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Comparison of Intrathecal Clonidine in Bupivacaine, Bupivacaine only with Placebo in Patients Scheduled for Lower Limb Orthopaedic Surgery

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Abstract

Background and Objectives: Clonidine is a partially selective alpha-2 adrenergic agonist and has extensively been studied intrathecally in regional anaesthesia. With this background, the present study was conducted to compare the clinical efficacy of two different doses of intrathecal clonidine in hyperbaric bupivacaine with hyperbaric bupivacaine alone in terms of duration of post-operative analgesia, quality of surgical anaesthesia, incidence of hypotension and bradycardia in lower limb orthopedics surgeries.

Methods: Total of 150 patients was randomly allocated to 3 groups of 50 patients each. Group I received 2.5 ml of 0.5% hyperbaric bupivacaine+1 ml NS (Normal Saline); Group II received 2.5 ml of 0.5% hyperbaric bupivacaine+0.5 ml clonidine (75 mcg)+0.5 ml NS; group III received 2.5 ml of 0.5% hyperbaric bupivacaine+1 ml clonidine (150 mcg). Intraoperatively, onset of sensory and motor block, highest sensory level achieved, time to reach it, haemodynamic parameters and sedation scoring were noted. Postoperatively haemodynamics, duration of sensory/motor block, sedation and duration of effective analgesia were noted.

Results: Group II patients had effective postoperative analgesia with excellent quality of surgical anaesthesia, effective sedation score and showed significant hypotension. Group III patients had highest incidence of bradycardia.

Conclusion: This study concluded that 75 mcg clonidine is an effective adjuvant to 0.5% hyperbaric bupivacaine when used intrathecally in lower limb orthopaedic surgeries. Incidence of hypotension and bradycardia is lesser in 75 mcg than 150 mcg clonidine.

Keywords: Clonidine • Adjuvant • Intrathecal • Bupivacaine • Orthopaedic

Introduction

Regional Anaesthesia (RA) for lower limb orthopaedic surgery is safer than General Anaesthesia (GA). The problems related to GA are avoided as there is reduction of surgical stress with attenuation of plasma catecholamines rise during laryngoscopy. RA provides intra-operative and post-operative pain relief with full preservation of mental status and reflexes [1,2].

Many intrathecal adjuvants have been used that improvise the efficacy of local anaesthetics. Clonidine is a partially selective alpha-2 adrenergic agonist that potentiates the effect of local anaesthetics by local vasoconstriction and by altering the local anaesthetic disposition. It also has a direct analgesic effect on alpha-2 adrenoceptors in substantia gelatinosa of the spinal cord [1,2].

The purpose of this study was to compare the clinical efficacy of two different doses of clonidine (75 mcg-150 mcg) when added to 0.5% hyperbaric bupivacaine, intrathecally, with 0.5% hyperbaric Bupivacaine alone. Also it was planned to determine the benefits and undesirable effects of clonidine when used as an adjuvant to local anaesthetic in orthopaedic surgery.

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Methods

After approval from the institutional ethical committee, the present study was conducted in the Department of Anaesthesiology at a tertiary level hospital of northern India. This was a double-blinded, prospective, randomized controlled study among ASA Grade I and II patients aged 20-60 years, of either sex undergoing elective orthopedic surgery.

The primary outcome of the study was to compare the effects of two different doses of clonidine (75 mcg-150 mcg) when added to 0.5% hyperbaric bupivacaine, intrathecally, with 0.5% hyperbaric Bupivacaine alone. Also the secondary outcomes were to determine the benefits and undesirable effects of clonidine when used as an adjuvant to local anaesthetic in lower limb orthopaedic surgery.

Patients having any contraindication to regional anaesthesia taking alpha-adrenergic receptor antagonists, calcium channel blockers and ACE inhibitors or any other antihypertensive drug; showing dysrhythmias or bradycardia on the Electrocardiogram (ECG) having a history of low back surgery; obese (>100 kg) or height <150 cm were excluded from the study. Those patients who had history suggestive of any cardiac, renal or hepatic dysfunction; with a known allergy to clonidine or any other drug used or concomitantly taking clonidine, were also not included.

