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The effects of morphine and fentanyl alone or in combination added to intrathecal bupivacaine in spinal anesthesia for cesarean section

Sezaryen operasyonlarında spinal anestezide intratekal bupivakaine eklenen morfin, fentanil veya kombinasyonlarının etkileri

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Summary

Objectives: This randomized double-blind controlled trial examined the effects of fentanyl and morphine, alone and in combination, as adjuncts to spinal anesthesia for elective cesarean section.

Methods: Sixty women undergoing elective cesarean section, with spinal anesthesia using 0.5% hyperbaric bupivacaine, were randomly allocated to receive morphine 0.2 mg, fentanyl 25 μg, or fentanyl 12.5 μg plus morphine 0.1 mg, intrathecally. The start of spinal block, the time to T10 level, the highest sensorial and motor block level, time to regression of sensory block to T10, time to resolution of motor block, surgical characteristics, maternal side effects, Apgar and NACS scores, umbilical blood gas evaluations, and time to first analgesic requirement were recorded.

Results: No patient experienced pain during the intraoperative period. The degree and time of sensorial and motor block were similar in both groups, and there was no difference in time to T10 level and time to reversal of motor block. The difference in time to first postoperative analgesic requirement was statistically significant. There was no difference between groups in postoperative side effects. There were no neonatal differences in Apgar and NACS scores or umbilical blood gas evaluations.

Conclusion: The quality of postoperative analgesia with morphine, when used alone, was found to be superior to that with fentanyl. The combination of opioids offered no advantages over morphine alone.

Key words: Cesarean section; fentanyl; intrathecal bupivacaine; morphine; morphine/fentanyl.

Özet

Amaç: *Elektif sezaryenlerde, spinal anestezide intratekal morfin, fentanil ya da kombinasyonlarının randomize, çift kör kontrollü olarak karşılaştırılması amaçlandı.*

Gereç ve Yöntem: *Elektif sezaryenlerde %0.5 hiperbarik bupivakain ile spinal anestezi uygulanan 60 gebeye randomize olarak intratekal morphine 0.2 mg, fentanil 25 μg, ya da fentanil 12.5 μg ile beraber morfin 0.1 mg uygulandı. Spinal bloğun başlangıcı, T10 seviyesine ulaşma zamanı, duyusal ve motor bloğun en üst seviyeler duyusal bloğun T10'a gerilemesi, motor bloğun gerilemesi, cerrahi özellikler, maternal yan etkiler, Apgar ve NAKS skorları, umblikal kan gaz analizleri, ilk analjezik gereksinim zamanı kaydedildi.*

Bulgular: *İntraoperatif dönemde hiçbir hastada ağrı görülmedi. Sensoriyal ve motor bloğun derecesi ve süresi her üç grup arasında benzer olup T10'a gerileme ve motor bloğun kalkma zamanları arasında fark bulunmadı. Postoperatif ilk analjezik gereksinim zamanı fentanilin tek başına kullanıldığı grupta diğer gruplara göre çok kısa olup aralarındaki fark istatistiksel olarak anlamlı idi. Postoperatif yan etkiler ve hemodinamik etkiler açısından her iki grup arasında fark yoktu. Neonatal bulgular açısından APGAR ve umblikal kan gazı değerlerinde fark bulunmadı.*

Sonuç: *Postoperatif analjezide morfinin fentanile göre üstün olduğu; bupivakain/morfin kombinasyonuna fentanil eklenmesinin de ek klinik yarar sağlamadığı kanaatine varıldı.*

Anahtar sözcükler: Sezaryen; fentanil; intratekal bupivakain; morfin; morfin/fentanil.

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Introduction

Since the discovery of opiate receptors in the brain and spinal cord, the use of intrathecal opioids has become common practice as on effective method of analgesia. Hydrophilic opioids such as morphine provide excellent selective spinal analgesia because of small volume of distrubution and slow clerance from the spinal cord.[1] However, slow spinal cord penetration and prolonged duration in cerebrospinal fluid (CSF) caused by hydrophilicity also results in slow onset, prolonged duration of action, and risk of delayed respiratory depression from rostral spread in CSF. Lipophilic opioids have a more favorable clinical profile of fast onset, modest duration, and little risk of delayed respiratory depression.[2] Fentanyl is the most commonly used spinal lipophilic opioids. The combination therefore, has, the advantage of a prompt onset of analgesia and a long action, and has been used for spinal anesthesia in obstetric.

