Original Article

The Effects of Adding Various Doses of Clonidine to Ropivacaine in Spinal Anesthesia

Spinal Anestezide Ropivakaine Farklı Dozlarda Klonidin İlavesinin Etkileri

Gonul Sagiroglu[1], Tamer Sagiroglu[2], Burhan Meydan[1]

[1]Göztepe Education and Research Hospital, Department of Anesthesiology, İstanbul, Turkey
[2]Kartal Dr. Lütfü Kırdar Education and Research Hospital, Transplantation Center, İstanbul, Turkey

Correspondence to: Gonul Sagiroglu, Göztepe Education and Research Hospital, Department of Anesthesiology, İstanbul, Turkey.
Phone: +90.212.3166333, e-mail: tamersagiroglu@gmail.com

Abstract

Objective: In this study, we compared the clinical effects of combined doses of ropivacaine and clonidine.

Materials and Methods: Seventy-five patients between ages 18 and 75, in ASA I-III groups who were to undergo elective lower extremity surgery, were included in the study with informed consent. Subjects were randomly assigned to 3 groups. Group I: % 1 ropivacaine 12 mg, group II: % 1 ropivacaine 12 mg + clonidine 15 µg, group III: % 1 ropivacaine 12 mg + clonidine 30 µg. Mean arterial pressure, breathing, heart rate and peripheral oxygen saturation, total amount of ephedrine and atropine used, sensory and motor block levels, level of sedation, pain level and complications were monitored.

Results: The mean arterial pressure recorded in group III decreased significantly at 75, 105 and 120 min compared to groups I and II. In group I, time to two segment regression and time to sensory block to S2 was shorter when compared to the other groups (P<0.0001). The time to voiding and the duration of motor blockade was significantly longer in group I in comparison to the other groups. The need for atropine in group III was significantly higher (P<0.001). The incidence of hypotension and the requirement for ephedrine were significantly higher in groups II and III as compared to group I (P<0.01). Similarly, sedation in group III was significantly higher compared to the other groups (P<0.05).

Conclusion: In summary, our study revealed that clonidine can be added to ropivacaine for spinal anesthesia in surgical interventions to obtain deeper and longer sensory and motor block. However, hypotension, bradycardia and sedation should be monitored closely.

Keywords: Spinal anesthesia, Clonidine, Ropivacaine

Özet

Amaç: *Çalışmamızda intratekal olarak uygulanan ropivakaine iki farklı dozda klonidin ilavesinin klinik etkilerini karşılaştırmayı amaçladık.*

Gereç ve Yöntem: *Bilgilendirilmiş onam alınmış ASA I-III grubunda, 18-75 yaşlarında, elektif alt ekstremite ameliyatı planlanan 75 hasta çalışmaya alındı. Olgular rasgele örnekleme tekniğiyle 3 gruba ayrıldı. Grup I: % 1 ropivakain 12 mg, grup II % 1 ropivakain 12 mg + klonidin 15 µg, grup III % 1 ropivakain 12 mg + klonidin 30 µg. Ortalama arter basıncı, solunum sayısı, kalp atım hızı, periferik oksijen satürasyonu, kullanılan toplam efedrin ve atropin dozları, sensoriyal ve motor blok seviyesi, sedasyonun derecesi, ağrı seviyesi ve komplikasyonlar takip edildi.*

Bulgular: *Ortalama arter basıncı, grup III'te grup I ve II ile karşılaştırıldığında 75, 105, 120. dk'larda anlamlı düşüş gösterdi. Grup I'de sensoriyal bloğun 2 segment gerileme süresi ve sensoriyal bloğun S2 düzeyine inme süresi diğer iki gruptan anlamlı derecede kısaydı (p<0.0001). Motor blok kaybolma süresi ve idrar yapma zamanı grup I'de diğer iki gruba göre anlamlı derecede uzundu. Atropin gereksinimi grup III'te diğer gruplara göre anlamlı derecede fazla idi (p<0.001). Hipotansiyon ve efedrin gereksinimi ise grup II ve grup III'te grup I'e göre anlamlı derecede fazla bulundu (p<0.01). Sedasyon grup III'te diğer gruplara göre anlamlı derecede fazla idi (p<0.005).*

Sonuç: *Çalışmamızda, ropivakainle yapılan spinal anestezi girişimlerinde daha derin ve daha uzun süreli sensoriyal ve motor blok elde etmek için klonidin ilave edilebileceğini; ancak klonidin ilave edildiğinde hipotansiyon, bradikardi ve sedasyon açısından hastaların dikkatli izlenmesi gerektiği sonucuna vardık.*

Anahtar Kelimeler: *Spinal anestezi, Klonidin, Ropivakain*

Introduction

Due to significant progress in the safety of anesthesia, intubation, low intra-operative blood loss, and continued analgesia in the post-operative period, spinal anesthesia and other regional techniques are frequently used in lower extremity operations [1].