After a detailed pre-anaesthetic evaluation, an informed consent was taken from all the patients who volunteered to be a part of this study. Patients were kept fasted overnight, and tablet 0.25 mg Alprazolam was given a night before surgery. On the operating table, baseline values of Heart Rate (HR), respiratory rate, NIBP (Non-Invasive Blood Pressure) and Pulse Oximetry (SpO_2) were noted. An 18G cannula was placed in the dorsum of non-dominating hand and preloading with 500 ml of lactated Ringers solution (10 ml/kg) was done. A subarachnoid block was instituted in L3-L4 interspace using 25 g spinal needle in the left lateral position under full aseptic precautions.

Randomization was done using a computer generated random number table and allocation was done by a sealed envelope technique. A sealed envelope was randomly selected and opened by an assistant, with instructions to draw up the relevant drug. The patient was randomized to one of the three groups: Group I (control group) (n=40) received 2.5 ml of 0.5% hyperbaric bupivacaine+1 ml NS (Normal Saline) alone (to a total volume of 3.5 ml). Group II (n=40) received 2.5 ml of 0.5% hyperbaric bupivacaine +75 mcg clonidine (0.5 ml)+0.5 ml NS (to a total volume of 3.5 ml). Group III (n=40) received 2.5 ml of 0.5% hyperbaric bupivacaine +50 mcg clonidine (to a total volume of 3.5 ml). The assistant who prepared the drug was not involved in the study and the drug administered was not known to the anaesthesiologist performing the spinal block. The coding was maintained till the study was completed.

Intra-operatively, the various parameters were observed by an anaesthesiologist who was blinded to the type and amount of drug given to the patient. ECG and SpO_2 were observed continuously. NIBP and HR data was noted at 5 min intervals (for the first 15 min), at 15 min intervals for 15 min-150 min, and then every 30 min. A hypotension episode was defined as a systolic blood pressure less than 90 mmHg or a decrease in systolic blood pressure more than or equal to 30% of the baseline value. It was managed with 3 mg IV mephenteramine in incremental doses. Bradycardia was defined as a heart rate less than 50 beats/min. and was managed with 0.6 mg IV atropine (to a maximum of 5 doses).

Onset time of sensory block was taken as time to achieve loss of pinprick sensation till T10 level after administration of the drug. The time to reach the highest sensory level was also recorded. Onset time of motor block (time taken to achieve Bromage motor scale 3=3), was noted i.e. (0-Free movements of legs and feet, 1-Just unable to flex knees with free movement of feet, 2-Unable to flex knees, but with free movement of feet, [3] Unable to move legs or feet).

Sedation score was noted every 15 min intra-operatively using Ramsay scale [4] (1-Patient anxious, agitated or restless, 2-Patient cooperative, oriented or tranquil, 3-Patient responds to verbal commands only, 4-A brisk response to a light glabellar tap, 5-A sluggish response to a light glabellar tap, 6-No response to a light glabellar tap).

Quality of surgical anaesthesia was graded as excellent/good/poor. Excellent-No complaint from patient any time during surgery, Good-Patient allowed the surgery but required midazolam for sedation or fentanyl 1 mcg/kg intravenously for analgesia, Poor-If anaesthesia was inadequate and required supplementation with intravenous or inhalational anaesthesia. Side effects of hypotension, bradycardia and sedation were noted intra-operatively.

After the surgery was over, the patient was shifted to the post-operative room. NIBP and HR were noted every half hourly for first two hours, then two hourly. The duration of anaesthesia (taken as time for regression of anaesthesia below L1 dermatome by pinprick), was noted every 30 minutes. The duration of effective analgesia (taken as time interval between the administration of subarachnoid block and the first request for rescue analgesia) was noted. Injection Diclofenac Sodium 75 mg intravenously by slow infusion was administered as rescue analgesic. The study was terminated when rescue analgesic was administered.