The primary outcome of our study was to see whether morphine 0.2 mg could provide analgesia during surgery equal to fentanyl 25 µg, or fentanyl 12.5 µg in combination with morphine 0.1 mg when used as an adjunct to bupivacaine in spinal anesthesia for cesarean section. Secondary outcomes were; time to block, ephedrine use, analgesic use, nausea and vomiting, pruritus and sedation during and after surgery.

Materials and Methods

After approval from the local Ethics Committee of University Hospital and written informed consent from each patients, 60 women (physical ASA status I or II) scheduled for elective cesarean section participated in the study. The indication for cesarean sections were either primary elective or repeat cesarean section with no evidence of fetal distress in any of the patients. Parturients were not studied if they had any contr-indication to regional anesthesia, had pre-eclampsia, weighed more than 100 kg, were less than 150 cm or greater than 180 cm in height. Women were fasted and did not receive premedication, and were randomly distributed according to a computer-generated random number list into three groups of 20 patients each.

All parturients were given 15 ml/kg Ringer's lactate solution infusion in 10-15 min through a 16 G peripheral cannula before operation. All women were received ranitidine 50 mg iv and metoclopramide 10 mg iv before spinal procedure. Hemodynamic monitoring consisted of a five-lead electrocardiogram, noninvasive blood pressure and a peripheral oxygen saturation. Spinal anesthesia was performed at the sitting position and intrathecal injections were given at the L3-4 level, through a 25-G Quincke spinal needle (Exelint Int.®, USA). After clear CSF flow was observed, patients in Group M were given intrathecal 0.2 mg (0.5 mL) morphine and patients in Group F were given fentanyl 25 µg (0.5 mL), and patients in Group MF 0.1 mg morphine plus 12.5 µg fentanyl as an adjunct to intrathecal 2 mL 0.5% bupivacaine heavy (patients taller than 165 cm, were given additional intrathecal 0.3 mL 0.5% bupivacaine heavy). The dose of the study drug used was unknown to the anesthesiologist administering the anesthesia or to the anesthesiologist who evaluated patient's responses.

Immediately after the intrathecal injection, patients were placed in the supine position, with the wedge under the right hip to maintain left uterine displacement. Oxygen (5 L/min) by facemask was given until delivery. Hypotension was defined as a decrease of more than 30% in systolic arterial pressure or a systolic arterial pressure below 100 mmHg. Hypotension was treated by intravenous fluid loading and 5 mg ephedrine iv. Bradycardia was defined as a heart rate below 55 beats/min and as treated with 0.01-0.02 mg/kg atropine iv. ECG, heart rate, pulse oximetry, and blood pressure were monitored continuously during surgery. Noninvasive systolic, diastolic and mean arterial pressure, heart rate and peripheral oxygen saturations were measured every 2 min for the first 20 min and then every 5 min throughout the procedure (Hewlett Packard, Viridia 24 C, Germany).

Observation and assesment of the block was made by one of the authors who was unaware of the composition of the intrathecal injection. Sensorial block level was evaluated with bilateral pin-prick test at the midclavicular line and motor block was evaluated by Bromage scale (0= none, 1= just able to move the foot only, 3= unable to move the knee

or foot) every two minutes until skin incision. The time to initiation of sensorial block, time to reach T10 sensorial block, time to reach highest sensory block and highest sensorial block degree, regresion time to T10 sensorial block, time to resolution of motor blockade were recorded. Surgery was started when sensorial block level reached T4. The times to skin incision, uterine incision, delivery of baby and last surgical suture were recorded. The surgical technique was uniform for all patients. At delivery, blod samples were collected from the umbilical artery and vein for blood gas analyses. Apgar scores at 1, 5 min and NACS scores at 2, 24 h were recorded. The quality of intraoperative analgesia was judged by the investigator at the end of surgery as exellent (no discomfort or pain), good (mild pain or discomfort, no need for additional analgesics), fair (pain that required additional analgesics), or poor (moderate or severe pain that required more than fentanyl 50 µg or general anesthesia). Postoperative analgesia was evaluated by determining the time interval between subarachnoid injection and the need for analgesia. Intra and postoperative occurrence of maternal side-effects such as nausea, vomiting, pruritus, and respiratory depression were recorded. Metoclopramide was given in case of vomiting or after two successive episodes of nausea. Pruritus was treated with 20 mg difenhidramin HCl iv. Sedation was scored as follows every 15 min throughout the operation; 0 = awake, 1 = drowsy, 2 = asleep but rousable, 3 = unrousable. Urinary retention was not assessed as every patient had a urethral catheter in situ for 24 h. In the postanaesthesia care unit heart rate, mean arterial pressure, oxygen saturation and respiratory rate were continuously monitorized for 24 hours. Intramuscular diclofenac sodium 75 mg (Voltaren®, Novartis, Swiss) was prescribed to be given postoperatively every 8 h on demand. Supplemental analgesia was provided with intramuscular meperidine 1 mg/kg on demand. The interval between the end of surgery and the first request for supplementary intramuscular analgesia was recorded.

