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ORIGINAL ARTICLE

What is the optimal dose of intrathecal meperidine in open prostate surgery? A prospective double-blind randomized study

Açık prostat cerrahisinde intratekal meperidinin optimal dozu nedir? Bir prospektif çift-kör randomize çalışma

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Summary

Objectives: This study was an analysis of the effect of different dosages of intrathecal meperidine (40 mg, 50 mg, 60 mg, and 70 mg) on hemodynamic parameters, the duration of neural blockade, and the incidence of meperidine-related side effects in patients who underwent an open prostatectomy.

Methods: Sixty patients who underwent an open prostatectomy with combined spinal-epidural anesthesia were included. The patients were allocated to receive 1 of 4 different dosages of intrathecal meperidine (n=15 for each group): Group I: 40 mg, Group II: 50 mg, Group III: 60 mg, and Group IV: 70 mg. The duration of the block procedure, surgery duration, highest sensory block level, and anesthetic complications were recorded and analyzed.

Results: At 20 minutes after the spinal injection, the maximum sensory block level was T6 in Group I and II, and it was T5 in Group III and IV. The mean motor block scores at 20 minutes after the spinal injection were lower in Group I compared with the other groups (p<0.001 for all). The motor block duration was significantly shorter in Group I and II than in Group III and IV (p<0.001 for all). Surgeon satisfaction was greater in Group II, III, and IV compared with Group I (p<0.001 for all). Patient satisfaction was better in Group III and IV compared with Groups I and II (p<0.001 for all).

Conclusion: Intrathecal meperidine at a dose of 60 mg exerted a sufficient analgesic effect with minimum side effects in patients undergoing open prostatectomy.

Keywords: Intrathecal meperidine; open prostatectomy; optimal dose; patient satisfaction.

Özet

Amaç: Bu çalışmada; açık prostatektomi uygulanan hastalarda, farklı dozlarda intratekal meperidinin (40 mg, 50 mg, 60 mg ve 70 mg) hemodinamik parametreler, nöral blokaj süresi ve meperidine bağlı yan etki görülme sıklığı üzerindeki etkisini araştırdık.

Gereç ve Yöntem: Kombine spinal epidural anestezi ile açık prostatektomi uygulanan 60 hasta çalışmaya alındı. Hastalar dört doz intratekal meperidinden birini almak üzere (her grup için n=15) sahip olmak üzere ayrıldı: Grup I: 40 mg, Grup II: 50 mg, Grup III: 60 mg, Grup IV: 70 mg. Blok işleminin süresi, ameliyat süresi, en yüksek duyusal blok düzeyi ve anestezik komplikasyonlar kaydedildi.

Bulgular: Spinal enjeksiyondan 20 dakika sonra, grup I ve II'de maksimum duyusal blok seviyesi T6 idi ve grup III ve IV'de T5 idi. Spinal enjeksiyondan 20 dakika sonra ortalama motor blok skorları grup I'de diğer gruplara göre daha düşük olarak bulundu (hepsi için p<0.001). Motor blok süresi grup I ve II'de grup III ve IV'e göre anlamlı olarak daha kısaydı (hepsi için p<0.001). Cerrah memnuniyeti grup II, III ve IV'de grup I'e göre daha iyiydi (hepsi için p<0.001). Hasta memnuniyeti, grup I ve II'ye göre grup III ve IV'de daha iyiydi (hepsi için p<0.001).

Sonuç: Altmış mg dozda intratekal meperidin açık prostatektomi uygulanan hastalarda minimum yan etki ile yeterli analjezik etki gösterir.

Anahtar sözcükler: İntratekal meperidin; açık prostatektomi; optimal doz; hasta memnuniyeti.

