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Post-operative Analgesic Characteristics of Intrathecal Adjuvant Agents Including Ketamine, Fentanyl, Sufentanyl, Neostigmine, Dexmedetomidine, Midazolame and Droperidole and their Effects on Spinal Anesthesia

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Abstract

Aim: This study was designed to compare the intraoperative, postoperative analgesic characteristics and adverse effects of intrathecal combinations of several adjuvant agents combined with hyperbaric bupivacaine in the cases who underwent spinal anaesthesia.

Materials and methods: 180 cases were randomized to 9 groups of 20 cases (n=20). 15 mg of 0.5% hyperbaric bupivacaine and 0.5 ml of serum physiological were administrated to the control group (group-0). In the other groups, instead of serum physiological: Group-1 (2.5 mg hyperbaric bupivacaine), Group-2 (12.5 mg ketamine), Group-3 (25 µgr Fentanyl), Group-4 (2.5 µg sufentanyl), Group-5 (2 µg dexmedetomidine), Group-6 (250 µg neostigmine), Group-7 (500 µg midazolame), Group-8 (1.25 mg Droperidole) were combined with hyperbaric bupivacaine. Total spinal drug volume was 3.5 ml. Intraoperative and postoperative side effects, time to the first pain, and the characteristics of spinal anaesthesia were recorded.

Results: Intrathecal adjuvant agents had no effects on the characteristics of the spinal anaesthesia ($p>0.05$). Time to the first pain was similar between the groups ($p>0.05$). The most common side effect was pruritus in Group-3 and Group-4 ($p>0.05$), nausea-vomiting in Group-6 ($p>0.05$), urinary retention in Group-2 and Group-4 ($p>0.05$), and PSBA in Group-1 and Group-3 ($p>0.05$).

Discussion: No differences in the time to the first pain were found between intrathecal adjuvant agents. Their effects on the characteristics of spinal anaesthesia were similar. Each adjuvant agent causes specific side effects. However, postoperative analgesic requirement was not considered in our study, and dose-finding studies (which are performed to determine the adjuvant agent doses that cause minimal and maximal side effects) were not performed. Further studies should be performed to evaluate those factors.

Keywords: Post-operative analgesic characteristics; Intrathecal; Ketamine; Dexmedetomidine

Introduction

In spite of the development of pain management in the postoperative period, most of the patients still experience problems due to postoperative pain. It's very hard to obtain an effective postoperative pain management regimen which has an acceptable side effect profile. Intrathecal opioids are widely used and effective; however, their indications are limited due to their side effects [1]. If a lower dose of each analgesic drug can be used, combination therapy may also reduce the incidence and the severity of the side effects. For this reason, multimodal or balanced analgesia is a very important new approach in the postoperative pain management [2-8]. The recent studies focus on non-opioid receptors that inhibit the transmission of the painful stimulus. The studies showed that intrathecal opioids (µ,Δ,K receptor agonists) midazolam (GABA-A agonist), droperidole (D2 receptor antagonist), neostigmine (acetylcholine esterase inhibitor), ketamine (NMDA receptor antagonist) and dexmedetomidine (α2 adrenoceptor agonist) produce analgesia in several species including humans, and that the combinations with local anaesthetics decrease the side effects associated with local anaesthetics and reduce the usage of postoperative analgesics [9-12]. Previously, several studies investigated whether each of these adjuvant agents combined with local anaesthetics produce analgesia via the receptors they affected; however, such a study was not performed for droperidol [12-14]. Besides in this study, all adjuvant agents were compared in the same study and in larger population (n=20) for postoperative analgesia durations and side effects, and control group and adjuvant agents were stratified by postoperative analgesia durations. In our study, we aimed to compare the adjuvant agents according to analgesia duration, and investigated whether each of these adjuvant agents produce analgesia via the specific receptors they affected and whether these agents cause specific side effects and whether they have effect on spinal anaesthesia.