Ropivacaine is less toxic to the central nervous system and the cardiovascular system and is widely used as an alternative to bupivacaine. The level of motor block is similar to bupivacaine, but with a later onset of motor block and a shorter duration [2]. Clonidine is a partial agonist of the α2-adrenoreceptor and acts as an analgesic and as a sedative. During spinal anesthesia, clonodine is administered as an additional local anesthetic to (a) decrease the time to onset of block, increase its depth and increase its duration, (b) decrease the amount of bleeding from the surgery field, (c) lower the dose of local anesthetic, reduce systemic absorption and therefore prevent side effects.

In our study, we aimed to compare the clinical effects of adding two different doses of clonidine to intrathecally administered ropivacaine.

Materials and Methods

After obtaining approval from the Ethics Commission and informed consent from patients, 75 cases in the ASA I-III group, between the ages of 18-75 with planned elective lower extremity surgeries, were enrolled in the study.

Cases with a history of < 55 beat/min heart rate, idiopathic sub-aortic stenosis and narrowed aorta, liver and renal disorder, psychosis, dementia and other cooperation disorders, peripheral neuropathy, demyelinating central nervous system disorder, scoliosis, antihypertensive medicine use, chronic analgesic use, known hypersensitivity to drugs, heparin use, aspirin and other anti-aggregan drug use were excluded from the study.

Thirty minutes before local anesthetic administration, vein access was established and 15 ml/kg ringer lactate was administered. After ensuring sterile conditions, spinal anesthesia was performed by accessing the subarachnoid space with a 25 G atraumatic spinal needle via the L4-5 or L3-4 inter-vertebral space in a sitting position.

Cases were randomized into three groups. Group I: % 1 ropivacaine 12 mg, group II: % 1 ropivacaine 12 mg + clonidine 15 µg, group III: % 1 ropivacaine 12 mg + clonidine 30 µg.

Throughout the study, systolic arterial pressure (SAB), diastolic arterial pressure (DAB) mean arterial pressure (OAB), respiratory rate (SS), heart rate (KAH) and peripheral oxygen saturation (SpO2) were measured every 5 minutes during the first 30 minutes, with 10 minute intervals between 30 and 120 minutes and with 30 minute intervals after 120 minutes in all cases. A decrease of more than 30% from the pre-operative value in OAB was considered as hypotension and 10 mg IV ephedrine was administered. In addition, a decrease in KAH below 50 beats/min was considered as bradycardia and 0.5 IV atropine was administered. Total doses of ephedrine and atropine used were recorded.

Table 1. Modified Bromage scale.

Score	Definition
1	Total motor block
2	Total motor block, patient can only move his/her feet
3	Partial motor block, patient can move his/her knees
4	Patient can lift his/her leg but cannot hold the position
5	No hip function, patient can lift and hold his/her leg for ten seconds
6	No motor block

Table 2. Ready sedation scale.

Score	Definition
0	Awake
1	Poor (tendency for sleep, can be easily awakened)
2	Moderate (frequently asleep, can be easily awakened)
3	Sleep (normal sleep, can be easily awakened)
4	Severe (somnolence, hard to wake)

Table 3. Patient demographics and duration of surgery.