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Introduction

Open prostate surgery is common among elderly patients. These patients have increased risk of perioperative mortality and morbidity due to additional co-morbidities such as cardiac, renal, cerebral and respiratory diseases.[1] It has been shown that the use of regional anesthesia during open prostate surgery reduces intraoperative blood loss and provides shorter durations of surgery, less postoperative pain, less analgesic supplemental use and a faster postoperative recovery compared with general anesthesia.[2]

Meperidine, a synthetic phenylpiperidine-derivative opioid has local anaesthetic properties.[3] For perineal and anorectal surgeries, the use of low dose intrathecal meperidine (30 mg) provides good haemodynamic stability and quality postoperative analgesia without additional analgesia requirement.[4–6] Studies demonstrated that intrathecal meperidine (1 mg/kg) reveals adequate sensory and motor blockades and prolonged postoperative analgesia for lower abdomen and limbs surgeries.[7–9]

On the other hand, intrathecal meperidine is often accompanied with minor side effects such as nausea, vomiting, bradycardia, respiratory depression, itching, hypotension and bronchospasm.[10,11] Clinicians tend to use smaller doses of intrathecal meperidine to reduce the incidence of side effects. The objective of this present study was to determine the optimal dose of intrathecal meperidine that produces satisfactory analgesia with minimum side effects in patients undergoing open prostatectomy. For this purpose, this present study investigated the effect of different dosages of intrathecal meperidine (40 mg, 50 mg, 60 mg and 70 mg) on hemodynamic parameters, the duration of neural blockade and the incidence of meperidine-related side effects in patients undergoing open prostatectomy. Primary outcome was to evaluate the patient's satisfaction. Secondary outcomes included the surgeon satisfaction, hemodynamic and anesthetic parameters.

Material and Methods

This prospective double-blind randomised study was approved by the Ethics Committee of Atatürk University, Medical Faculty (date: 08.06.2007; number: 52). Sixty consecutive patients with ASA (the classification of the American Society of Anaesthesiologists) I or II physical status who had consented in writing to undergo open prostatectomy for benign prostate hyperplasia under combined spinal-epidural anesthesia (CSE) were included. Patients with uncontrolled hypertension, neurologic diseases, hypersensitivity to meperidine and contraindications to spinal anesthesia such as coagulation disorder and infection at the puncture site were excluded from the study. Before transfer to the operating room, patients were allocated (using a computer-generated table of random numbers) to receive one of four doses of intrathecal meperidine (n=15, for each group): Group I: 40 mg, Group II: 50 mg, Group III: 60 mg, Group IV: 70 mg.

Premedication was provided with intramuscular 3 mg intravenous (IV) midazolam in all patients. Before entering the operating room, all patients received 15 mL/kg lactated Ringer's solution via IV cannula over 30 minutes. Standard monitoring including non-invasive arterial pressure, electrocardiography and pulse oximetry was established in the operating room. Before the operation; age, weight and height of the patients, ASA physical status, preoperative electrocardiogram findings, mean arterial blood pressure (MBAP), heart rate (HR) and peripheral oxygen saturation (SpO_2) values were recorded. Placing a combined-spinal and epidural anaesthesia set was planned to provide additional analgesia during surgery if needed and to use of epidural analgesia in post-operative pain management. After skin infiltration with 2% lidocaine, 18G Tuohy needle (Set for combined-spinal and epidural anaesthesia, Braun®, Melsungen, Germany) was inserted through the L2-3 intervertebral space with loss of resistance technique.[12] The needle was filled with saline and epidural space was localized when a clear loss-of-resistance of saline was detected. A 27-gauge pencil point needle was inserted intrathecally using the needle-through-needle technique. Once free flow of the cerebrospinal fluid was obtained, meperidine with a dose of 40 mg, 50 mg, 60 mg or 70 mg was injected over five seconds. The needle was removed and epidural catheter was inserted 3 cm into epidural space and secured in place. Following the placement of an epidural catheter, the patient was turned into the supine position without any tilt of the table. Sensory and motor block levels were tested every 5 min before, during, and after surgery by an anes-