Materials and Methods

All patients signed informed consent form by the authorization of T.C. Fırat University Faculty of Medicine Ethics Committee. 180 male patients (ASA-I, age range 20 to 30 years) who were planned to undergo inguinal and perianal surgery under spinal anaesthesia were recruited in the study. Power analyses was performed and number of cases in each group was determined to be n=20. The study was designed as randomized, double-blinded, and placebo-controlled study. 0.09% NaCl infusion was initiated for the patients without premedication at a rate of 10 $ml.kg^{-1}/sa^{-1}$ following routine monitorization in the operation room. 25G spinal needle was inserted through L3-4 space after the skin was infiltrated with 2 ml 2% prilocaine in the sitting position.

The cases were randomized into nine groups: Group-0 (control group) (n=20): 15 mgr 0.5% hyperbaric bupivacaine +0.5 ml serum physiological, Group-1 (3.5 ml bupivacaine) (n=20): 17.5 mgr 0.5% hyperbaric bupivacaine, Group-2 (bupivacaine+ketamine) (n=20): 15 mgr 0.5% hyperbaric bupivacaine+12.5 mg ketamine, Group-3 (bupivacaine +Fentanyl) (n=20): 15 mgr 0.5% hyperbaric bupivacaine+25 µgr Fentanyl,Group-4 (bupivacaine+sufentanyl) (n=20): 15 mgr 0.5% hyperbaric bupivacaine+2.5 µgsufentanyl, Group-5 (bupivacaine+dexmedetomidine) (n=20): 15 mgr 0.5% hyperbaricbupivacaine+2 µgr dexmedetomidine, Group-6 (bupivacaine+neositigmin) (n=20): 15 mgr 0.5% hyperbaricbupivacaine+250 µgr neositigmin, Group-7 (bupivacaine+midazolam) (n=20): 15 mgr 0.5% hyperbaric bupivacaine+500 µgr midazolam, Group-8 (bupivacaine +droperidol) (n=20): 15 mgr 0.5% hyperbaric bupivacaine+1.25 mg droperidol. Total of 3.5 ml volume was given to all groups.

Then, at the fifth and 20th minutes of the supine position, sensorial block level by pinprick test, sympathetic block level by cold application, and motor block level by Bromage scale (0=full movement of feet and knees, 1=just able to move knees, 2=able to move feet only, 3=unable to move feet or knees) were evaluated. Mean arterial pressure (MAP), heart rate (HR) and peripheral oxygen saturation (SpO_2) were reported before and during the procedure. Intraoperative side effects (bradycardia, hypotension, nausea-vomiting, sedation etc.) were recorded.

If the MAP decrease is above 20%, intravenous 10 mg ephedrine+liquid infusion was given. HR below 50 $pulse.dk^{-1}$ was considered as bradycardia and intravenous 0.5 mg atropine was given. Intravenous 20 mg metochlopramide was given for nausea-vomiting.

Time to Bromage 2 score was evaluated as spinal anesthesia duration. The time when the pain occurred was recorded. Then, intramuscular lornoxicam 8 mg was administrated to all cases.

Patient characteristics, hemodynamic data, time to the first pain, sympathetic and sensorial block levels (at the fifth and 20th minutes), Bromage scores (at the fifth and 20th minutes) between groups were compared by N-Par tests Kruskal-Wallis test model. The type of the surgery and the side effects were compared by Chi-Square tests model. Bonferroni-adjusted Mann-Whitney U test was used for binary comparisons of the groups to identify the group which makes a difference. $p<0.05$ was accepted as significant.

Results

The group characteristics and anaesthesia durations were found to be comparable **(Table 1)**. HR, MAP and SpO_2 values were similar in the intraoperative and postoperative period. The characteristics of spinal anaesthesia were reported in **Table 2**. Postoperative time to the first pain was reported in **Table 3**. Intraoperative and postoperative side effects were summarized in **Table 4**.

Table 1 Distribution of the case characteristics by the groups (Mean SD).

