RESEARCH ARTICLES

SYNERGISTIC EFFECT OF INTRATHECAL BUPIVACAINE AND FENTANYL IN SPINAL ANESTHESIA

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Gazi Medical Journal 1999; 10 : 100-105

SUMMARY

Purpose : *This study was designed to investigate the clinical effects of the combination of intrathecal fentanyl and bupivacaine in spinal anesthesia.* ***Methods :*** *Eighty patients undergoing elective lower extremity or lower abdominal operations were included in the study. No premedication was used. The patients were randomly divided into two groups. In group I, 0.5% hyperbaric bupivacaine, 10 mg (2 ml) and saline 0.25 ml (control group) were administered intrathecally. In group II, 0.5% hyperbaric bupivacaine 10 mg (2 ml) and fentanyl 0.25 ml (12.5 μg) (fentanyl group), were administered intrathecally.* ***Results :*** *The study groups were comparable with respect to the hemodynamic parameters ($p > 0.05$). The time when two segments regression and postoperative pain started were significantly longer in Group II than in Group I ($p < 0.01$). Respiratory depression and sedation were not observed in any of the patients. The most common side effect was pruritus in Group II.* ***Conclusion :*** *The results indicated that administration of bupivacaine and fentanyl showed antinociceptive synergism, but motor blockade was not affected by this combination.*

Key words : *Spinal Anesthesia, Spinal Injections, Epidural Injections, Bupivacaine, Fentanyl.*

INTRODUCTION

In spinal anesthesia, better perioperative and prolonged postoperative analgesia can be obtained by using opioids in conjunction with local anesthetics (1-3). The effect of fentanyl, a lipophilic opioid, starts immediately after intrathecal administration. However, the duration of its effect is dose dependent (3-5). In spinal anesthesia, hyperbaric bupivacaine combined with fentanyl, 6.25 mg or more, facilitates precise perioperative analgesia (4) with minimal side effects (6-7).

In this study, we used the combination of bupivacaine and fentanyl in spinal anesthesia to investigate its influence on the sensory and motor blocks, and postoperative pain, as well as complications.

PATIENTS AND METHODS

Eighty patients (ASA I or II) undergoing elective lower extremity or lower abdominal operations were included in this study, and approval from the ethical committee was obtained. Preoperative physical examination was performed in each patient. Patients at risk of developing sepsis, bacteriemia, wound infection

and intracranial pressure increase and ASA III-V group patients were excluded from the study.

None of the patients had premedication. Peripheral oxygen saturation (SpO2), noninvasive arterial pressure (AP) as well as electrocardiography (ECG) were continuously monitored (Drager Cato 8040). A vascular line was created through a large antecubital vein with an 18-gauge catheter and crystalloid solution, 10 ml/kg, was administered. Preoperative systolic, diastolic and mean arterial pressures, peripheral oxygen saturation, heart rate and respiratory rate were recorded.

In CSEA, the patients were placed in the lateral decubitus position, and an 18 gauge Tuohy needle was introduced into the epidural space through the corresponding intervertebral space (L3-4 or 4-5) as described by Rawal, et al (8). A 26 gauge Quincke type spinal needle was introduced through the 18 gauge epidural Tuohy needle. Following the flow of cerebrospinal fluid through the needle, either 0.5% hyperbaric bupivacaine, 10 mg (2 ml) and saline 0.25 ml, or 0.5% hyperbaric bupivacaine, 10 mg (2 ml) and fentanyl 0.25 ml (12.5 mg) injection was made through the spinal needle. The former (group I) constituted the control group, and the latter (group II) constituted the fentanyl group. The anesthesiologist who administered the drugs to the patients was unaware of the combination being used.

The spinal needle was removed, and a 20 gauge catheter was introduced 3-5 cm into the epidural space through the cranially directed Tuohy needle. After negative aspiration, the catheter was secured and the patient was placed in the supine position.

For the first 30 minutes during and after the spinal injection, systolic, diastolic and mean arterial pressures, heart rate, SpO2 and respiratory rate were recorded every five minutes. Systolic blood pressure 20% below the preoperative control level was considered as hypotension, and a heart rate below 50 beats / minute was considered as bradycardia. In case of bradycardia or hypotension, atropine, ephedrine or intravenous fluids were given. A respiration rate less than 10 per minute and SpO2 less than 90 % were considered respiratory depression. In such a case, oxygen application with a mask was planned. All patients were monitored and observed for at least three hours postoperatively in the recovery room in order to record complications and adverse drug reactions.