thetist blinded to the dose of meperidine injected. Sensory block level was tested using pinprick tests and motor block level was evaluated with Modified Bromage scale (scale 0=full flexion of foot, knee and hip, ie, no motor block; scale 1=full flexion of foot and knee, unable to hip flexion; scale 2=full flexion of foot, unable to knee and hip flexion; scale 3=total motor block; unable to foot, knee, and hip flexion). When the sensory block reached the T8 dermatome, surgery was initiated. If no signs of analgesia were observed within the first 10 min after the intrathecal injection, spinal anesthesia was considered as failed. Additional 5 ml solution of 1.5% lidocaine was administered through the epidural catheter at 5-min intervals by limiting the total dose of 15 mg until a T8 level of the sensory block was achieved. When the satisfactory block level was provided, surgery was initiated in both groups. General anaesthesia protocol was administered for patients with three unsuccessful attempts to reach to spinal space. Also, if adequate surgical anaesthesia was not achieved after 30 minutes in patients, technique was considered as failure and general anaesthesia protocol was planned for these patients. Oxygen was delivered with a face mask during surgery.

Patients' MABP, HR and oxygen saturation values were recorded at the beginning of anaesthesia procedure and surgery, every 5 minutes during surgery and at 1 hour after surgery by an observer who was blinded to study groups. Ephedrine (IV, 10–15 mg) was administered in the case of hypotension (a 30% decrease in systolic blood pressure compared with preoperative values) and atropine (IV, 0.5 mg) was applied when bradycardia (the heart rate <45 beats/minute) was observed. Duration of surgery (the time from the start of the surgical incision to the completion of surgery), maximal sensory block level, anesthetic complications and the number of patients with failed spinal anesthesia were recorded. All surgical procedures were performed by the same three surgeons with same surgical technique. After surgery, all patients were transferred to the recovery room. In the recovery room, an independent observer blinded to the group assignment recorded the following data at 30 min and 1st, 2nd, 4th, 6th, 12th and 24th hours post-operatively: Visual analogue scale (VAS, 0 cm= no pain, 10 cm= worst pain imaginable) scores for pain severity at rest, status of patient and surgeon satisfactions (0=dissatisfied, 2=satisfied, 3=very satisfied), anesthetic complications (e.g., nausea, vomiting and headache), sensory block time (from the local anaesthetic injection to the recovery of S2 dermatome), motor block duration (the time from the local anaesthetic injection to the complete motor function recovery) and duration of analgesia (the time until the patients felt the surgical wound pain and requested supplemental analgesics after the intrathecal injection). In the case of VAS >3 in a patient, rescue analgesia was provided with 5 ml solution of 1.5% lidocaine through the epidural catheter.

Sample size was calculated as minimum 15 patients, based on our preliminary results to detect a minimum difference of 40% in the patient satisfaction among groups with a power of 84% and α of 0.05. Data were analysed using SPSS software 12.0. Results were calculated as mean±standard deviation and $p<0.05$ was considered as significant. The Kolmogorov-Smirnov test was used to assess the normal distribution of data. If data was not normally distributed, comparisons were determined using Mann-Whitney U-test. Comparisons were determined using the Anova test when data was normally distributed. Fisher's exact test was used to compare the percentage values.

Results

Eligible patients for this study were analysed in the CONSORT flow diagram (Fig. 1). During study period, one hundred patients were screened for eligibility. Seventy patients met the inclusion criteria. However, ten patients refused to participate in the study. Eventually, the study population consisted of sixty patients (n=15, for each group).

There were no significant differences among groups in terms of demographic data and duration of surgery (Table 1). At 20 minutes after spinal injection, maximum sensory block level was T6 in groups I and II and it was T5 in groups III and IV. Duration of analgesia was found to be lower in group I compared with other groups ($p<0.001$). Also, group II had lower duration of analgesia compared with groups III and IV ($p<0.001$, for all). Mean motor block scores at 20 minutes after spinal injection were observed to be lower in group I compared with other groups ($p<0.001$, for all). Motor block duration was significantly shorter in