Demographics	Group-0 (n=20)	Group-1 (n=20)	Group-2 (n=20)	Group-3 (n=20)	Group-4 (n=20)	Group-5 (n=20)	Group-6 (n=20)	Group-7 (n=20)	Group-8 (n=20)
ASA-I	20	20	20	20	20	20	20	20	20
Age (year)	21.9 ± 2.2	22.2 ± 2.5	21.3 ± 1.8	21.6 ± 1.6	22.9 ± 3.5	21.8 ± 1.4	21.6 ± 1.8	21.8 ± 1.3	22.6 ± 2.3
Height (cm)	174.2 ± 7.2	174.2 ± 6.3	175.9 ± 4.9	176.6 ± 6.3	175.9 ± 5.3	173.0 ± 6.3	178.7 ± 6.2	174.5 ± 6.6	172.3 ± 15.6
Weight (kg)	72.1 ± 9.2	69.9 ± 9.9	72.4 ± 7.7	78.2 ± 15.0	75.8 ± 11.3	72.6 ± 7.8	75.8 ± 7.7	73.2 ± 8.2	72.9 ± 7.9
Surgery Type (İ/P)	14/6	14/6	14/6	15/5	13/7	20/0	12/8	14/6	13/7
Surgery Duration (minute)	41.3 ± 3.6	49.7 ± 5.8	57.4 ± 3.9	61.1 ± 6.2	51.6 ± 4.5	66.7 ± 7.6	43.1 ± 3.2	53.7 ± 4.2	47.8 ± 6.5
Anaesthesia Duration (minute)	134.6 ± 15.2	138.4 ± 14.9	156.8 ± 13.3	164.3 ± 15.4	178.6 ± 12.7	198.7 ± 14.3	164.3 ± 14.3	168.9 ± 13.6	152.7 ± 16.2

The data of group demographics and anaesthesia durations found to be comparable. HR, MAP and SpO_2 values were similar in the preoperative and postoperative period. When the sensorial block levels were compared; Group-2 was the group that make a difference in the 20th minute as compared

to the other groups and the level was significantly higher ($p<0.05$).

Sympathetic block levels in the 20th minute was significantly different between Group-1 and Group-8, and the highest level was in Group-8, and the lowest level was in Group-1 ($p<0.05$). Sympathetic and sensorial block levels in the fifth minute was not significantly different between groups ($p>0.05$). When the motor block levels were compared; levels in the group-1 were significantly higher than the other groups in the fifth minute ($p<0.05$), and no significant differences were found between groups in the 20th minute ($p>0.05$).

Table 2 Distribution of the spinal anesthesia characteristics by the groups (Mean SD).

Time	Group-0 (n=20)	Group-1 (n=20)	Group-2 (n=20)	Group-3 (n=20)	Group-4 (n=20)	Group-5 (n=20)	Group-6 (n=20)	Group-7 (n=20)	Group-8 (n=20)
Sensorial block (Pin-prik)									
5 Minutes	$T_{7.05} \pm 2.78$	$T_{7.00} \pm 3.17$	$T_{7.00} \pm 2.40^{*}$	$T_{6.85} \pm 3.13$	$T_{7.30} \pm 2.71$	$T_{9.15} \pm 3.39$	$T_{8.00} \pm 3.61$	$T_{6.65} \pm 2.39$	$T_{7.60} \pm 2.34$
20 Minutes	$T_{5.50} \pm 1.84$	$T_{5.85} \pm 2.27$	$T_{4.05} \pm 1.46$	$T_{4.10} \pm 1.61$	$T_{4.20} \pm 2.01$	$T_{5.55} \pm 1.43$	$T_{6.00} \pm 4.01$	$T_{4.45} \pm 2.16$	$T_{4.40} \pm 1.27$
Sympathetic block (cold application)									
5 Minutes	$T_{4.20} \pm 3.03$	$T_{4.55} \pm 2.66^{**}$	$T_{4.3}0 \pm 2.88$	$T_{5.00} \pm 2.67$	$T_{6.80} \pm 2.78$	$T_{6.20} \pm 2.68$	$T_{6.40} \pm 3.57$	$T_{6.25} \pm 2.86$	$T_{6.35} \pm 2.20^{**}$
20 Minutes	$T_{4.40} \pm 2.08$	$T_{4.85} \pm 2.81$	$T_{3.00} \pm 1.77$	$T_{3.10} \pm 2.82$	$T_{3.50} \pm 2.13$	$T_{4.55} \pm 1.90$	$T_{3.95} \pm 3.39$	$T_{3.40} \pm 1.69$	$T_{2.90} \pm 1.33$
Motor block (Bromage score)									
5 Minutes	1.80 ± 0.61	2.70 ± 0.47#	2.10 ± 0.44	2.25 ± 0.85	2.00 ± 0.45	1.75 ± 0.78	2.05 ± 0.68	2.10 ± 0.55	2.20 ± 0.61
20 Minutes	2.75 ± 0.63	2.95 ± 0.22	2.70 ± 0.47	2.65 ± 0.58	2.80 ± 0.41	2.80 ± 0.52	2.55 ± 0.68	2.65 ± 0.48	2.85 ± 0.36

