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Analgesic Effect of Clonidine Added to Bupivacaine in Spinal Anesthesia for Cruciate Ligament Repair

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Background: Several researchers have suggested that addition of local anesthetics to spinal anesthesia increases the duration of post-operative analgesia.
Objectives: This study sought to assess the effect of addition of clonidine to bupivacaine in spinal anesthesia on analgesia after cruciate ligament repair.
Patients and Methods: This double-blind clinical trial was conducted on 50 American Society of Anesthesiologists (ASA) class I or II patients who were candidates for cruciate ligament repair. Patients were randomly assigned to two groups; one group received 15 mg of bupivacaine (group B) and the other 15 mg of bupivacaine plus clonidine (75 μg, group BC). The two groups were compared in terms of post-operative analgesia and related factors using the SPSS software version 20.
Results: All patients were males with a mean age of 24.9 years in group B, and 25.2 years in group BC ($P > 0.05$). In group BC, time lapse to request analgesics was 160 minutes longer and the Visual Analog Scale (VAS) at this time was 0.3 units less than group B. The time to regression of sensory block by two dermatomes was seven minutes longer, VAS in the recovery room was 1 unit less and Bromage scale in the recovery room and ward was 0.6 and 0.9 units more, respectively in the BC group. Hypotension and ephedrine usage was 36% more in the BC group ($P < 0.05$).
Conclusions: Clonidine plus bupivacaine can increase the duration of motor and sensory block in arthroscopic cruciate ligament repair under spinal anesthesia. However, due to significant hemodynamic changes, further studies are required to determine a safer dose.

*Keywords:*Clonidine; Bupivacaine; Arthroscopy; Anesthesia Spinal; Anterior Cruciate Ligament; Pain Postoperative

1. Background

Uncontrolled post-operative pain can activate the sympathetic system, increase the myocardial oxygen consumption/demand and play a role in ischemia and myocardial infarction (1). Increased sympathetic activity delays stomach and intestinal movements and can cause paralytic ileus (2).

Stress responses can increase post-operative coagulation, increase the risk of deep vein thrombosis (DVT) and myocardial infarction and can also cause immunosuppression (1). Hyperglycemia as the result of stress response can delay wound healing (3). Management of physiological processes that are associated with acute post-operative pain can regulate the stress response, sympathetic output and spinal inhibitory reflexes and subsequently decrease morbidity and mortality. By doing so, patient satisfaction and quality of life improve as well (2).

Anterior Cruciate Ligament (ACL) is injured in athletes and trauma victims (3, 4). The exact incidence rate of ACL rupture is unknown, and it is best repaired via arthroscopy (3). The optimal anesthesia technique for this procedure is the regional anesthesia technique (4).

General anesthesia is not preferred for arthroscopy due to post-operative nausea, vomiting and pain (3). For knee arthroscopy, intra- and extra-auricular anesthetics can be injected as well (3-5). Reconstruction of ACL also requires muscle relaxation and flaccidity. Spinal anesthesia provides perfect anesthetic conditions for this operation (3, 6). Clonidine is an α-2 agonist used as an additive in spinal anesthesia, in order to prolong motor and sensory block. Its mechanism of action is through vascular contraction and anti-nociception due to stimulation of α-adrenergic receptors (1-3, 5). Its exact mechanism of action is unknown (1-3). Clonidine has been assumed to have an inhibitory effect on afferent neurons in the posterior spinal horn, which may be due to the activation of noradrenergic descending pathways. Many studies have suggested administration of 15 - 75 μg, and 0.75, 1 and 2 μg/kg doses of clonidine with no serious complications in children and adults (7-11).

2. Objectives

Anterior Cruciate Ligament rupture has a high preva-

lence (3). Many studies have been conducted on clonidine and its positive effects have been confirmed by several studies. However, since clonidine has recently been introduced to the Iranian market, particularly in its injection form, studies evaluating its efficacy are scarce (3, 6, 8-10). Thus, this double-blind clinical trial sought to assess the effect of clonidine on post-operative analgesia and hemodynamic status of patients undergoing ACL reconstruction surgery.

3. Patients and Methods

This double-blind clinical trial was approved by the Ethics Committee of Baqiyatallah University of Medical Sciences and the Iranian Registry of Clinical Trials (IRCT2014062117413N5). The sample size of 25 patients in each group was calculated using the following Equation:

(1) $$n = \left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \frac{\left(SD_1^2 + SD_2^2\right)}{(\mu_2 - \mu_2)^2}$$

Fifty candidates of ACL reconstruction surgery under spinal anesthesia were enrolled at Baqiyatallah Hospital. Patients were over 18 years old, and ASA class I and II. All patients signed a written informed consent. Those with a history of chronic pain, multiple trauma, long-term consumption of opioids and analgesics, history of alcohol consumption, those with absolute or partial contraindication for spinal injections and subjects with allergy to clonidine and bupivacaine were excluded. All patients received 0.1 mg/kg of diazepam orally, the night before the operation.