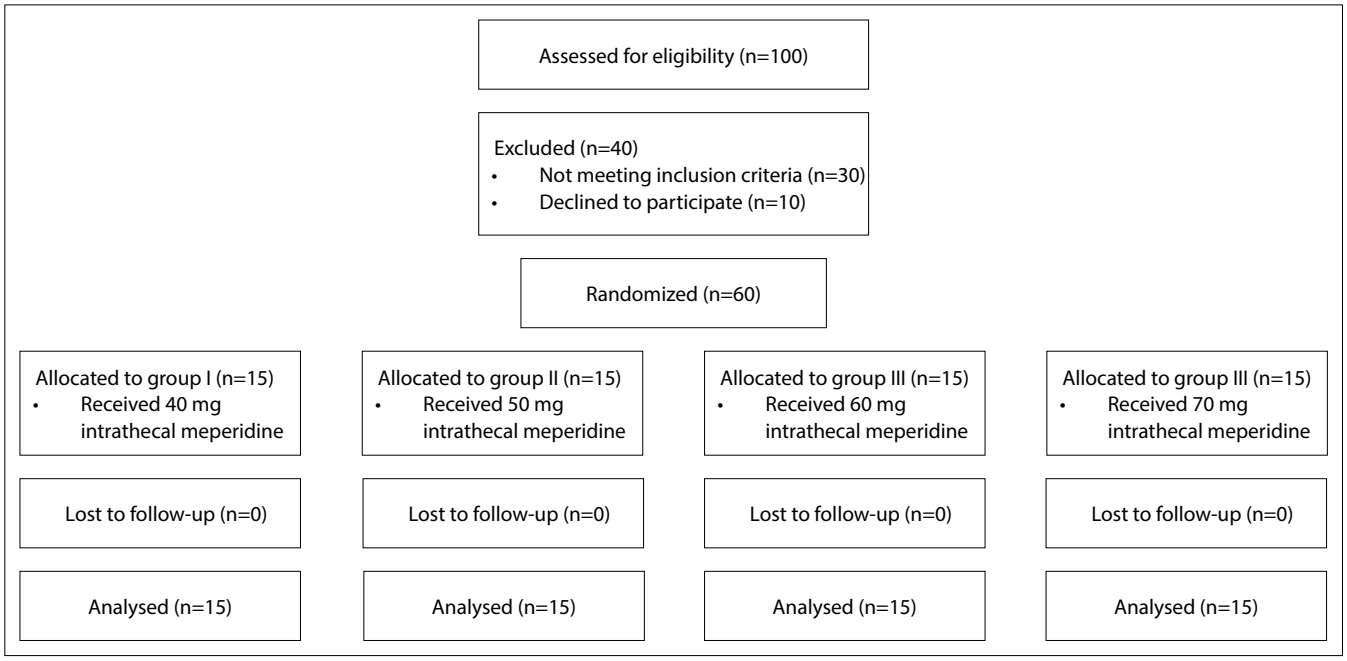

Figure 1. CONSORT flow diagram. The course of patients during study period was shown.

Table 1. The demographic and clinic characteristics of patients in groups

	Group I (n=15) Mean±SD	Group II (n=15) Mean±SD	Group III (n=15) Mean±SD	Group IV (n=15) Mean±SD	p
Age (year)	70.5±7.8	66.9±6.4	65.3±3.7	71.0±3.2	0.115
Weight (kg)	76.9±7.0	75.8±6.0	76.0±5.0	80.0±5.8	0.372
Height (cm)	168±5.8	171±8.2	165±6.4	169±7.0	0.874
Surgery duration (minutes)	85±11	81±7	79±7	81±9	0.365

SD: Standard deviation. Patients were allocated to receive one of four doses of intrathecal meperidine: Group I: 40 mg, Group II: 50 mg, Group III: 60 mg, Group IV: 70 mg.

Table 2. The comparison of study groups in terms of mean motor block scores and maximum sensory block level at 20 minutes after spinal injection, motor block duration and analgesia duration

	Group I (n=15)	Group II (n=15)	Group III (n=15)	Group IV (n=15)
Motor block scores	1 (0–2)*	3 (2–3)	3 (3)	3 (3)
Maximum sensory block level	T6 (T5-T6)	T6 (T5-T6)	T5 (T3-T6)	T5 (T3-T5)
Motor block duration (minutes)	140±2.8	142±3.2	170±1.4	173±3.0
Analgesia duration (minutes)	244±34*	346±42**	588±82	568±108