Spread of the sensory block was recorded on the midclavicular line, using the pinprick test. The records were obtained every two minutes for the first 10 minutes, every five minutes for the second 20 minutes and every 15 minutes until two segmental regression occurred. In the case of prolongation of the anticipated operation duration, administration of 1.5 ml bupivacaine 0.5% for each unblocked segment via the epidural catheter was planned.

Motor block was recorded every two minutes for the first 10 minutes, every five minutes for 20 minutes and every 15 minutes until motor block resolution. Motor blockade was assessed using modified Bromage criteria (0 = full ability to move legs, I = ability to move toes and partially move knees, II = ability to move toes but not knees, III = inability to move toes or knees).

Onset of two segmental regression of the sensory block, completion and resolution times of the motor blockade and time of onset of the postoperative pain were recorded.

When postoperative analgesia was needed, 12.5 mg bupivacaine 0.5% (2.5 ml) in 7.5 ml saline was given as a bolus injection through the epidural catheter. The epidural catheter was removed forty-eight hours after the operation.

The Mann Whitney U test was used for the statistical analysis of two segmental regressions of the sensory block and postoperative pain onset time. Other data was assessed by the student- t test and a p value < 0.05 was considered statistically significant.

RESULTS

There was no statistically significant difference between the groups with regard to age, sex and body weight (Table 1). The mean operation times for groups I and II were 79.5 ± 27.6 and 78±17.2 minutes, respectively. The operation times of the groups were not significantly different. Patient-related vital parameters (heart rate, systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, peripheral oxygen saturation and respiratory rate

as well as the changes of these parameters prior to or after spinal injection) were not significantly different between the groups.

The time related parameters of sensory and motor blocks are summarized in Table II.

Perioperative additional epidural doses were needed in 8 (20%) and 1 (2.5%) patients in group I and group II, respectively ($p<0.01$).

Postoperative pain began within 121±25 minutes in group I and 205 ± 30.5 in group II.

Table 1 : Characteristics of the groups.

	Group I (n=40) Mean ± SD (range)	Group II (n=40) Mean ± SD (range)
Age (year)	32 ± 3.1 (21-57)	33 ± 2.1 (20-59)
Body Weight (kg)	71.2 ± 10.74 (54-90)	75.06 ± 11.27 (58-97)
Height (cm)	170.6 ± 7.49 (150-184)	172.23 ± 8.76 (155-190)
Sex (M/F)	33/7	32/8
Duration of surgery (min)	79 ± 27.64 (50-185)	78.83 ± 17.2 (40-145)

Table 2 : The time related parameters of sensory and motor blocks in the groups (*P 0.01).

	Group I (n=40)	Group II (n=40)
Onset time of sensory block (min)	4.73 ± 0.98 (4-6)	4.53 ± 1.16 (2-6)
Two segment regression of sensory block (min)	74.5 ± 8.23 (60-100)	108 ± 11.49 (90-125)*
Complete motor block time (min)	7.8 ± 1.76 (6-10)	7.5 ± 2.14 (4-15)
Complete resolution time of motor block (min)	130.62 ± 15.62 (100-160)	135.51 ± 20.32 (150-185)
Postoperative pain onset time (min)	121.25 ± 16.43 (95-160)	205 ± 30.47 (150-285)*

The highest sensory block was achieved at T8 (T6-10) and T7 (T6-9) in group I (control) and group II (fentanyl), respectively. Time of onset for sensory block was 4.73 ± 0.98 minutes for group I and 4.53 ± 1.16 minutes for group II. The difference was not significant.

Two segment regression of the sensory block occurred within 74.5±8.2 and 108±11.5 minutes in group I and II, respectively. The difference was statistically significant ($p<0.01$). Intraoperative additional dose of the epidural injection was not needed in any of the patients.

Complete development of the motor block took 7.8±1.76 and 7.5±2.14 minutes in group I and II, respectively. There was no significant difference between the groups ($p>0.05$).

Delay of pain initiation time in group II was statistically significant ($p<0.01$).

Pre-and postoperative complications are summarized in Table III. No patient experienced respiratory depression, sedation or headache. There was no significant difference between the groups in terms of hypotension, bradycardia, nausea, vomiting and back pain. Those who had hypotension or bradycardia had their legs elevated and were infused quickly with intravenous fluid. Ephedrine administration was not needed. Symptomatic treatment was preferred for those who had nausea and vomiting. Only two patients had back pain within 24 hours postoperatively.

Table 3 : Perioperative and postoperative complications (*p 0.05).