The intraoperative analgesia was used as the main criterion for statistical analysis. By using the ANOVA test and setting the α risk at 5% and the β risk at 20%, a sample size of 20 would be sufficient to detect a reduction in intraoperative analgesia at least 20%. SPSS® 10.0 (SPSS Inc., Chicago, IL, USA) was used for data entry and analyses. The results are presented as mean ± standard deviation, median (range), or frequencies as appropriate. Continuous variables were analyzed using one-way ANOVA test. Nominal or ordinal variables were analyzed by χ^2 test and Fisher's exact test or Mann-Whitney U test. $P<0.05$ was considered statistically significant.

Results

There were no significant differences among the groups with respect to demographic characteristics, gestational age, parity of the women and duration of surgery (Table 1). Surgical variables such as spinal anesthesia induction to delivery time, skin incision to delivery time, uterine incision to delivery time and duration of surgery were similar in both groups. Apgar scores at 1, 5 min and NACS scores at 2, 24 h were not significantly different among the groups. Umbilical gases (arterial and venous) were part of the obstetric routine at the study hospital and were

Table 1. Patient variables

	Morphine (M) (n=20)	Fentanyl (F) (n=20)	Combined (MF) (n=20)
Age (yr)	31.5±5.9	30.9±4.5	32.1±5.4
Weight (kg)	75.8±10.3	73.7±9.2	75.8±10.3
Height (cm)	163.5±6.2	162.2±5.9	161.5±6.6
Gestational age (wk)	39.2±1.2	38.7±1.5	38.2±1.3
Nulliparous (n)	12	11	12
Multiparous (n)	8	9	8
Duration of surgery (min)	59.8±11.3	60.3±10.7	59.2±10.3

Data are given mean ± SD or as number of patients (n). No significant differences between groups.

Table 2. Neonatal condition

	Morphine (M) (n=20)	Fentanyl (F) (n=20)	Combined (MF) (n=20)
Apgar score			
1 min	9 (8-10)	9 (8-9)	9 (6-10)
5 min	10 (10-10)	10 (9-10)	10 (8-10)
Apgar score < 7 (n)			
1 min	0	0	1
5 min	0	0	0
NACS			
2 h	35.3±2.0	36.4±2.1	35.5±2.1
24 h	37.8±1.3	38.6±1.0	37.6±1.1
Umbilical artery pH	7.29±0.8	7.34±1.0	7.30±1.0
Umbilical vein pH	7.30±0.8	7.35±0.9	7.33±0.8

Apgar scores are given as median (range). Apgar scores <7 are given as number of patients. The remaining data are given as mean ± SD. No significant differences between groups; NACS: Neurologic and adaptive capacity score.

therefore recorded for 100% of patients. These values were within normal limits and without significant differences among the groups (Table 2).

The characteristics of spinal block are summarized in Table 3. There were no significant differences among the groups in the time to initation sensorial block (time to reach L1 sensory block), time to T10 sensory block, time to highest sensory block, highest sensory block level, time to regression of sensory block to T10 level and time to resolution of motor blockade.

There were no differences among the groups with respect to overall quality of intraoperative analgesia. None of the patients received any supplemental analgesics or sedatives during the intraoperative period. The time to first postoperative analgesic request was significantly longer in the group M when compared with the group F and group MF ($p<0.05$) (Table 4). Patients in groups F and MF made significantly more request for suplementary analgesia ($p<0.01$) (Table 5).