All values were given as mean±standard deviation or median (range). Patients were allocated to receive one of four doses of intrathecal meperidine: Group I: 40 mg, Group II: 50 mg, Group III: 60 mg, Group IV: 70 mg. *: p<0.001, compared with other groups; **: p<0.001, compared with Groups III and IV.

groups I and II than in the groups III and IV (p<0.001, for all) (Table 2). Surgeon satisfaction was better in groups II, III and IV compared with group I (p<0.001, for all). Patient satisfaction was better in groups III and IV compared with groups I and II (p<0.001, for all) (Table 3). There were no significant differences among groups as regards meperidine-related side effects, including hypotension, bradycardia, nausea-vomiting, shivering and pruritus. Two patients in group I, 8 patients in group II, 8 patients in group III and 9 patients in group 4 had pruritus, but these differences were not statistically significant (p>0.05) (Table 4). No neurological complication was observed in all patients during postoperative follow-up. Also, respiratory depression or desaturation was not observed in any of the patients. No patients required additional anal-

Table 3. Status of surgeon and patient satisfactions in groups

	Group I (n=15)		Group II (n=15)		Group III (n=15)		Group IV (n=15)	
	n	%	n	%	n	%	n	%
Surgeon satisfaction								
Dissatisfied	6	40*	0	0	0	0	0	0)
Satisfied	9	60*	2	13.3	0	0	0	0
Very satisfied	0	0*	13	67.7	15	100	15	100
Patient satisfaction								
Dissatisfied	3	20**	1	10**	0	0	0	0
Satisfied	12	80**	14	90**	3	20	6	40
Very satisfied	0	0**	0	0**	12	80	9	60

*: p<0.001, compared with other groups; **: p<0.001, compared with Groups III and IV. Patients were allocated to receive one of four doses of intrathecal meperidine: Group I: 40 mg, Group II: 50 mg, Group III: 60 mg, Group IV: 70 mg.

Table 4. The comparison of meperidine-related side effects in groups

	Group I (n=15)		Group II (n=15)		Group III (n=15)		Group IV (n=15)		p
	n	%	n	%	n	%	n	%	
Hypotension	0	0	2	13.3	4	26.7	6	40	0.113
Bradycardia	0	0	1	7.1	4	26.7	5	33.3	0.156
Nausea-vomiting	2	13.3	3	20.0	5	33.3	8	53.3	0.214
Shivering	5	33.3	0	0	0	0	2	13.3	0.125
Pruritus	2	13.3	8	53.3	8	53.3	9	60	0.138

Patients were allocated to receive one of four doses of intrathecal meperidine: Group I: 40 mg, Group II: 50 mg, Group III: 60 mg, Group IV: 70 mg.

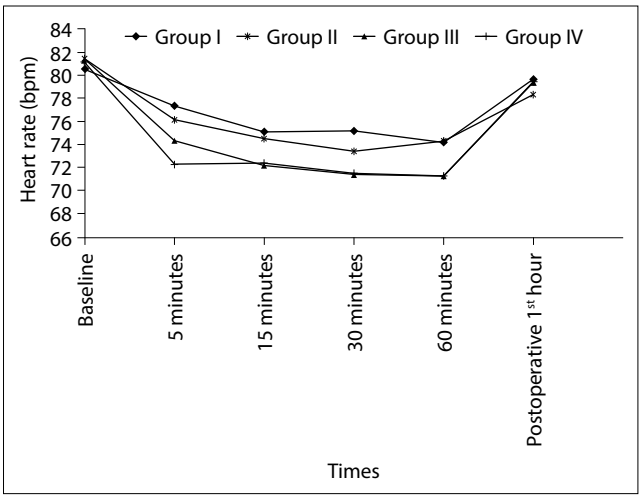

Figure 1. The comparison of heart rate values in groups. Patients were allocated to receive one of four doses of intrathecal meperidine: Group I: 40 mg, Group II: 50 mg, Group III: 60 mg, Group IV: 70 mg.

