbaric bupivacaine and patients who received a conventional dose (10 mg; 0.5%) of hyperbaric bupivacaine for Cesarean section. They found that the mean time to onset of sensory block at T10 was significantly shorter and the duration of effective analgesia significantly prolonged in patients who received additional fentanyl (P < 0.001) (5). Bozdoğan, et al. compared the quality of anesthesia in three groups of patients who received intrathecal 2.2 ± 0.2 mL 0.5% levobupivacaine, 2.2 ± 0.2 mL 0.5% levobupivacaine plus 2.5 mcg sufentanyl, and 2.2 ± 0.2 mL 0.5% levobupivacaine plus 10 mcg fentanyl, respectively. They found that mean time to onset of sensory block at T10 was significantly shorter in patients who received any of the two opioids as compared to those who did not, but was similar between patients who received additional sufentanyl or fentanyl (9). They also demonstrated that the onset of motor blockade was significantly faster in patients who received sufentanyl or fentanyl as compared to those who did not receive opioids. Consistently, we found that mean time to onset of sensory block at T10 was shorter in patients who received fentanyl as compared to those who did not. The difference was particularly significant in patients who received 25 mcg fentanyl. We also found that time to onset of complete motor block was shorter in patients who received 25 mcg fentanyl: 4 seconds (2-5) in Group I, 4 (2-4) in Group II, and 3 seconds (2-5) in Group III (p<0,001).

Y. Demiraran et al. compared the effects of increasing doses of intrathecal sufentanyl (1.5, 2.5 and 5.0 mcg) when combined with hyperbaric bupivacaine 0.5% (12.5 mg) for spinal anesthesia for elective cesarean section. They showed that patients who received additional sufentanyl had significantly longer duration of analgesia as compared to patients who did not (10). Bozdoğan, et al, found that time to first request for analgesia was significantly longer in patients who received either sufentanyl (218.96 ± 52.76 min) or fentanyl (174.72 ± 25.16 min) as compared to those who did not receive opioids (141.11 ± 26.17) (P <0.001). Although not significant, they also found that the duration of motor block was longer in patients who received opioids (9). Our results are consistent with the literature, time to the first request for analgesia was prolonged in patients who received additional opioids. We also found that the duration of motor block was slightly longer in patients who received opioids, this increment, however, was not as significant as others reported (Table 2). This may relate to the reduced amount of hyperbaric bupivacaine (10 mg) in patients who received additional opioids as compared to patients in the no-opioid group who received 12,5 mg.

Hypotension is one of the most frequent and potentially serious complications of cesarean delivery under spinal anesthesia (11, 12). The density of the anesthetic solution and the patient's position are the most important factors affecting intrathecal drug spread. Compared with plain solutions, the use of hyperbaric local anesthetics prevents cephalad spread, prolongs block duration and provides a better recovery profile. The use of prophylactic vasoconstrictor agents, preoperative fluid loading and left lateral positioning have been recommended to prevent hypotension (13). Lee et al. compared 2.6 mL 0.5% levobupivacaine with 2.3 mL of 0.5% levobupivacaine plus fentanyl in spinal anesthesia for urological surgery and found a similar incidence of hypotension

(14). In a randomized study Gunusen et al. compared different doses of intrathecal levobupivacaine combined with fentanyl for elective Cesarean section. The first group included patients who received intrathecal 5 mg of levobupivacaine combined with 25 mcg fentanyl, the second included 7.5 mg of levobupivacaine and 15 mcg fentanyl and the third 10 mg of levobupivacaine combined with 10 mcg fentanyl. Patients in the latter group had the highest incidence of hypotension (13). Bozdoğan, et al, found that while SBP and DBP values at 3-minute were significantly lower than baseline values in all three groups, the decrease was more significant in patients who received sufentanyl as compared to those who did not receive opioids. Similarly, they found that patients who received sufentanyl required more ephedrine than those who received fentanyl or non-opioid solutions (9). Our results were comparable with those of Bozdoğan, et al. SBP and DBP values at 3-minute were significantly decreased in all three groups ($p<0,05$). The difference in-between the three groups, however, was not significant ($p>0,05$).