Patients were randomly divided to two groups by a computed generalized list. A nurse measured the block spread (eight patients in each block), an anesthesiologist prepared the drugs, and another anesthesiologist injected the drugs for the patients. The first group received 0.5% bupivacaine with a total dose of 15 mg plus 0.5 mL of saline solution, and the second group received 15 mg of 0.5% bupivacaine plus 75 μg of clonidine with a total volume of 0.5 mL, intrathecally.

The patients received 1 - 2 mg of midazolam for sedation prior to surgery and 5 mL/kg of saline solution during 15 - 20 minutes. During the operation, oxygen supplementation was carried out through a green mask at a rate of 6 L/minute.

Patients were placed in a seated position. The injection site was cleaned with Betadine and spinal anesthesia was induced using a number 26 needle inserted through L3 - L4 or L4 - L5 with the midline method. The drug volume was 3.5 mL injected during 15 seconds. The anesthetic drug was prepared and injected by an anesthesiologist other than the one in charge and only the code of drug was given to the researcher. During the operation, 1 mg of midazolam was administered if sedation was needed. Patient's blood pressure was taken and recorded using the non-invasive technique (NIBP) immediately after the spinal injection and every two minutes for the first ten minutes and every five minutes thereafter until the end of the operation. The blood pressure was monitored in the recovery room and in the ward.

In addition to systolic and diastolic blood pressure, Ramsay score, Bromage scale, Visual Analog Scale (VAS), SpO_2 and pulse rate per minute were also measured and recorded every 15 minutes (five times: before the operation, the mean of the first 15 minutes after anesthesia induction, the mean during the operation, in the recovery room and in the ward). Patients' level of pain was measured using the VAS score, level of sedation using the Ramsay score, and motor block using the Bromage scale. Time to request analgesics and the VAS score at the time of request were also recorded. These data were compared for the two groups using the SPSS software version 20, descriptive statistics and t-test, repeated measures ANOVA, chi square test and Fisher's exact test.

4. Results

A total of 50 patients underwent ACL reconstruction surgery. Patients were all males and had no significant difference in terms of demographic information, risk factors and duration of operation ($P > 0.05$) (Table 1). The mean time to request analgesics was 217.3 minutes in the bupivacaine and 377 minutes in the clonidine group ($P < 0.001$). The VAS score at the time of requesting analgesics was 5.7 for the bupivacaine and 5.4 for the clonidine group ($P = 0.028$). The time to regression of sensory block by two dermatomes was 97.8 minutes for the bupivacaine and 124.5 minutes for the clonidine group (after the injection) ($P = 0.001$). The mean time to first post-operative urination was 437.8 minutes for the bupivacaine and 598 minutes for the clonidine group ($P < 0.001$).

Time to motor recovery was 135.4 minutes for the bupivacaine and 251.8 minutes for the clonidine group ($P < 0.001$). Time to recovery room discharge was 129.3 minutes for the bupivacaine and 144.2 minutes for the clonidine group, and was not significantly different between the two groups ($P = 0.143$). Figure 1 compared times of operation, two sensory dermatome regression, needing analgesia, voiding, motor regression and recovery stay in the two groups.

The mean VAS before the operation, during the operation and in the recovery was not significantly different between the two groups. However, in the ward, this score was 1 unit higher in the bupivacaine group compared to the clonidine group (1.5 and 0.5, respectively). This difference was statistically significant ($P < 0.001$).

The mean Bromage scale before and during the operation was not significantly different between the two groups. However, this scale was 1 unit higher in the bupivacaine group in the recovery room and in the ward. This difference was statistically significant ($P < 0.001$). The mean Ramsay sedation score during the first 15 minutes after anesthesia was 0.22 units higher in the bupivacaine

group (P = 0.005). This rate during the operation was 2.26 for the B and 2.33 for the BC group (P = 0.95). This rate in the recovery room was 0.19 units lower in the B group (2 and 2.19, respectively, P = 0.01). In the ward, no significant difference was found between the two groups in this respect (P = 0.93).

The systolic blood pressure (BP) before the operation, during the first 15 minutes after the anesthesia and during the operation was not significantly different between the two groups (P > 0.05). Systolic BP in the recovery room was 8.1 mmHg lower in the clonidine group (116.6 and 108.5, respectively). In the ward, systolic blood pressure was also 5.2 mmHg lower in the clonidine group (113.6 versus 108.4 mmHg) (P < 0.001).