* Group-2 Sensorial block levels in the 20th minute were significantly higher in Group-2 as compared to the other groups and this group was the group which made a difference ($p=0.002<0.05$)

** Group-1 Sympathetic block levels in the 20th minute was significantly different between Group-1 and Group-8, and the highest level was in Group-8, and the lowest level was in Group-1, and these were the groups which made a difference ($p=0.025<0.05$)

Group-1 When the 5th minute motor block levels were compared; levels in the Group-1 were significantly higher than the other groups ($p=0.000<0.05$)

Table 3 Evaluation of the time to the first pain (Mean SD).

Time	Group-0 (n=20)	Group-1 (n=20)	Group-2 (n=20)	Group-3 (n=20)	Group-4 (n=20)	Group-5 (n=20)	Group-6 (n=20)	Group-7 (n=20)	Group-8 (n=20)
Time to the first pain (minute)	220.7 ± 112.7	271.7 ± 143.0	262.00 ± 167.6	245.7 ± 126.0	322.2 ± 196.5	371.5 ± 223.5	284.7 ± 176.4	220.2 ± 162.4	274.0 ± 169.4

Table 4 Distribution of the side effects by the groups.

Variables	Group-0 (n=20)*	Group-1 (n=20)	Group-2 (n=20)	Group-3 (n=20)	Gorup-4 (n=20)	Group-5 (n=20)	Group-6 (n=20)	Group-7 (n=20)*	Group-8 (n=20)*
Hypotension	14	5	2	5	3	6	0	12	0
Bradycardia	11	8	8	6	8	8	9	7	3
Vomiting/Nausea	2	1	1	0	1	4	5**	0	0
Pruritus	0	0	0	6***	3***	0	0	0	0
Sweating	0	0	0	0	0	0	0	0	0
Tremor	2	9#	0	9#	2	4	2	4	5
Sedation	0	0	0	0	0	0	0	0	0
Dizziness	0	0	0	0	0	0	0	0	0
Respiratory depression	0	0	0	0	0	0	0	0	0
Urinary retention	3	2	11##	4	13##	6	5	2	8

Post spinal headache	0	5###	3	5###	0	2	1	0	1

* Group-0 and Group-7 had significantly higher incidence, Group-8 de had significantly lower incidence (p=0.000<0.05)

** Group-6 had significantly higher incidence as compared to the other groups (p=0.019<0.05)

*** Group-3 and Group-4 had significantly higher incidence as compared to the other groups (p=0.000<0.05)

Group-1 and Group-3 had significantly higher incidence as compared to the other groups (p=0.02<0.05)

Group-2 and Group-4 had significantly higher urinary retention incidence as compared to the other groups (p=0.000<0.05)

Group-1 and Group-3 had significantly higher PSBA incidence as compared to the other groups (p=0.014<0.05)

When the time to the first pain were compared, no differences were found between groups (p>0.05). When the hypotension was compared in the intraoperative and postoperative period, Group-1, Group-7 and Group-8 have made a difference (p<0.05). Hypotension incidence was minimum in Group-8, and maximum in Group-0. Hypotension incidence was significantly higher in Group-7 as compared to other groups (p<0.05). No significant differences in the bradycardia, sweating, dizziness, respiratory depression, sedation and increased salivation were found between groups (p>0.05).