	Group I (n=40)	%	Group II (n=40)	%
Respiratory depression	0	0	0	0
Sedation	0	0	0	0
Nausea	4	10	4	10
Vomiting	1	2.5	2	5
Hypotension	3	7.5	4	10
Bradycardia	2	5	1	2.5
Shivering	12	30	5*	12.5
Itching	0	0	8*	20
Postspinal headache	0	0	0	0
Back pain	1	2.5	1	2.5

Shivering was significantly ($p<0.01$), less common in group II (12.5%) than group I (30%). It was treated by warming the patient with an electric blanket.

Itching was not observed in group I, but it was seen in 8 (20%) patients in group II. The difference was significant ($p<0.01$). It was not too severe to upset the patients and was not treated.

DISCUSSION

It was reported that CSEA combines the advantages of spinal and epidural anesthesia, facilitates adequate sensory block and analgesia, and also makes it possible to adjust the level and duration of the sensory block with epidural application of local anesthetic, and the epidural catheter can be used for postoperative analgesia (1, 9).

Wang et al (10) found experimentally that there was a potential synergism between intrathecal fentanyl and bupivacaine. In a rat model, intrathecal opioids and local anesthetics showed analgesic synergism in the sensory and motor nociception, while antinociception did not affect the motor functions (11). In central nerve blockade, it was reported that the use of local anesthetic in conjunction with the fentanyl facilitated a comfortable intraoperative analgesia and extended the duration of postoperative analgesia (4).

The lipophilic opioid, fentanyl, in contrast to a hydrophilic opioid when used in conjunction with a local anesthetic, has an earlier onset of effect, and this is an advantage for the postoperative period (12). According to Hunt et al (4), the synergism between fentanyl and bupivacaine does not affect the onset of sensory block and the duration of motor block, but it facilitates an effective perioperative analgesia. Liu et al (13) reported that administration of 20mg fentanyl during lidocaine induced spinal anesthesia prolonged the duration of sensory block, while the duration of motor resolution and the time onset of sensory and motor block did not change. According to Randalls et al. (1), intrathecal bupivacaine plus 10 mg fentanyl resulted in precise intraoperative and elongated postoperative analgesia (201 ± 29 min). In addition, this protocol decreased the side effects as compared to the control group.

In a study by Belzarena (7), intrathecal application of 0.5 and 0.75mg/kg fentanyl in conjunction with bupivacaine, extended the duration of postoperative analgesia (640±142 min. and 787±161 min., respectively). However, with his protocol, perioperative respiratory rate decreased, patients were heavily sedated, but felt itchy.

Sigh et al (3) postulated that in spinal anesthesia with 25 mg fentanyl and bupivacaine, the duration of two segment sensory block (110±33 min) and regression to L1 dermatome (141 ± 37 min) were prolonged, while the motor block resolution and sensory and motor block onset times did not change. Furthermore, they reported that fentanyl administration delayed the time of onset of early postoperative pain and subsequently less analgesic was needed in the early postoperative period.

According to Chu et al. (6), intrathecal bupivacaine with 7.5mg fentanyl did not change the result significantly. However, with a dose of 12.5mg fentanyl, a precise surgical anesthesia was obtained and postoperative onset of pain (201,3±16.4) was delayed significantly compared to the control group.

According to the results of this study, in the group given intrathecal bupivacaine with 12.5 mg fentanyl, the onset of motor and sensory blocks and motor resolution time did not change when compared to the control group. However, two segment sensory block regression time (108 and ±11.49 min) and postoperative pain onset time (205±30.47) were prolonged compared to the control group. As a result of delayed sensory block regression by fentanyl, the need for perioperative additional doses of epidural drug was less needed (2.5%) in group I than in group II (20%).

Liu et al. (13) postulated that they did not observe any respiratory depression with the combination of intrathecal lidocaine and 20mg fentanyl. According to Varrasi et al. (14), in elderly patients who had spinal anesthesia, respiratory depression was not observed with lidocaine in combination with 12.5 and 25mg fentanyl, while respiratory depression was observed with 50mg fentanyl by 28.5 % at 90 and 150 minutes.

Randalls et al. (1) did not report any sedation with local anesthetics and 10mg fentanyl intrathecally. Hunt (4) and Varrassi, et al. (14) did not report respiratory depression with intrathecal administration of bupivacaine and 12.5mg fentanyl.

In this study, we also did not observe sedation or respiratory depression. Our results are comparable with the results of Liu (13) and Varrassi (14), et al. Absence of sedation or respiratory depression in this study may be possibly due to the involvement of younger patients as well as use of lower doses of highly lipophilic fentanyl.