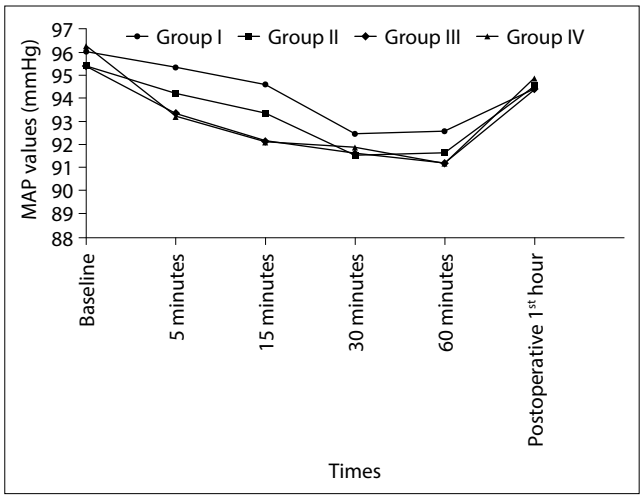

Figure 2. The comparison of MABP values in groups. Patients were allocated to receive one of four doses of intrathecal meperidine: Group I: 40 mg, Group II: 50 mg, Group III: 60 mg, Group IV: 70 mg.

gesia during surgery. Patients in all groups had significantly lower MABP and heart rate values during surgery compared to the baseline values (p<0.05, for all). But, there were no significant differences among groups in terms of MABP and heart rate values during surgery and postoperatively (Fig. 2, 3).

Discussion

Pethidine, a phenylpiperidine-derived, has local anesthetic effect. Intrathecal meperidine provides prolonged postoperative analgesia with fewer side effects and the addition of meperidine to spinal anesthesia has been used for postoperative analgesia after many surgical procedures.[4–9] On the other hand, intrathecal meperidine is often accompanied by adverse effects such as pruritus, fatigue, nause, hypotension and respiratory depression. Clinicians tend to use smaller doses of meperidine to reduce the incidence of adverse effects. This present study defined the optimal dose of intrathecal meperidine for open prostatectomy as the dose that would minimize adverse effects without reducing analgesia. Intrathecal mepheridine at a dose of 60 mg produced a sufficient anesthesia with minimum side effects.

Bakhsha and Behnampour[13] investigated the duration of the painless period and complications after the administration of low dosage intra-thecal pethidine (30 mg) in patients undergoing perineal and anorectal surgeries. They reported that intra-thecal pethidine provides good intraoperative anesthesia and longer duration of pain-free period after surgey with minimum side effects. Unlike our study, they performed saddle block with 30 mg pethidine. In saddle block anesthesia, the cause of longer duration of pain-free period after surgey may be due to the high amount of local anesthetic per dermatomal segment. We reported that using intra-thecal pethidine with dose of 40 mg, 50 mg, 60 mg or 70 mg for open prostatectomy provides acceptable intra-operative quality anesthesia.