Diastolic blood pressure before the operation and during the first 15 minutes was not significantly different between the two groups (P > 0.05). However, the mean diastolic BP in the clonidine group was 3.5 mmHg lower (67.1 and 63.6 mmHg, respectively) during the operation and 9.3 mmHg lower in the recovery room (70 and 60.7, respectively) and 8.9 mmHg lower in the ward (70.2 and 61.3 mmHg, respectively). These differences were statistically significant (P < 0.05). A SpO_2 of below 97% was not recorded in any patient. Among the side effects, BP drop and use of ephedrine were observed in nine patients from the BC group (P < 0.05); among which, two patients required more than 10 mg of ephedrine. In the BC group, two patients developed urinary retention requiring catheter insertion and three cases had decreased heart rate requiring 1 mg of atropine (P > 0.05). Nine patients in the clonidine group had a BP drop and required ephedrine; out of which, two required more than 10 mg of ephedrine for BP control.

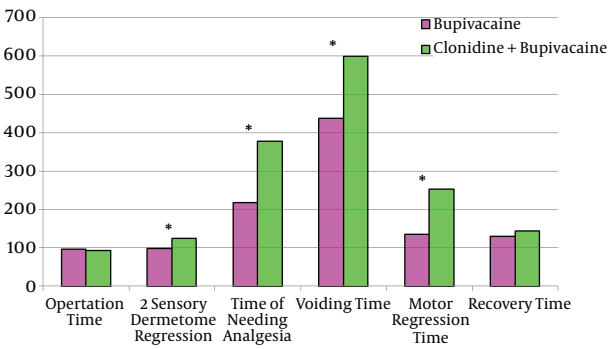

Figure 1. The Mean Amounts of Operation Time, Two Sensory Dermatome Regression, Time of Needing Analgesia, Voiding Time, Motor Regression Time and Recovery Time in the Two Groups

Table 1. Patients' Characteristics [a]

Variables	B (Bupivacaine)	BC (Bupivacaine + Clonidine)	P Value
Age, yr	24.9 ± 5.4	25.2 ± 5.3	0.228
BMI, kg/m^2	24.8 ± 2.3	26.9 ± 3.5	0.079
Operation Time, min	96.3 ± 22.37	93 ± 31.5	0.873
Two Sensory Dermatome Regression [b]	97.8 ± 19.2	124.5 ± 34.1	0.001
Time of Needing Analgesia [b]	217.3 ± 12.8	377 ± 93.4	0.000
VAS Score on Time of Needing Analgesia	5.7 ± 0.67	5.4 ± 0.94	0.028
Voiding Time [b]	437.8 ± 101.6	598 ± 128.5	0.000
Motor Regression [b]	135.4 ± 15.5	251.8 ± 77.7	0.000
Recovery Time [b]	129.3 ± 22.4	144.2 ± 49.5	0.143
Ephedrine	0 (0)	9 (36)	0.01
Atropine	0 (0)	3 (12)	0.11

[a] All Amounts are Mean ± SD or NO. (%).
[b] Values are based on minutes.

Table 2. Comparison of Visual Analogue Scale (VAS), Bromage Scale, Ramsay Sedation Score, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Heart Rate in the Two Groups [a]

	B (Bupivacaine)				BC (Bupivacaine + Clonidine)				Between Groups P Value
	Pre-Op	Recovery	Ward	Within Group	Pre-Op	Recovery	Ward	Within Group	
VAS	0	0.06 ± 0.3	1.48 ± 0.76	0.000	0	0	0.46 ± 0.2	0.000	0.000
Bromage Scale	0	2.4 ± 0.99	0.4 ± 0.51	0.000	0	2.98 ± 0.08	1.22 ± 0.74	0.000	0.000
Ramsay Score	1.65 ± 0.47	2.10 ± 0.22	2.0 ± 0.0	0.004	1.68 ± 0.51	2.19 ± 0.37	2.15 ± 0.28	0.09	0.27
SBP	124.7 ± 8.1	116.6 ± 6.2	113.6 ± 4.4	0.000	132.6 ± 15	108.5 ± 12.4	108.4 ± 7.9	0.000	0.000
DBP	76.1 ± 8.6	70.0 ± 7.2	70.2 ± 5.1	0.125	80.9 ± 10.9	60.7 ± 7.2	61.3 ± 6.21	0.032	0.002
Heart Rate	82.9 ± 14.5	68.3 ± 8.1	67.6 ± 4.8	0.031	85.8 ± 15.3	62.8 ± 7.7	64.2 ± 6.8	0.073	0.000

[a] All amounts are Mean ± SD.

5. Discussion

In our study, the results regarding the complications and benefits of clonidine as an additive to spinal anesthesia were in accordance with the majority of previous study results. However, incidence of hemodynamic drop in our study was higher than similar studies.