Although regional anesthesia is accepted to be safer than general anesthesia for the newborn, hypotension may reduce uterus perfusion and cause fetal acidosis (15, 16). In a large epidemiologic study, Mueller et al. showed that the incidence of fetal acidemia (pH < 7.10) was significantly higher in patients who underwent spinal anesthesia (4.67%) or epidural anesthesia (2.39%) as compared with those who underwent general anesthesia (17). Patients receiving spinal anesthesia should be closely followed for hypotension and treated using vasoconstrictor agents and/or ephedrine. Dourado et al. compared the effects of sufentanyl combination with low-dose hyperbaric bupivacaine in spinal anesthesia for Cesarean section and found no difference at 1- and 5-minute Apgar scores (18). Gandam et. al. compared the combination of low dose bupivacaine and 25 mcg fentanyl with a conventional dose of hyperbaric bupivacaine for Cesarean section and, similarly, found no difference at 1- and 5-minute Apgar scores (5). Apgar scores were also similar among groups in the study by Demiraran et al. who compared different doses of intrathecal sufentanyl for spinal anesthesia for elective cesarean section (10). Our results were in line with the literature, 1- and 5-minute Apgar scores, as well as 5- and 10-minute heart rates and saturation levels were similar among the groups.

Intrathecal opioids have been reported to cause maternal pruritus, nausea, vomiting and respiratory distress(1) and neuraxial opioid-induced pruritus is more frequent in parturients (60 -100 %) than in non-parturients (30-100%) (19). The mechanism of neuraxial opioid-induced pruritus is controversial. The cephalad spread of neuraxial opioids in cerebrospinal fluid and their influence on 5HT3 receptors, the increase in the release of prostaglandins (PGE1 and PGE2) and the likelihood of using the same sensory neurons with the pain pathway are some of the postulated mechanisms so far (19). Bozdoğan et al. reported more pruritus in patients who received sufentanyl as compared to those who received fentanyl, and no pruritus in patients who did not receive opioids (9). In the study by Wang et al., patients who received intrathecal sufentanyl, but not those who received intravenous sufentanyl, reported pruritus (1). Gandam, et al, however, reported only one case of pruritus in patients who received intrathecal fentanyl (5). In the current study, one patient in Group I and two in group III experienced pruritus. These patients, however, had elevated liver enzymes and had already pre-operative pruritus. Nausea and vomiting was observed in only one patient in Group III.

CONCLUSION

To conclude, we believe that fentanyl combination should be considered for spinal anesthesia for Cesarean section and unless contraindicated, neuro-axial anesthesia should be preferred. The use of 25 mcg intrathecal fentanyl was not superior to 10 mcg intrathecal fentanyl. We recommend the use of intrathecal fentanyl because it shortens the onset time of anesthesia, increases the quality of intraoperative analgesia, prolongs the duration of sensorial block and delays the onset of postoperative pain.

Study Limitations

Given the retrospective design, we were not able to report post-operative 24-hour pain scores. Instead, we reported data related with time to first request for analgesia.

Ethics

Ethics Committee Approval: The study was approved by Ethics Committee of Ankara Etlik Zubeyde Hanim Maternity and Gynecology Training and Research Hospital. (approval number: 2018/7, 04.04.2018).

Informed Consent: Consent form was filled out by all participants.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.K.A., Z.Ö.U, Concept: F.K.A., G.Ö., Design: F.K.A., *B.G.A, G.Ö, Data Collection or Processing:* F.K.A., Z.Ö.U, G.Ö, Analysis or Interpretation: *F.K.A., S.Ö, Literature Search:* F.K.A, B.G.A., Writing: F.K.A., S.Ö, G.Ö.

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