	Group I	Group II	Group III
Age (year)	39.3±12.5	43.0±15.0	45.4±13.0
Sex (F/M)	12/13	9/16	15/10
Weight (kg)	70.0±10.3	75.1±12.0	78.1±12.1
Height (cm)	167.7±6.4	167.8±9.5	165.1±6.7
ASA (I/II/III)	21/4/-	18/6/1	16/8/1
Duration of surgery (min)	56.6±20.9	60.8±23.8	61.0±31.0

In all cases, the level of sensory-motor block and the sedation degree were evaluated at 6, 8, 10, 12, 15, 20, 30, 45, 60, 75, 90, 105, 120, 150, 180, and 210 minutes. The sensory block level was evaluated with the pin-prick test, the motor block level with a modified Bromage scale and the sedation degree with the Ready sedation scale (Tables 1 and 2) [2]. During the tracking of the sensory block levels in patients, (a) the maximum sensory block level, (b) time to achieve maximum sensory block, (c) 2-segment regression time of the sensory block, and (d) time for sensory block to reduce to S2 level were monitored. While tracking the motor block level, (a) the maximum motor block level, (b) time to achieve maximum motor block, (c) duration of motor block (Bromage 6; time when feet could be moved freely) were monitored. Urination time was also recorded.

During the operation, the pain levels of patients were evaluated with a visual analog scale (VAS). In cases where severe pain was expressed (VAS>5), 0.5 mg/kg IV ketamine was administered. All cases were post-operatively followed for 24 hours for nausea, vomiting, post-operative headache and urine retention.

Statistical evaluation was performed using SPSS software. To compare the numerical data, the Kruskall-Wallis test was used. For non-numerical data, ANOVA and the Tukey-Kramer multi-comparison test was used. Data are presented as means ± standard deviation, and a p value of < 0.05 was considered as statistically significant.

Results

No statistically significant differences between patient demographics and surgical times were found between the three

Table 4. Mean arterial pressure.

Time	Group I	Group II	Group III
Baseline	96,80±10,46	98,76±13,63	99,96±12,19
0. min	91,12±12,52	97,88±14,62	94,76±8,80
5. min	91,76±11,73	95,44±14,27	93,48±12,35
10. min	93,36±15,92	91,12±16,98	87,12±12,22
15. min	91,08±13,38	91,00±19,10	86,56±11,01*
20. min	89,36±10,95	91,20±15,96	83,68±7,48*
25. min	89,12±11,58	86,32±15,93	82,67±12,79*
30. min	88,76±12,21	87,68±15,57	82,76±12,63*
45. min	88,20±13,75	87,28±13,86	82,24±11,53*
60. min	88,92±11,04	89,60±14,48	82,24±11,53*
75. min	89,48±10,11	87,12±12,64	80,08±10,38* +
90. min	88,36±11,45	88,56±11,85	81,92±9,49*
105. min	90,64±11,01	90,28±13,09	82,88±9,68* +
120. min	93,00±13,24	89,56±13,00	84,72±6,86* +
150. min	91,20±10,68	91,36±12,46	84,54±9,57*
180. min	91,50±9,58	88,76±12,42	83,76±11,43*
210. min	85,22±10,89	89,56±10,27	83,76±9,05*

*: p<0.001; compared to baseline values, +: p<0.05; compared to Group I and Group II

groups (Table 3).

While there were no statistically significant differences from the baseline OAB values at all time points for group I and group III, there was a significant reduction in group III between 15 and 210 minutes (p<0.001). When the comparison was performed simultaneously between groups, OAB was found to be significantly lower at 75, 105, and 210 minutes in group III compared to group I and group II (p<0.05) (Table 4).

KAH, SS and SpO2 were compared both within the groups and across groups, and no statistically significant differences were detected.

Sensory block levels were compared between the groups, and at 90 and 105 minutes the sensory block level was statistically significantly higher in group II and group III compared to group I (p<0.05) (Table 5). There were no statistically significant differences between groups in terms of the maximum sensory block level and time to reach the maximum sensory block level. However, compared to group I, two segment regression of the sensory block and the time to reduction of the block to the S2 level in group II and group III were significantly longer (p<0.0001) (Table 6).

Comparison of the motor block between groups revealed that motor block was significantly lower in group III at 20 minutes and between 90-180 minutes, compared to group I and group II (p<0.05) (Table 7). There were no significant differences among the groups for the maximum motor block level and the time to achieve the maximum motor block level. The duration of motor block and time to urination were found to be significantly longer in group II and group III compared to group I (p<0.05). There were no significant differences between groups II and III (Table 8).

No statistically significant differences were detected between the groups in terms of the level of intra-operative analgesia.