The duration of motor block was noted using Bromage motor scale at the end of surgery and thereafter every 30 min till Bromage scale reached 0. In addition Sedation score, using Ramsay score, was noted every 30 min, till 4 hours after giving subarachnoid block.

Statistical Analysis

Sample size calculation was based on the results of a previous study; at least 40 patients were required in each group for an alpha 0.05 and power of 80%. The statistical analysis between the various parameters among the three groups was done using the SPSS (Statistical Package for the Social Sciences) software version 14.0 for windows. The age, height, weight, mean blood pressure and pulse rate were compared using ANOVA and 2 sample t-test.

The duration of surgery, onset of sensory and motor block, duration of sensory and motor block and time of effective analgesia were compared in between the groups using non-parametric Kruskall-Wallis test and non-parametric Wilcock's and Mann-Whitney test. p-value of less than 0.05 was considered statistically significant.

Results

A total of 120 patients were enrolled in this study. The demographic data were similar in each group and were statistically insignificant (p>0.05) (Table 1).

The sensory block onset time was significantly shorter in group III and was statistically significant as compared to group I (p=0.011). The onset of motor block was significantly shorter in group II and III as compared to group I (p= 0.000) (Table 2).

The duration of sensory block was longest in group III and was statistically highly significant between groups I and II, I and III, and II and III (p=0.000). The duration of motor block (longest in group III and the findings were highly significant between groups I and II, I and III, and II and III (p=0.000). The duration of effective analgesia was statistically longest in group III as compared to the other groups (p=0.000), but in group II it was also significantly longer than group I (p=0.000) (Table 3).

All the patients in group II and III were comfortable throughout the surgery; they were sedated, and did not need any drug supplement. However, 5 out of 40 patients in group I required 1 mg IV Midazolam for anxiety and restlessness during the surgery. Sedation in the clonidine groups improved the quality of anaesthesia intra-operatively. The incidence of hypotension and bradycardia was highest in group III. The findings of hypotension was statistically significant between all the three groups (p=0.001). The findings of bradycadia were significant between groups I and III, II and III. Thirty one patients in group III required IV mephenteramine and the dose was highest as compared to the other groups [5]. (Table 4).

Fourteen patients in group III required atropine and they required higher doses as compared to the other groups. Twelve hours postoperatively, one patient in group III developed delayed hypotension and bradycardia and was treated with 15 mg IV mephenteramine and 0.9 mg Atropine along with

Table 1. Demographic profile of the patients.

Parameter	Group I	Group II	Group III	p-Value
Age (years) mean ± S.D	37.5 ± 14.4	35.9 ± 13.1	36.7 ± 12.5	p>0.05
Sex Male:Female	32:8	35:5	30:10	-
Weight (kg) mean ± S.D	60.6 ± 13.7	61.3 ± 13.0	62.8 ± 10.9	p>0.05
Height (cm) mean ± S.D	165.8 ± 11.7	164.3 ± 8.4	163.7 ± 6.9	p>0.05
Duration of surgery (min)	165.8 ± 11.7	164.3 ± 8.4	163.7 ± 6.9	p>0.05

Table 2. Sensory block and motor block.

Group	Group I (n=40)	Group II (n=40)	Group III (n=40)	p-Value
Onset of sensory block (min) mean ± S.D	11.4 ± 5.3	9.6 ± 4.1	8.6 ± 2.2	0.011
Onset of motor block (min) mean ± S.D	12.2 ± 4.5	9.8 ± 4.0	7.1 ± 2.5	p=0.000
Time to achieve highest level (min) Mean ± S.D	18.4 ± 4.0	16.6 ± 6.1	18.0 ± 5	-
Highest level achieved	T 6	T 6	T 6	-
Duration of surgery block (min) mean ± S.D	149.1 ± 28.6	193 ± 43.2	221 ± 31.8	-
Duration of motor block (min) mean ± S.D	173.5 ± 38.6	230.5 ± 48.7	257.4 ± 29.6	

Table 3. Duration of effective analgesia and qualitu of surgical anaesthesia.