Meperidine is highly lipophilic opioid and has a rapid onset of action. Intrathecal meperidine may cause adverse effects such as hypotension, bradycardia, nausea, vomiting and pruritus.[10,11] The incidence of pruritus varies between 0 and 100% and there is no correlation between itch intensity and opioid dose. Researchers suggested that pruritus may be due to alteration in sensory modulation following opioid spread over the spinal cord to the brain. Hypotension and bradycardia may occur as a result of the cardiovascular effect associated with the sympathetic blockage caused by the spinal anesthesia. Also, nausea and vomiting may be due to rostral spread of opioid to the vomiting centre and to the chemoreceptor trigger zone.[14–16] In this current study, there were no significant differences among groups as regards meperidine-related side effects. But, there was a dose dependent increase in the number of patients that experienced side effects such as bradycardia, hypotension, nausea/vomiting and pruritus. Neurological complication and respiratory depression were not observed in any of the patients. Anaraki et al.[17] compared the effect of adding meperidine to the intrathecal mixture anesthesia (0.2, 0.3 and 0.4 mg per kg) on the incidence of meperidine-related side effects after spinal anesthesia for cesarean delivery. In accordance with our results, they reported that adding meperidine, in increasing small dosages, to the intrathecal mixture anesthesia increases undesirable side-effects nausea, vomiting and pruritis as the dose of meperidine increased. In a study conducted by Hansen et al.,[6] authors investigated the effects of three different doses of meperidine (1.2 mg/kg, 1.5 mg/kg and 1.8 mg/kg) for spinal anesthesia on the duration of sensory block and the incidence of side effects in male patients, undergoing either transvesical prostatectomy (retropubic approach), hernia repair, or hemorrhoidectomy. They found that meperidine 1.5 mg/kg provides a longer duration of sensory block than 1.2 mg/kg. Also, they reported similar block onset time, block duration and block levels in patients received intrathecal meperidine with dose of 1.5 mg/kg and 1.8 mg/kg. They found no differences in the incidence of side effects among the groups. They concluded that increasing the dose of meperidine for spinal anesthesia from 1.2 to 1.5 mg/kg provides a longer duration of sensory block without affecting the sensory level, the time to maximal spread, or the incidence of side effects. Anaraki et al.[18] investigated the effect of adding meperidine to intrathecal heavy lidocaine on hemodynamic changes and blood loss in patients undergoing elective suprapubic open prostatectomy. They reported that adding low dose of meperidine to lidocaine induces minimal effect on blood pressure change in operating room. In another study, Atalay et al.[9] compared te effects of intrathecal hyperbaric bupivacaine and low-dose intrathecal plain bupivacaine plus different doses of meperidine (25, 39 and 35 mg) on blood pressure stability, post-operative analgesia and incidence of side-effects in patients undergoing cesarean section. They reported tahat sequential administration of 5 mg plain bupivacaine

and 25 mg meperidine intrathecally provides better blood pressure stability and a lower incidence of side-effects than bupivacaine alone, without affecting quality of anaesthesia or surgical and patient satisfaction. Similar to their results,[6,9,17] we found that intrathecal meperidine administration with dose of 40 mg, 50 mg, 60 mg or 70 mg can provide surgical anaesthesia and postoperative analgesia for about four to six hours. Also, no cases of respiratory depression were reported in association with spinal anaesthesia by meperidine.

The optimal anesthetic technique should provide excellent operating conditions, minimal postoperative side effects and high patient's satisfaction. The patient satisfaction with anesthesia is important indicator of a well-functioning health service system. Although many factors contribute to patient satisfaction, including the kind of anesthesia, interpersonal relationships and competence of health professionals; unwished events such as pain, nausea and vomiting during recovery from anesthesia.[19] In this current study, greatest patient satisfaction was reported in patients received intrathecal meperidine with doses of 60 mg. In these patients, analgesia and motor block durations were long without increases in meperidine-related side effects. In a recent study, Canakcı et al.,[20] investigated the effect of adding different doses of meperidine (15 or 30 mg) to intrathecal hyperbaric bupivacaine on postoperative pain relief in patients undergoing elective transurethral resection of prostate surgery. They reported greatest patient satisfaction level in patients received adding intrathecal meperidine compared with patients received only intrathecal hyperbaric bupivacaine. These results were consistent with our findings.

Limitations

In our clinic, transurethral resection of prostate surgery is usually used for benign prostate hyperplasia. Open prostatectomy is preferred for large prostates and the number of cases with large prostate is rare. So, the limitation of this present study was the relatively small patient population.

Conclusion

This study investigated the effect of different dosages of intrathecal meperidine on hemodynamic parameters, the duration of neural blockade and the incidence of meperidine-related side effects in patients undergoing open prostatectomy. We found that increasing the dose of intrathecal meperidine from 40 to 70 mg increased the analgesia and motor block durations, but not the sensory block level without an increase in meperidine-related side effects. Intrathecal meperidine at a dose of 60 mg exerts a sufficient analgesic effect with minimum side effects for patients undergoing open prostatectomy. Clinical studies including a larger number of patients are needed to confirm our findings.

Ethics Committee Approval: This prospective double-blind randomised study was approved by the Ethics Committee of Atatürk University, Medical Faculty (date: 08.06.2007; number: 52).

Conflict-of-interest issues regarding the authorship or article: None declared.

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