All patients were hemodynamically stable during the perioperative period. The hypotensive response to the spinal block, as well as ephedrine requirements were similar in three groups. The mean of efedrine requirements for group M 14.7 mg (±10.1 mg), group F 15.8 mg (±11.3 mg) and group MF 15.2 mg (±11.9 mg). There were no significant differences among groups intraoperative and postoperative nausea, vomiting and pruritus incidences (Table 6). Respiratory parameters were also stable

Table 3. Block characteristics

	Morphine (M) (n=20)	Fentanyl (F) (n=20)	Combined (MF) (n=20)
Time to initiation of sensorial block (min)	3.10±1.7	2.01±0.8	2.3±1.2
Time to T10 sensory block (min)	4.1±1.7	3.8±1.4	4±1.5
Time to highest sensory block (min)	7.6±2.3	7.5±2.1	7.4±2.4
Highest sensory block level	T4 (1-4)	T4 (1-4)	T4 (1-4)
Time to regresion of sensory block to T10 (min)	164±11.5	148.9±12.9	162.7±9.9
Time to resolution of motor blockade (min)	278±16.5	225±32.9	263±23.3

Highest sensory block level is given as median (range). The remaining data are given as mean ± SD.

and oxygen saturation values did not decrease to less than 97% in any patient, at any time during the study period. There were no significant differences between the groups with respect to sedation scores intraoperatively (Table 7).

Discussion

The addition of opioid to local anesthetic is widespread accepted in anesthesiologic practice in the management of spinal anesthesia for cesarean section. In this study, we have shown that the addition

Table 4. Efficacy of spinal anesthesia

	Morphine (M) (n=20)	Fentanyl (F) (n=20)	Combined (MF) (n=20)
Quality of intraoperative analgesia			
Excellent	17	19	19
Good	3	1	1
Fair	0	0	0
Poor	0	0	0
Time to first analgesic request (h)	20.5±6.7*	4.2±3.9	12.7±4.1

Data are given as n (%) or mean ± SD. * p<0.05.

Table 5. Analgesic requirement in the first 24 h

	Morphine (M) (n=20)	Fentanyl (F) (n=20)	Combined (MF) (n=20)
Diclofenac sodium in 24 h (mg)	18.7±33.3	142.5±59.1	63.7±44
Meperidine in 24 h (n)	0	9	3

Data are given mean±SD and as number (%) of patients.
Groups F and MF requested significantly more doses than group M (p<0.01).

Table 6. Intraoperative and postoperative side effects

	Morphine (M) (n=20)	Fentanyl (F) (n=20)	Combined (MF) (n=20)
Pruritus intra-/ postoperatively	1/7	3/11	1/8
Nausea intra-/ postoperatively	1/9	3/5	2/7
Vomiting intra-/ postoperatively	0/2	0/0	0/1

Data are given mean±SD and as number (%) of patients.
Groups F and MF requested significantly more doses than group M (p<0.01).

Table 7. Intraoperative sedation scores

	Morphine (M) (n=20)	Fentanyl (F) (n=20)	Combined (MF) (n=20)
Awake	12	9	11
Drowsy	8	9	8
Asleep but rousable	0	2	1
Unrousable	0	0	0

Data are given number of patients (n).
Worst sedation score during the perioperative period. No significant differences between groups.

of morphine and fentanyl to hyperbaric bupivacaine produces good quality of intraoperative analgesia and the addition of morphine increases the duration of analgesia compared with the fentanyl groups.

Intrathecal morphine in doses of 0.1-0.2 mg and fentanyl 10-25 μg are commonly used in obstetric analgesia.[1] But there is no consensus yet about the optimal choice of opioid and dosage. Intrathecal fentanyl has been shown to improve intraoperative analgesia in doses ≥6.25 μg. Hunt et al. studied intrathecal fentanyl doses ranging from 6.25 to 50 μg with a standart bupivacaine spinal anesthetic.[3] No additional benefit was found by increasing the intrathecal fentanyl dose. Likewise, Chu et al. studied intrathecal fentanyl (0-15 μg) as a suplement to bupivacaine spinal anesthesia.[4] Ten micrograms of fentanyl were needed to improve intraoperative analgesia; 12.5 μg lengthened postoperative analgesia. In contrast to these studies suggesting a ceiling effect of intrathecal fentanyl, Belzarena examind higher doses of intrathecal fentanyl (0.25-0.75 $\mu g \cdot kg^{-1}$) as a supplement to bupivacaine spinal anesthesia.[5] Postoperative analgesia increased in duration with increasing fentanyl doses, while spinal anesthetic motor and sensory recovery times were not prolonged. Hamber and Viscomi recommend using 20-30 μg fentanyl intrathecally to supplement bupivacaine spinal anesthesia for cesarean section.[2] In the present study, intrathecal 25 μg fentanyl provided effective analgesia in the first 4 h postoperatively.