When the vomiting-nausea was compared, Group-6 has made a difference (p<0.05); vomiting-nausea incidence was significantly higher. When the pruritus was compared; Group-3 and Group-4 have made a difference (p<0.05); pruritus incidence was higher as compared to other groups. When the tremor was compared; Group-1 and Group-3 have made a difference (p<0.05), tremor incidence was significantly higher as compared to other groups. When the time to the first pain were compared no differences were found between groups (p=0.363>0.05). When the urinary retention was compared, Group-2 and Group-4 have made a difference (p<0.05), the incidence was highest in Group-4. When P.S.H was compared, Group-1 and Group-3 have made a difference (p<0.05), the incidence was higher as compared to other groups.

Discussion

In this dose-response study, seven different intrathecal adjuvant agents combined with hyperbaric marcaine were given to the patients in nine groups, and no superiority for the time to the first pain was shown between groups. Acceptable side effects were developed in all groups. In a study performed by Roelants F, additive neuroaxial drugs decrease the side effects of the combined drugs and increase their analgesic efficacy. Clonidine and neositigmin may be used for obstetrics under specific conditions [15]. In a study performed by Tryba et al. adjuvant agents for regional anaesthesia, general anaesthesia and postoperative periods have been investigated. Undoubtedly, clonidine increases the analgesic effects of systemic or spinal opioids and prolongs the analgesic effects of several local anaesthetics [16,17].

In our study, Group-0 and Group-1 were compared with the other groups for the time to the first pain, fifth and 20th minute Bromage scores, sympathetic and sensorial block levels and side effects. Hypotension incidence was highest in Group-0 as compared to the other groups. No differences in the other parameters and side effects were found between groups. Hypotension was more common in this group because visceral pain due to peritoneal manipulations were more common in this group. Group 1 had the lowest sympathetic block levels in the 20th minute because hyperbaric marcaine precipitating within BOS was evaluated as “lower sympathetic block levels”. However, sympathetic block levels did not decrease so much in Group-0 because of the serum physiologic (added in local anaesthetic) which decreases hyperbaricity. When the motor block levels were compared; levels in the Group-1 were significantly higher than the other groups in the fifth minute. Because, motor block levels were increased by the increases in the local anaesthetic dose. No superiority in the time to the first pain was found between groups. When the side effects were compared, tremor and P.S.H. incidences were significantly higher in group-1 as compared to the other groups. Sensorial block levels in the 20th minute were significantly higher in Group-2. Urinary retention was significantly higher in Group-2 as compared to the other groups.

Ketamine acts on more than one regions, and opens the calcium channels and causes spinal block in this way. Systemic ketamine causes central summation in the second-order pain neuron and decreases severe pains including neurogenic pain, postherpetic neuralgia and phantom pain [12].

We used two different intrathecal opioids in Group-3 and Group-4 and we found no superiority for the time to the first pain among them. When the side effects were evaluated, pruritus incidence was significantly higher in Group-3 and Group-4 as compared to the other groups. Besides, tremor was significantly higher in Group-3 as compared to the other groups. PSBA incidence was significantly higher in Group-3 as compared to the other groups.

Opioids have different selectivity for different pain types. Opioid mu agonists are effective on burn pain. Kappa opioid agonists are more effective on pressure or visceral pain models [12].

In a study performed by Kim et al. 5 µgr sufentanyl or 25 µgr fentanyl with lower dose isobaric bupivacaine produce optimal anaesthesia in the patients for TUR-P operation without hemodynamic instability. However sufentanyl was superior to fentanyl in the high-quality spinal block [11]. In our study, sufentanyl dose was lower; therefore, we did not find any difference in the spinal block quality between Group-3 and Group-4.

In another study performed by Kamphuis et al. hyperbaric lidocaine combined with sufentanyl was used for spinal

anesthesia; and the bladder contractility was improved later than the sensorial functions in the sacral dermatome S3 levels [18]. Our study was compatible with this study, and the urinary retention incidence was found to be significantly higher in group-4 as compared to the other groups.

5 mg intrathecal bupivacaine combined with 25 µgr Fentanyl produce stable hemodynamia, lower motor block (satisfying the patient and the surgeon) and effective sensorial block during transurethral prostate surgery. This combination may be used as an alternative to the lower dose of bupivacaine [10]. In our study, effective sensorial block (satisfying for the patient and the surgeon) was obtained in Group-3 but since bupivacaine dose was higher, no difference in the motor block level was found between other groups.