Group	Duration of effective analgesia (min)	Quality of surgical anaesthesia			p value
	(Mean ± S.D.)	Excellent	Good	Poor	
Group I (n=40)	229.4 ± 70.1	35 (87.5%)	35 (87.5%)	35 (87.5%)	0.00
Group II (n=40)	313.8 ± 84.0	40 (100%)	0 (0%)	0 (0%)	
Group III (n=40)	387.0 ± 98.7	40 (100%)	0 (0%)	0 (0%)	

Table 4. Incidence of intra-operative hypotension and bradycardiasedation scores peri-operatively (using ramsay scale).

Parameter	Group I (n=40)	Group II (n=40)	Group III (n=40)	p-Value
Hypotension no. of patients (%)	3 (7.5%)	17 (42.5%)	31 (77.5%)	
Dose of mephenteramine (mg) mean ± S.D	7.0 ± 6.9	9.3 ± 6.4	14.7 ± 6.4	0.001
Bradycardia no. of patients (%)	18.4 ± 4.0	16.6 ± 6.1	18.0 ± 5	
Dose of atropine (mg) mean ± S.D	0.6 ± 0.0	0.4 ± 0.17	0.67 ± 0.28	-
Intra-operative sedation score	1.9 ± 0.1	2.3 ± 0.5	2.6 ± 0.5	-
Post-operative sedation score	1.7 ± 0.2	1.8 ± 0.2	2 ± 0.4	-

intravenous fluids (Ringer Lactate) (Table 4).

Discussion

Clonidine is commonly used because of its safety and various advantages over other adjuvants. The mechanism by which clonidine prolongs motor and sensory block is not well-known. It produces analgesia by depressing the release of C-fiber transmitters and by hyperpolarization of postsynaptic dorsal horn neurons [6]. Binding of clonidine to motor neurons in the dorsal horn may prolong motor block. In our study, two doses of clonidine, 75 microgram and 150 microgram, as an adjuvant to 0.5% hyperbaric bupivacaine were compared to the control group (NS with 0.5% hyperbaric bupivacaine). Previously, it was demonstrated that the addition of clonidine to bupivacaine intrathecally can shorten the onset of motor block; increase the duration of sensory and motor block; prolong the duration of effective analgesia and improve the quality of surgical anaesthesia by providing adequate intra-operative sedation. The onset of sensory block in the present study was significant between group I and III only. W. Klimscha, et al. [5]. The authors evaluated the analgesic efficacy and hemodynamic and respiratory safety of clonidine when added to bupivacaine for caudal blocks in 58 children aged 38 ± 2 months (mean ± SEM). They were randomly given a caudal injection (0.75 mL/kg) of saline placebo, bupivacaine, 0.25%, bupivacaine plus epinephrine 1:200,000, bupivacaine plus clonidine 1 microgram/kg, or bupivacaine plus clonidine 2 micrograms/kg. They found that the onset time for anaesthesia (T11) was comparable by addition of clonidine to either epidural or intrathecal bupivacaine. P. De Negri et al. [7] and G.E. Kanazi et al. [8] also studied the effect of intrathecal clonidine on bupivacaine spinal block and found no difference in the speed of onset of sensory block. The addition of intrathecal clonidine to bupivacaine resulted in a higher spread of sensory level. In group III and group II it was T6, as compared to T8 in group I. However, Jean P. Racle, Abdellatif Benkhadra et al. [9] found that the mean maximal levels of anaesthesia were similar in groups receiving 15 mg bupivacaine with saline and 15 mg bupivacaine with 150 mcg clonidine. The results of Stephan Strebel et al. [10] were also not in concordance with our study. They compared the effects of 18 mg isobaric bupivacaine plus saline with clonidine 37.5 mcg, 75 mcg, and 150 mcg. This difference may have been because of use of isobaric bupivacaine in their study.