Evaluation of the requirement for atropine, ephedrine and analgesic revealed that the need for atropine in group III was significantly higher compared to that in other groups (p<0.001), and the need for ephedrine was significantly higher in group II and group III compared to group I (p<0.01). There were no differences between the groups in terms of the need for analgesic (Table 9).

Hypertension in group II and group III was significantly higher than in group I (p<0.007). Sedation in group III was significantly higher in group III compared to the other groups (p<0.05). While all cases were awake in group I and group II, five cases of sedation were observed in group III. There were no statistically significant differences among the groups with regard to other complications (Table 10).

Table 5. Sensory block level.

Time	Group I	Group II	Group III
6. min	$T_{11 \pm 1,72}$	$T_{11 \pm 1,38}$	$T_{11 \pm 1,40}$
8. min	$T_{10 \pm 1,77}$	$T_{11 \pm 1,56}$	$T_{10 \pm 1,20}$
10. min	$T_{10 \pm 1,65}$	$T_{10 \pm 1,46}$	$T_{10 \pm 0,90}$
12. min	$T_{9 \pm 1,62}$	$T_{9 \pm 1,27}$	$T_{9 \pm 0,88}$
15. min	$T_{9 \pm 1,33}$	$T_{8 \pm 1,17}$	$T_{9 \pm 0,76}$
20. min	$T_{8 \pm 1,14}$	$T_{8 \pm 0,86}$	$T_{8 \pm 0,41}$
30. min	$T_{8 \pm 0,82}$	$T_{8 \pm 0,70}$	$T_{8 \pm 0,41}$
45. min	$T_{8 \pm 0,81}$	$T_{8 \pm 0,70}$	$T_{8 \pm 0,41}$
60. min	$T_{9 \pm 0,92}$	$T_{8 \pm 0,77}$	$T_{8 \pm 0,56}$
75. min	$T_{9 \pm 1,14}$	$T_{8 \pm 1,04}$	$T_{8 \pm 0,59}$
90. min	$T_{10 \pm 1,35}$*	$T_{8 \pm 1,42}$	$T_{8 \pm 0,83}$
105. min	$T_{11 \pm 1,52}$**	$T_{9 \pm 1,63}$	$T_{8 \pm 1,33}$
120. min	$T_{11 \pm 1,43}$	$T_{11 \pm 1,73}$	$T_{9 \pm 1,90}$
150. min	$T_{11 \pm 0,79}$	$T_{12 \pm 1,40}$	$T_{11 \pm 2,04}$
180. min	$T_{11 \pm 0,61}$	$T_{12 \pm 0,62}$	$T_{12 \pm 1,43}$
210. min	$L_{1 \pm 0,75}$	$T_{12 \pm 0,00}$	$T_{12 \pm 0,74}$

*: p<0.002, **: p<0.004; Group I compared to Group II and Group III

Table 6. Sensory block level.

	Group I	Group II	Group III
Maximum sensory block level	8.12±2.51	7.16±2.43	7.28±2.54
Time to onset of maximum sensory block (min)	18.88±9.28	20.04±9.10	19.56±7.09
Time to two segment regression (min)	96.60±14.20*	111.00±19.84	119.20±18.47
Time to reduction to S_2 level (min)	200.20±21.82*	238.00±25.21	246.60±18.69

*p<0.0001; Group I compared to Group II and Group III

Discussion

Various studies have been performed to evaluate the effects of bupivacaine and ropivacaine administration on blood pressure. Gautier et al. [3] intrathecally administered 0.2% (8 mg) bupivacaine and 0.3% (8, 10, 12, 14 mg) ropivacaine and reported hypotension in three patients (10%) in the 8 and 14 mg ropivacaine with bupivacaine group, respectively, and in two patients (6 %) in the 12 mg ropivacaine with bupivacaine group. Namee et al. [4] reported intra-operative hypotension in 24% of patients that were intrathecally administered 0.75 % (18.75 mg) and 1% (25mg) ropivacaine, respectively. In a study carried out by Malinovsky et al. [5], 2 ml ropivacaine at concentrations of 0.2 %, 0.75%, 1% and 2% were administered for spinal anesthesia, and significant hypotension was reported in 2% of the group.