When 20 µgr Fentanyl or 2.5 µgr sufentanyl was combined with 0.5% of hyperbaric bupivacaine for spinal anaesthesia, they produce optimal intraoperative analgesia without significant side effects in the mother and the neonate [6]. The results of this study were in line with the results of Group-3 and Group-4 in our study.

No significant differences in the time to the first pain, sensorial, sympathetic and motor block levels (at the fifth and 20^{th} minutes) and side effects were found between Group 5 and the other groups.

Dexmedetomidine is a α_2 adrenergic agonist with a high α_2 selectivity and efficacy. Spinal and epidural dexmedetomidine produces strong segmental analgesia in the non-anaesthetic dogs. Spinal dexmedetomidine produces respiratory changes due to the spinal redistribution [19]. Because of the segmental distribution, we couldn't find any significant differences for Group-5. The local anaesthetic we used had segmental distribution.

In a study performed by Kanazi et al. intrathecal bupivacaine combined with 3 µgr dexmedetomidine or 30 µgr clonidine maintained hemodynamic stability and prolonged the motor block and sensorial block similarly without the need of sedation [20]. However in our study, no differences in the motor block sensorial block and sedation were observed in Group-5. If we had used lower doses of local anaesthetic or if we had increased the dose of dexmedetomidine, we could have obtained a different result as compared to the other adjuvant agents.

In a dog study performed by Sabbe et al. skin twitching during painful stimuli and stimulation of the back paw retraction during mechanical press was decreased following intrathecal, epidural and intravenous dexmedetomidine [19]. Maximum drug effect was observed at the 15^{th} minute following the intrathecal administration. Drug effect with the maximum effective dose continues for the next 90 minutes following the intrathecal administration. These results were consistent with our results, and it's shorter than the intrathecal effect time of our local anaesthetic. Antinociceptive effects following intrathecal administration are highest in the neighbourhood of the dermatomes proximal to the catheter tip. These results were consistent with our results, and parallel to the dermatomal spreading of our local anaesthetic.

No differences in the time to the first pain, sensorial, sympathetic and motor block levels (at the fifth and 20^{th} minutes) were found between Group-6 and the other groups. Significant differences in the side effects (vomiting-nausea) were found in Group-5 as compared to the other groups.

Cholinesterase inhibitor neostigmin produces spinal analgesia in the preclinical models. This effect is mediated by muscarinic receptors and the increase of acetylcholine efficacy. Neurotoxicity of spinal neositigmin was not observed in the animals. When the sub analgesic doses (30-70% of the analgesic dose) were combined with opioids, minimal nausea-vomiting was observed [12]. In our study, vomiting-nausea incidence was significantly higher in Group-6 as compared to the other groups.

Intrathecal neositigmin produce analgesia by the inhibition of (endogenous spinal neurotransmitter) acetylcholine destruction via muscarinic and cholinergic receptors located at dorsal horn of spinal cord; substantia gelatinosa, and in lesser amounts at lamina III and V [4]. The studies performed on the volunteers showed that the analgesic effect of intrathecal neostigmin continues for 4-6 hours, this duration prolongs with pain and intrathecal morphine produce analgesia for 24-36 hours [1,21]. However, in our study, no significant differences in the time to the first pain were found between Group-6 and the other groups. However, postoperative analgesic requirement was not considered in our study.

In a study performed by Ross et al. hourly perinatal bupivacaine requirement was decreased by 19-25% when 4 µgr/ml epidural neositigmin was added during patient-controlled epidural analgesia. In our study, no differences in the time to the first pain were observed between Group-6 and the other groups. However, the effect time of our local anaesthesia might have masked the effect time of the adjuvant agent. If we had performed postoperative pain evaluation and had determined the analgesic requirement, differences might have been observed between all groups [19].

No differences in the time to the first pain, sensorial, sympathetic and motor block levels (at the fifth and 20^{th} minutes) were found between Group-7 and the other groups. Hypotension incidence was significantly higher in Group-7 as compared to the other groups.