The results of present study were similar to Dobrydnjov et al. [11] who conducted a randomized double blinded study using 15 mcg clonidine and 30 mcg plus bupivacaine during spinal anaesthesia and found a higher cephalad spread of sensory block with clonidine. Similarily, G.E. Kanazi et al. [8] also found that the median peak sensory level with 12 mg hyperbaric bupivacaine was T6 as compared to T6.5 with the addition of 30 mcg clonidine.

The duration of sensory block was found to be significantly longer in group II and III. Similar findings were seen by Jean P. Racle et al. [9], L. Niemi [12] and W. Klimscha et al. [5] who studied the effect of 150 mcg intrathecal clonidine and bupivacaine. P. De Negri et al. [7], I. Dobrydnjov [13] and K. Axelsson et al. [11] also found that the addition of intrathecal clonidine to bupivacaine prolonged the sensory block significantly compared to bupivacaine alone.

In 2004, Stephan Strebel et al. [9] compared three doses of intrathecal clonidine plus bupivacaine with bupivacaine alone. The duration of sensory block was prolonged by the addition of clonidine in a dose-dependent manner. Time to regression below level L1 was +8% with 37.5 mcg clonidine, +13% with 75 mcg clonidine and +17% with 150 mcg clonidine as an adjuvant.

In the present study, the onset of motor block was earliest in group III. G. E Kanazi et al. [7], found that the time to reach Bromage score 3 motor block was significantly shorter with the addition of 30 mcg clonidine (11.7 minutes ± 5.9 minutes) as compared to 12 mg bupivacaine alone (20.7 min ± 10.3 min.), (p=0.002). In 2010, H. Saxena and coauthors [14] also found that the mean time of onset of motor blockade with intrathecal clonidine was quicker as compared to the control group. We found that the regression of motor block was significant and prolonged by the addition of intrathecal clonidine. Many studies have used intrathecal clonidine in the dose range 75 mcg-150 mcg. Jean P Racle et al. [9], S. Kapral et al. [15], L. Niemi [12], P. De Negri et al. [7], Dobrydnjov and J. Samarutel et al. [12] etc, also determined that addition of clonidine prolonged the duration of motor block.

The duration of effective analgesia was longer in group II and III. These results were similar to the findings of D.J. Fogarty et al. [16], L.Niemi [12], W. Klimscha and et al. [5] P. De Negri and et al. [7] and I. Dobrydnjov et al. [11] who determined that the mean time to first request for analgesia was significantly longer in the intrathecal clonidine group as compared to the control group. Stephan Strebel and coauthors [10] studied the effects of 37.5 mcg, 75 mcg and 150 mcg intrathecal clonidine with isobaric bupivacaine.

H. Saxena and coauthors [14], investigated the effects of clonidine in the doses of 15 mcg, 30 mcg, 37.5 mcg added to intrathecal hyperbaric bupivaciane. In both these studies, the analgesia time was significantly prolonged. Their results also showed a dose-dependent prolongation of the pain-free interval which was similar to our study. We found that the duration of analgesia with 150 mcg clonidine was significantly longer as compared to 75 mcg clonidine (p=0.000).The quality of surgical anaesthesia was excellent in all the patients in both the clonidine groups (II and III). P. De Negri and et al. [7] compared 105 mcg intrathecal clonidine plus bupivacaine with bupivacaine alone. Patients treated with clonidine were found to be more sedated. According to them, this effect could not be considered as a drawback for long term surgery. We also considered this as a beneficial effect in our study as it made the patients more comfortable by reducing

anxiety and restlessness.