The intraoperative effectiveness of intrathecal morphine in spinal anesthesia has been described previously.[6,7] Nevertheless, its slow onset of action has raised doubts about its intraoperative effectiveness in anesthesia for cesarean section where pain is visceral and caused mostly by peritoneal traction. In this study, none of the patients complained of discomfort during surgery, so no supplemental analgesia was given. This confirmed the primary outcome of the study, showing that morphine could provide analgesia equivalent to fentanyl during surgery.

In patients undergoing cesarean section with spinal anesthesia, intrathecal opioids may cause additional pruritus, nausea, vomiting, respiratory depression and urinary retention due to μ and K opioid receptor activations.[8] In all of the dose-response studies for cesarean section, the most consistent side effect was pruritus.[9] Although pruritus was generally described as mild, it is occasionally very distressing to the patient and may require pharmacologic intervention. Dahl et al. demonstrated in their retrospective study which included 485 patients, that the incidence of pruritus is very high but similar in all opiod groups.[10] In this study, there was no difference between the groups for the incidence of pruritus and most pruritus cases were mild and only three patients in the morphine group required treatment.

Although nausea is generally considered a significant side effect of opioid administration, intrathecal opioids may actually protect againts intraoperative nausea and vomiting. Intraoperative nausea and vomiting is frequently observed during cesarean sections performed under regional anesthesia, particularly with exteriorization of the uterus and during peritoneal closure. Palmer et al. reported a significant decrease in the incidence of perioperative nausea and vomiting during Cesarean delivery with the addition of intrathecal fentanyl 15 μg to a standardized hyperbaric lidocaine.[11] Similarly, Dahlgren et al. found a reduced requirement for intraoperative antiemetic medication when spinal opioids were added to the local anesthetic spinal for cesarean section.[12] Finally, Cooper et al. reported a statistically significant decrease in intraoperative nausea with the addition of intrathecal fentanyl (25 μg) to a standardized spinal anesthetic for cesarean section.[13] Sibilla et al. showed that spinal opioids cause more nausea given in combination than if given alone.[14] However, in this study, there was no statistically difference between groups with regard to nausea and vomiting.

Sedation was shown to be less with opioids administered centrally than via the parenteral route. Sedation induced by lipophilic opioids has generally not ben reported except with doses exceeding those commonly used in current clinical practice.[15] In this study, 60% of patients in group M, 45% of patients in group F and 55% of patients in group MF were completely awake.

There are conflicting data about the incidence of late respiratory depression after intrathecal opioid administration. In a prospective study on 856 pa-

tients, there were eight cases of respiratory depression after 0.2 mg intrathecal morphine.[15] Swart et al. reported one case of respiratory depression at postoperative 14 hours after the administration of 0.1 mg intrathecal morphine in addition to bupivacaine in thirty patients undergoing cesarean section with spinal anesthesia.[16] This respiratory depression was attributed more to postoperative parenteral opioid consumption (24 mg morphine) by patient-controlled analgesia than spinal opioid. In different studys with hyperbaric bupivacaine plus different doses of fentanyl no respiratory depression was determined.[14,17]

The low lipid solubility of morphine accounts for its slower onset but longer duration of action. When administered intrathecally, its duration of action is 12-24 h. The effectiveness and safety of the administration of intrathecal 0.2 mg morphine combined with hyperbaric bupivacaine providing an average of 14 h of analgesia has been reported in earlier studies.[18] Abboud et al. studied 35 patients undergoing cesarean section with spinal anesthesia using either 0.1 mg morphine, 0.25 mg morphine or saline as an adjuvant to hyperbaric bupivacaine.[19] In patient groups receiving morphine 0.1 and 0.25 mg, excellent postoperative analgesia with long duration (27.7±4.0 h and 18.6±0.9 h, respectively) was obtained. All patients in the saline group required additional subcutaneous morphine (8 mg) within three hours of spinal anesthesia. In another study, the effects of adding 0.2 mg morphine sulfate to hyperbaric spinal bupivacaine were evaluated in 34 patients undergoing cesarean section.[19] The patients given intrathecal 0.2 mg morphine in addition to hyperbaric bupivacaine did not request additional analgesia for 27±0.7 h, compared with 2±0.3 h in patients given saline.

In conclusion these results demonstrated that 0.2 mg intrathecal morphine is as effective as 25 fentanyl for intraoperative analgesia and produces better postoperative analgesic quality than fentanyl. The combination of these opioids at lower doses does not increase intraoperative analgesic quality neither decreases advers effects.

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