In a study performed by Murali Krishna et al. lower doses of midazolam and ketamine combined with intrathecal bupivacaine decreased hemodynamic imbalances and prolonged analgesia duration [8]. However in our study, no significant differences in the time to the first pain were found between Group-7, Group-2 and the other groups. However in our study hypotension incidence was significantly higher in Group-7 as compared to the other groups.

In a study performed by Boussofara et al. postoperative analgesia was not potentiated but motor block prolonged when intrathecal midazolam was added [11]. The results of this study are in line with our results; but no significant differences in the time to the first pain were found between Group-7 and the other groups in our study, and postoperative analgesic requirement was not considered.

In a rat study performed by Lim et al. short-acting intrathecal benzodiazepine midazolam (once a day) decreased thermal hyperalgesia and mechanic allodynia (caused by chronic nerve compression) for the first postoperative seven days [7]. This study showed that intrathecal midazolam cannot be used for regional anaesthesia but may be used for certain chronic pain types.

Epidural methylprednisolone combined with intrathecal midazolam prolongs the analgesia duration in the patients with post herpetic neuralgia at lumbosacral dermatomes. The antinociceptive effects of epidural methylprednisolone and intrathecal midazolam at the spinal rods complete each other's effects [13]. In another study it was observed that, 1 mg intrathecal midazolam combined with lidocaine decreased the postoperative pain effectively in the patients who had undergone open inguinal hernia surgery [22], and had no adverse effects. However in our study, postoperative analgesic requirement was not considered and the midazolam dose was low. Therefore no significant differences in the time to the first pain were found between Group-7 and the other groups in our study; however hypotension incidence was significantly higher in Group-7 as compared to the other groups.

No differences in the time to the first pain, sensorial, sympathetic and motor block levels (at the fifth and 20th minutes) were found between Group-8 and the other groups. However the highest sympathetic block levels in the 20th minute were observed in Group-8. This might have been associated with the sympatholytic effects of droperidol. No hypotension was observed in Group-8 and the hypotension incidence was significantly lower in Group-8 as compared to the other groups.

In a clinical study performed by Grip et al. lower epidural doses of D2 receptor antagonist droperidol potentiated the antinociceptive effects of epidural morphine [14,23,24]. However, intrathecal droperidol had no antinociceptive effect on rats. In our study, as in the rat models, no significant differences in the time to the first pain were found between group-8 and the other groups.

In our study, we aimed to compare adjuvant agents combined with hyperbaric bupivacaine according to spinal anaesthesia duration, sensorial, sympathetic and motor block levels, and time to the first anaesthesia, hemodynamic data and side effects.

No differences in the time to the first anaesthesia were found between all groups. Therefore we firstly suggested that, the effect time of these adjuvant agents were similar or lower than the concomitant local anaesthetics. However when we identified differences in the following studies, we suggested that the effect time might have been short in our study since our adjuvant doses might have been low. We can overcome this issue by identifying minimal side effect and maximum efficacy doses of the adjuvant agents in the new dose-escalation studies. In our study we evaluated time to the first pain, but we didn't perform quantitative pain assessment. Besides, postoperative analgesic requirement was not considered and we didn't determine which adjuvant agent decreases the postoperative pain requirement to what extent. These parameters should be evaluated in the further studies. In addition, the combinations of these adjuvant agents with each other and with local anaesthetics may be tested in the further studies. In this way, the side effects of the local anaesthetics and the adjuvant agents might be decreased. For example, optimal doses of droperidol, neositigmin and bupivacaine may prolong the quality and the duration of analgesia without vomiting-nausea, and decrease the dose of local anaesthetic. In addition, amitriptilin, baclofen, calcium channel blockers (as adjuvant agents) may be tested in the further studies.

Conclusion

In conclusion, even though there are some limitations in these studies, number of the adjuvant agents are increased day by day, and they should be used in central and peripheral regional blocks and chronic pain management. In our study, several adjuvant agents were used and even though no statistical significant differences were found, time to the first pain may be listed in the order of (longer to shorter): Group-5>Group-4>Group-6>Group-8>Group-1>Group-2>Group-0>Group-7.

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