Sklitsi et al. [6] intrathecally administered 0.5 % (12.5 mg) and 0.75 % (18.75 mg) ropivacaine to patients undergoing total hip replacement surgery and found the incidence of cardiovascular side effects to be similar. Griffin et al. [7] demonstrated the similar hypo-tensive effects of intrathecally administered ropivacaine and bupivacaine.

Eisenach et al. [8] suggested that hypotension arising from epidural clonidine is more likely to be associated with plasma concentrations than BOS concentrations and that the location

Table 7. Modified Bromage scale points.

	Group I	Group II	Group III
6. min	3,21±1,74	3,68±1,38	2,83±1,40
8. min	2,72±1,77	2,88±1,565	2,17±1,20
10. min	2.,32±1,65	2,32±1,46	1,75±0,90
12. min	2,040±1,62	1,88±1,17	1,33±0,76
15. min	1,88±1,33	1,88±1,17	1,33±0.76
20. min	1,72±1,14	1,64±0,86	1,08±0,41*
30. min	1,40±0,82	1,36±0,70	1,08±0,41
45. min	1,36±0,81	1,36±0,70	1,08±0,41
60. min	1,56±0,92	1,44±0,77	1,17±0,56
75. min	1,84±1,14	1,60±1,04	1,21±0,59
90. min	2,60±1,35	2,12±1,42	1,46±0,83*
105. min	3,33±1,52	2,68±1,63	2,13±1,33*
120. min	4,2±1,43	3,60±1,73	2,96±1,90*
150. min	5,72±0,79	4,84±1,40	4,33±2,04*
180. min	5,88±0,61	5,84±0,62	5,04±1,43*
210. min	5,81±0,75	6,00±0,00	5,75±0,74

*: p<0.05; Group III compared to Group I and Group II

of the effect is central. De Kock et al. [9] reported a statistically significant reduction of OAB in a study in which 45 µg and 75 µg clonidine was added to 8 mg of intrathecal ropivacaine. In our study, OAB was found to be significantly lower in the 30 µg clonidine group at 15 and 120 minutes compared to baseline values. Moreover, at 75, 105 and 120 minutes, these values were lower compared to the clonidine free group and the clonidine administered (15 µg) groups. De Kock et al. [9] did not report a significant difference in heart rate in their study in which they added 45 µg and 75 µg clonidine to 8 mg ropivacaine and performed the administration intrathecally. In our study, no significant differences were detected in KAH in the three groups compared to baseline values and in simultaneous comparisons between the groups.

A high dose (700 µg) of epidural clonidine was reported to cause severe sedation and a minor increase in PaCO2 (3 mmHg) [8]. Hayashi et al. [10] reported that clonidine decreases respiratory rates, but does not cause respiratory depression or a decrease in O2 saturation , and that opioids do not increase respiratory depression. In our study, respiratory depression was not observed in any of the cases and SpO2 remained above 94%.

In a study conducted by McNamee et al. [4], various doses and concentrations of intrathecal ropivacaine were compared, and compared to intrathecal administration of 7.5 mg/ml (18.75 mg) ropivacaine, the time to reduction to T10 and the duration of total motor block were longer with 10 mg/ml (25 mg) intrathecal ropivacaine. Van Kleef et al. [11] intrathecally administered ropivacaine at 0.5% (1.5 ml) and 0.75 % (1.5 ml) concentrations and found the total motor block rate (90%) to be significantly higher and the duration of motor block (268 min) to be significantly longer in the 75% ropivacaine administered group In our study, while total motor block was observed in 84% of the cases in the 12 mg ropivacaine group, the duration of the motor block was determined to be 138 minutes.

In a study carried out by Çınar at al. [12] in which 50 µg fentanyle or 75 µg clonidine was added to 0.5 % epidural bupivacaine, the onset of sensory block (T10) was significantly shorter in the clonidine group and the maximum dermatome (T4) achieved was found to be significantly higher in the clonidine group. Klimscha et al. [13] reported that the combined spinal and epidural administration of 150 µg clonidine significantly shortens the onset of sensory block and the level of sensory block reaches up to the T4 dermatome. Racle et al. [14] intrathecally administered % 0.5 (15 mg) bupivacaine, 20 µg or 15 µg clonidine together with 0.5 % (15 mg) bupivacaine in planned hip surgery cases. The duration of sensory and motor block as well as the two segment regression were found to be statistically significant in the clonidine groups. In addition, the total motor block rate was also significantly higher in the clonidine group. De Kock et al. [9] compared sensory and motor blocks by intrathecally administering ropivacaine 8 mg with various doses of clonidine (15, 45, 75 µg). While there were no differences in the time to onset of the maximum sensory and motor blocks, a two segment regression of the block, reduction to S2 level and duration of motor block and time to urination were significantly longer in the 5 µg and 75 µg clonidine groups. In our study, there were no differences between the groups in terms of time to onset of maximum sensory and motor blocks. However, compared to the clonidine free group, both the two segment reduction time and the time to reduction to the S2 segment were significantly longer in both clonidine groups.