Liu et al. (13) reported that addition of 20 mg fentanyl to lidocaine intrathecally did not change nausea incidence. According to Randalls et al. (1), intrathecal bupivacaine with 10mg fentanyl gives rise to minimal nausea and this result is similar to the control group. Hunt et al. (4) and Varrassi et al. (14) also reported similar results that intrathecal bupivacaine with 12.5mg fentanyl did not change the outcome of nausea significantly when compared to the control group.

The results of this study also revealed that addition of fentanyl to intrathecal bupivacaine resulted in a similar outcome in terms of nausea and vomiting in both study and control groups. Our results correlate with the results of the former studies.

It was shown in the animal studies that fentanyl, when combined with bupivacaine intrathecally, did not increase the effect of bupivacaine on the sympathetic efferent pathways (10). Liu et al. (13) observed hypotension and bradycardia in patients who were given lidocaine with 20mg fentanyl intrathecally as well as in the control group. According to Randalls et al. (1), the frequency of hypotension did not change significantly with addition of fentanyl to intrathecal bupivacaine. Our results are also comparable with the former ones, including those of Liu et al. and Randalls et al. with regard to the frequency of hypotension which was similar in both study and control groups.

According to Chu et al. (6), shivering subsided significantly with 12.5 mg fentanyl and bupivacaine combination intrathecally. Chow and Cho (15) reported that shivering could be controlled significantly by the administration of minor doses of intrathecal fentanyl (12.5mg) during spinal anesthesia when compared to the control group (from 65.8% to 12.2%). In this study, we found that the frequency of shivering significantly diminished with 12.5mg fentanyl intrathecally when compared to the control group (from 30% to 12.5%). Higher rate of shivering in the series of Chow and Cho might be attributed to utilization of huge amounts of cold fluids during the transurethral resection operation.

Norris et al. (16) reported that itching would be frequently encountered after intrathecal opioid application. According to Hunt et al. (4), 25 to 50mg fentanyl in addition to intrathecal bupivacaine increased the frequency of itching by 80%, which was statistically significant. According to Fernandez et al. (17), the rate of pruritus is higher with spinal 25 mg fentanyl-bupivacaine combination than bupivacaine alone in elderly patients. Liu et al. (13) noted that all patients had been itchy with 20mg fentanyl in addition to lidocaine intrathecally. Varrassi et al. (14) reported that intrathecal bupivacaine with 25 mg fentanyl resulted in itching in 57.1% while with 12.5 mg fentanyl the itching was not seen in any of the patients. According to our results, the rate of itching is higher by 20 % with intrathecal bupivacaine and fentanyl combination when compared to the control group. Our rate of itching was lower than that of Liu et al. (13) and Hunt et al. (4). This difference is attributable to the use of lower amounts of fentanyl in our study.

One of the worrisome problems after spinal anesthesia is the postspinal headache. Lynch et al. (18) reported minimal postspinal headache (0.5-0.8%) when they applied spinal anesthesia with a gauge 27 needle. Flatten et al. (19) reported that there was no postspinal headache with a gauge 29 needle, while the failure rate of the anesthesia increased and that postspinal headache was encountered in 2.13 % within the first forty-eight hours when a gauge 26 needle was utilized. According to Brownridge (20) and Casati et al. (21), the frequency of headaches is quite low with combined spinal epidural anesthesia and possibly, this is related to the thickness of the spinal needle used. A study by Norris et al. (16) revealed that placing the Tuohy needle parallel to the dural fibers also made the spinal needle

parallel to the dura which, in turn, decreased the frequency of headache. Stacey et al. (22) did not encounter headache in their series. In this study, none of the patients experienced postspinal headache. Our results were contradictory to the results of Flaatten et al. and Linch et al. who studied spinal anesthesia and did not make a comparison with CSEA.

In conclusion, we found that additional fentanyl did not change the onset of motor block and duration of resolution in spinal anesthesia induced with intrathecal bupivacaine with 12.5 mg fentanyl. Although the onset time of motor block remained unchanged, it was shown that the duration of two segments sensory block regression was prolonged. Furthermore, postoperative onset of pain was also prolonged and the frequency of side effects did not increase except for itching. It was found that intrathecal combination of bupivacaine and fentanyl shows antinociceptive synergism, and fentanyl could increase the sensory block in bupivacaine induced spinal anesthesia without any synergism with motor blockade.