Clonidine affects blood pressure in a complex fashion after neuraxial or systemic administration. It produces hypotension by activation of postsynaptic alpha-2 adrenoceptors in the brain stem and by directly inhibiting sympathetic presynaptic alpha-2 adrenoceptors neurons in the spinal cord [17]. Hypotension and bradycardia were known side effects with intrathecal clonidine. More patients in group II and III developed hypotension as compared to group I. All patients responded well to incremental doses of 3 mg intravenous mephenteramine and no other intervention was required. Bradycardia was observed in 14 patients of group III, 3 in group II and 1 in group I.

The incidence of hypotension and bradycardia were more in the clonidine groups, but more in group III. L. Niemi [12], W. Klimscha et al. [5] and P. De Negri et al. [7] studied the haemodynamic effects of clonidine plus bupivacaine in their respective studies. They all found a statistically significant lower mean arterial pressure in the clonidine group.

In 2010, H. Saxena and coauthors [14] compared the effects of 15 mcg, 30 mcg, and 37.5 mcg clonidine plus bupivacaine to bupivaciane alone. There was no statistical variation in the fall in MAP across the four groups. This could be explained by the lower doses of intrathecal clonidine used in their study. They concluded that studies using very low doses of intrathecal clonidine (15 mcg-30 mcg) found no haemodynamic instability.

One of the patients in group III developed delayed hypotension and bradycardia. 12 hours post-operatively, a B.P of 70/40 mm Hg and heart rate of 40/min were recorded. The patient was treated with intravenous mephenteramine (15 mg), intravenous atropine (0.9 mg) and intravenous fluids. L. Niemi [12] reported a similar case where one of the patients receiving 3 mcg/kg intrathecal clonidine plus bupivacaine developed a hypotensive episode in the night after surgery. It was treated with intravenous Ringer Lactate solution.

In our study, intra-operative sedation was seen with group III and group II but none with group I (Ramsay score 4<3). This was found to be a beneficial effect as it decreased the intra-operative requirement of midazolam and made the patients more comfortable and less anxious during the surgery. Two studies demonstrated a higher incidence of sedation in patients receiving intrathecal cloinidine [12,14]. Similarly, B. S. Sethi, Mary Samuel and Deepak Sreevastava [18] compared the effect of 1 mcg/kg intrathecal clonidine with bupivacaine alone and found the incidence of sedation to be higher in clonidine group. Spinal hypotension is caused by decrease in the systemic vascular resistance and n a decrease in cardiac output. In younger patients systemic vascular resistance decreases to lesser extent for the same level of spinal block than in geriatric age group. It has also been observed that crystalloid preloading alone may not be sufficient to compensate for the decrease in systemic vascular resistance fluids infusion during first few minutes of block and vasopressors can be used as we used injection mephentermine. It can be suggested that coload of both fluids and vasopressors can be done to combat hypotension if occurs. In the current study, patients were co-loaded and vasopressor was used at the first instance when hypotension occurred. In our study, intra-operative sedation was seen with group III and group II but none with group I (Ramsay score 4<3). This was found to be a beneficial effect as it decreased the intra-operative requirement of midazolam and made the patients more comfortable and less anxious during the surgery. L. Niemi [12] and H. Saxena et al. [14] demonstrated a higher incidence of sedation in patients receiving intrathecal cloinidine. Similarly, B. S Sethi et al. [18] compared the effect of 1 mcg/kg intrathecal clonidine with bupivacaine alone and found the incidence of sedation to be higher in the clonidine group. The studies that were conducted previously were well compared with the present study parameters. The dose of clonidine intrathecally was weighed with the adverse effects so that safe dose could be formulated.

Conclusion

This study suggested that the dose of 75 mcg clonidine was an effective adjuvant to 0.5% hyperbaric bupivacaine when used intrathecally in lower limb orthopaedic surgery. The incidence of hypotension and bradycardia was lesser and the duration of postoperative analgesia was significantly prolonged. Thus it can be safely used for lower limb orthopedic surgery.

The Authors declare that there is no conflict of interest.

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