Table 8. Motor block properties and time to urination by groups.

	Group I	Group II	Group III
Maximum motor block degree	1.28±0.68	1.36±0.70	1.08±0.40
Time to onset of maximum motor block (min)	16,40±10,27	15,16±8,42	11,36±4,64
Duration of motor block (min)	138,00±20,26*	162,60±35,03	172,20±37,78
Time to urination (min)	275,17±53,61*	311,14±42,28	309,77±35,10

*: p<0.05; Group I compared to Group II and Group III

Table 9: Patient's atropine, ephedrine, and analgesic need.

	Group I (n/%)	Group II (n/%)	Group III(n/%)
Atropine requirement	0	0	6/24*
Ephedrine requirement	0	5/20**	8/32**
Analgesic requirement	4/16	4/16	2/8

*: p<0.001; Group III compared to Group I and Group II, **: p<0.01; Group II and Group III compared to Group I

In a study conducted by De Kock et al. [9], in which various doses (15, 45, 75 µg) of clonidine were added to 8 mg intrathecal ropivacaine, analgesic use was necessary in 1 patient in the clonidine-free group and 2 patients in the 15µg group, while a need for extra doses of analgesics in the 45 and 75µg clonidine groups did not arise. In our study, the need for additional analgesics was diminished in the 30 µg clonidine group compared to the other groups.

Gentili et al. [15] intrathecally administered 0.5% bupivacaine (15 mg), clonidine (75 µg) or morphine (0.2 mg) together bupivacaine in 20 patients. During the first 24 hours, urine retention was observed in seven patients in the morphine group and in one patient in the clonidine group. Griffin et al. [7] intrathecally administered 0.5 % ropivacaine (15 mg) or 0.5 % bupivacaine (15 mg) and found side effects of headache in 1 case (2.70%), nausea in 4 cases (10.81 %), and bradycardia in 2 cases (5.40 %) in the ropivacaine group and nausea in 8 cases (22.85%) in the bupivacaine group. Kleef et al. [11] intrathecally administered 0.5 % and 0.75 % ropivacaine in 39 cases. Six cases in the 0.5% ropivacaine group and five cases in the 0.75% ropivacaine group developed post-spinal headache. In a study conducted by

De Kock et al. [9] with 15, 45, or 75 µg clonidine added to 8 mg intrathecal ropivacaine, all groups, with the exception of the 15 µg clonidine group, displayed significant delays in time to urination. In our study, nausea in one case in the 15µg clonidine group and urine retention requiring catheterization in one case in the 30 µg clonidine group were observed.

Carabine et al. [16] found sedation rates to be similar in their study in which bupivacaine alone or in combination with clonidine was used in spinal anesthesia. In the study performed by De Kock et al. [9], including 120 patients, various doses of clonidine were added to 8 mg ropivacaine. Sedation developed in two patients in the 75 µg clonidine group. In our study, sedation was observed in five cases in the ropivacaine plus 30 µg clonidine group.

Table 10: Complications.

	Group I (n/%)	Group II (n/%)	Group III(n/%)
Hypotension	0	5/20	8/32*
Nausea	0	1/4	0
Vomiting	0	0	0
Respiratory depression	0	0	0
Sedation	0	0	5/20*
Headache	0	0	0
Urine retention	0	0	0

*: p<0.05; Group III compared to Group I and Group II

In conclusion, the addition of clonidine to intrathecally administered ropivacaine increased the duration of sensory and motor block. However, when clonidine was added, careful monitoring of hypotension, bradycardia and sedation was necessary.

Conflict interest statement The authors declare that they have no conflict of interest to the publication of this article.

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