Thakur et al. in India reported that 15 μg and 30 μg of clonidine increased the time to regression of sensory block by the two dermatomes, sensory recovery in L3 and mean time to motor recovery; yet the 15 μg dosage was associated with less drop in mean systolic BP (11). Dobrydnjov in 2003 that 15 μg and 30 μg of clonidine were not significantly different in terms of duration of motor block (7).

Kaabachi in 2005 reported prolonged duration of sensory block, post-operative analgesia and motor block following administration of 1 μg/kg clonidine, which is in accordance with our results. However, they did not notice any side effects and other variables were not significantly different between the two groups of clonidine and bupivacaine (12).

van Tuijl et al. in 2006 suggested the safe use of addition of clonidine to bupivacaine for pregnant women undergoing Cesarean section and reported results similar to ours in terms of increased analgesia and duration of motor block. However, no significant difference was observed in terms of the need for analgesics in the first 24 hours post-operation between the two groups (8).

Grandge et al. in 2008 added 1 μg/kg of clonidine to bupivacaine for unilateral spinal anesthesia in 45 patients with lower limb orthopedic surgery and reported its safety without significant side effects. They reported results similar to ours in terms of duration of anesthesia and post-operative analgesia and motor block. However, no significant difference was reported regarding the duration of sensory block and other study variables (9).

According to Lavand'homme et al. bupivacaine-sufentanil-clonidine (75 μg), or bupivacaine-clonidine (150 μg) yielded results similar to our findings yet there was no significant difference in postoperative morphine consumption, pain score, duration and intensity of post-operative pain or side effects between the three groups of intrathecal bupivacaine-sufentanil, bupivacaine-sufentanil-clonidine (75 μg), and bupivacaine-clonidine (150 μg) (10). Bhure in 2011 used 75 μg of clonidine and reported results in accordance with our findings with no side effects (13). Imani et al. used 0.75 mg/kg of clonidine and stated less time to reach T10 anesthesia, more time to reach complete motor block, more time to request analgesics and greater drop in systolic BP (14).

Shah also used a similar dose of clonidine and reported significantly longer average two level regression time in the clonidine group (129 and 74 minutes, respectively). The mean duration of post-operative analgesia was longer in the clonidine group (8.8 hours versus 4.1, respectively). Heart rate was checked every 15 minutes, and was significantly lower in the clonidine group, and there were no complications in any of the groups requiring an intervention (such as bradycardia, BP drop or urinary retention) (15). The difference between our study and that of Joshi et al. in 2012 was the dosage of clonidine (30 μg in their study), objectives of the study and grouping. They divided their patients in three groups of intrathecal clonidine + bupivacaine, clonidine + pethidine (30 μg - 15 mg) and midazolam + bupivacaine (2 mg - 15 mg). They did not aim to compare clonidine and bupivacaine yet reported a 24% increase in incidence of BP drop, for 30 μg clonidine added to bupivacaine (16). The difference between our study and that of Gecaj-Gashi et al. was the dosage of clonidine (25 μg). They reported faster time to reach sensory and motor block in the clonidine group and also mentioned longer post-operative analgesia in those who received clonidine (17).

Jamliya et al. used 30 μg of clonidine and reported longer time to motor and sensory regression in the clonidine group, which is in agreement with our findings. They found no side effects for clonidine (18). Thakur et al. divided patients to three groups and compared the efficacy of 15 μg and 30 μg clonidine added to bupivacaine. Their results were consistent with ours, and a BP drop in the group receiving 30 μg of clonidine was reported (11).

In conclusion 75 μg clonidine plus bupivacaine may increase the duration of motor and sensory block in arthroscopic cruciate ligament repair under spinal anesthesia, and decrease consumption of analgesics. Considering the higher incidence of BP drop in our study compared to previous reports (5-20), further studies are required to determine the safe dose of clonidine. This drug combination is suitable for long-duration surgeries due to the increased duration of motor block and analgesia. Future studies are required to compare clonidine with other drug additives to intrathecal bupivacaine.

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Authors' Contributions

1- Study concept and design: Marzieh Lak. 2- Acquisition of data: Asghar Yousefi and Hamidreza Karimi-Sari, 3- Analysis and interpretation of data: Hamidreza Karimi-Sari. 4- Drafting of the manuscript: Asghar Yousefi and Hamidreza Karimi-Sari,. 5- Critical revision of the manuscript for important intellectual content: Marzieh Lak and Masoud Saghafinia. 6- Statistical analysis: Hamidreza Karimi-Sari. 7- Administrative, technical and material support: Marzieh Lak and Asghar Yousefi. 8- Study supervision: Marzieh Lak.

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