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REFERENCES

1. Randalls B, Broadway JW, Browne DA, Morgan BM. Comparison of four subarachnoid solutions in a needle-through-needle technique for elective caesarean section. Br J Anaesth 1991; 66: 314-318.
2. Abouleish E, Rawal N, Shaw J, Lorenz T, Rashad MN. Intrathecal morphine 0.2 mg versus epidural bupivacaine 0.125% or their combination: Effects on parturients. Br J Anaesth 1991; 74: 711-716.
3. Singh H, Yang J, Thornton K, Giesecke AH. Intrathecal fentanyl prolongs sensory bupivacaine spinal block. Can J Anaesth 1995; 42: 987-991.
4. Hunt CO, Naulty JS, Bader AM. Perioperative analgesia with subarachnoid fentanyl-bupivacaine for cesarean delivery. Anesthesiology 1989; 71: 535-540.
5. Al-Mufti R, Morey R, Shennan A, Morgan B. Blood pressure and fetal heart rate changes with patient-controlled combined spinal epidural analgesia while ambulating in labour. Br J Obstet Gynaecol 1997; 104. 554-558.
6. Chu CC, Shu SS, Lin SM. The effect of intrathecal bupivacaine with combined fentanyl in caesarean section. Acta Anaesthesiol Sin 1995; 33: 149-154.
7. Belzarena SD. Clinical effects of intrathecally administration fentanyl in patients undergoing cesarean section. Anest Analg 1992; 74: 653-657.
8. Rawal N, Schollin J, Wesström G. Epidural versus combined spinal epidural block for caesarean section. Acta Anaesthesiol Scand 1988; 32: 61-66.
9. Patel M. Combined spinal-extradural anesthesia (letter). Anesth Analg 1992; 75: 640-641.
10. Wang C, Chakrabati MK, Whitwam JG. Specific enhancement by fentanyl of the effects of intrathecal bupivacaine on nociceptive afferent but not on sympathetic efferent pathways in dogs. Anesthesiology 1993; 79: 766-773.
11. Maves TJ, Gebhart GF. Analgesic synergism between intrathecal opioids and local anesthetics (letter). Anesth Analg 1991; 73: 365-366.
12. Bohannon TW, Estes MD. Evaluation of subarachnoid fentanyl for postoperative analgesia. Anesthesiology 1987; 67: A-237.
13. Liu S, Chiu A, Carpenter RL, Mulroy MF, Allen HW, Neal JM, Pollock JE. Fentanyl prolongs lidocaine spinal anesthesia without prolonged recovery. Anesth Analg 1995; 80: 730-734.
14. Varrassi G, Celleno D, Capogna G. Ventilatory effects of subarachnoid fentanyl in the elderly. Anaesthesia 1992; 47: 558-562.
15. Chow TC, Cho PH. The influence of small dose intrathecal fentanyl on shivering during transurethral resection of prostate under spinal anesthesia. Acta Anaesthesiol Sin 1994; 32: 165-170.
16. Norris MC, Grieco WM, Borkowski M,Leighton BL, Arkoosh VA, Huffnagle HJ, Huffnagle S. Complications of labor analgesia: Epidural versus combined spinal-epidural techniques. Anesth Analg 1994; 79: 529-537.
17. Fernandez-Galinski D, Rue M, Moral V, Castells C, Puig MM. Spinal anesthesia with bupivacaine and fentanyl in geriatric patients. Anesth Analg 1996; 83: 537-541.
18. Lynch J, Kasper SM, Strick K, Topalidis K, Schaaf H, Zech D, Krings-Ernst I. The use of Quincke and Whitacre 27-Gauge needles in orthopedic patients: Incidence of failed spinal anesthesia and postdural-puncture headache. Anesth Analg 1994; 79:124-128.
19. Flaatten H, Rodt SA, Vamnes J, Rosland J, Wisborg T, Koller ME. A comparison between 26 and 29-gauge needles in young patients. Anaesthesia 1989; 44: 147-149.
20. Brownridge P. Epidural and subarachnoid analgesia for elective caesarean section (letter). Anaesthesia 1981; 36: 70.
21. Casati A, D'Ambrosio A, Negri P.D, Fanelli G, Tagariello V, Tarantino F. A clinical comparison between needle-through-needle and double-segment techniques for combined spinal and epidural anesthesia. Regional Anesthesia and Pain Medicine 1998; 23: 390-394.
22. Stacey RGW, Watt S, Kadım MY, Morgan BM. Single space combined spinal-extradural technique for analgesia in labour. Br J Anaesth 1993; 71: 499-502.