Research Article

Effect of adding clonidine versus fentanyl to intrathecal bupivacaine on spinal block characteristics in orthopedic procedures: A double blind controlled study

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Abstract

Background: Various adjuvants have been used in spinal anesthesia to avoid intraoperative visceral and somatic pain and prolonged postoperative analgesia. Clonidine, partially selective α_2-agonist drug, is now being used as a neuraxial adjuvant.

Objective: To compare the duration and quality of analgesia of clonidine and fentanyl used as adjuvants to intrathecal bupivacaine.

Materials and Methods: American Society of Anesthesiologist grade 1 and 2 patients (90 patients) were randomly divided into three groups of 30 patients each for lower limb orthopedic surgeries. Group A received intrathecal 15 mg hyperbaric bupivacaine and 1 ml normal saline, group B received 15 mg hyperbaric bupivacaine and 1 ml (50 μg) fentanyl, and group C received 15 mg hyperbaric bupivacaine and 1 ml (150 μg) clonidine. The onset and duration of sensory and motor block, quality of analgesia, and the incidence of side effects in three groups were observed and compared.

Results: Three groups were compared based on the demographic data, and the onset of sensory block at T_8 level and of motor block was compared among these groups. Significant prolongation of duration of sensory ($P = 0.0000001$) and motor block ($P = 0.0000001$) was found in group C. Significant hypotension was found in group C ($P < 0.05$) and the postoperative pain scoring chart (VAS chart) was 1.07 ± 0.87 in group C and 3.27 ± 0.67 in group B ($P < 0.05$).

Conclusion: Intrathecal clonidine is associated with prolonged motor and sensory block, hemodynamic stability, and low postoperative pain score compared to fentanyl.

KEY WORDS: Bupivacaine, clonidine, fentanyl, spinal anesthesia

Introduction

Neuraxial block was first introduced into clinical practice by August Bier in 1898 and since then neuraxial block has been the main support of anesthesia for surgery of lower abdomen and lower limb.

The major advancements of spinal anesthesia have come from the use of adjuvants. The commonly used adjuvants are opioids, clonidine, adrenaline, neostigmine, ketamine, midazolam, magnesium, and droperidol.

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Opioids and local anesthetics administered together intrathecally are known to have synergistic analgesic effects.[1] Fentanyl, a short-acting lipophilic opioid, was administered intrathecally along with local anesthetics by Belzarena.[2]

Clonidine, an α_2 adrenergic agonist, has been used as an antihypertensive agent for many years. Recently its desirable anesthetic properties in human have been highlighted, which include reducing anesthetic requirements, improving hemodynamic stability, and providing analgesia.[3–5]

The problem of postoperative pain relief seeks utmost attention since past few years. Postoperative pain treatment should be an integral component of the routine surgical and anesthetic management because it helps to reduce morbidity and complications as well as accelerate rehabilitation.[6] Good postoperative analgesia is an important avenue to attenuate the surgical stress response.[7]

When local anesthetic bupivacaine is combined with intrathecal clonidine, complete surgical anesthesia could be obtained along with intra- and postoperative pain relief with fewer side effects.[5,8–10] Clonidine has been used as an

adjuvant in connection with various regional anesthesia techniques,[11] including postoperative epidural analgesia.[12] Neuraxial clonidine is considered to be free from neurotoxic effects[13] even after prolonged intrathecal infusion.[14]

This study was carried out to compare intrathecal clonidine and intrathecal fentanyl as an adjuvant to bupivacaine in lower limb surgeries and assess their effects on onset and duration of sensory and motor block, hemodynamic parameters, and other side effects.

Material and Methods

Following approval from institutional ethical committee, a double-blind randomized controlled trial was performed with three groups of 30 patients each. Patients with American Society of Anesthesiologist grade 1 and 2, aged 25–50 years scheduled for lower limb orthopedic surgeries under spinal anesthesia were included for this study. Patients with contraindication to Sub Arachnoid Block and study medications (local anesthetics, narcotics and clonidine); or those with the history of psychiatric disorder, addiction and drug abuse; and those with cardiovascular, pulmonary, renal, hepatic disease were excluded for this study.

The patients were randomly segregated into three study groups according to list of random number table by means of a computer-generated randomization test or by another anesthetist not otherwise involved in this study. After preoperative examination and obtaining informed written consent, venous access was obtained with 18G or 20G intravenous cannula. Monitors were attached and baseline values of heart rate, blood pressure (BP), respiratory rate, and oxygen saturation were recorded. No premedication was administered.

Preloading was done with Ringer lactate at the rate of 1.5 ml/kg. Under all aseptic precautions, lumber puncture was performed in L_3–L_4 interface with 25G Quincke needle on patients in sitting position. The drug was injected intrathecally in randomized manner to the patients of the three groups. Group A received 0.5% heavy bupivacaine (3 ml) with 1 ml normal saline. Group B received 0.5% heavy bupivacaine (3 ml) with 50 μg (1 ml) fentanyl. Group C received 0.5% heavy bupivacaine (3 ml) with 150 μg (1 ml) clonidine. The study solution was prepared by another investigator and its contents were blinded to the anesthetist who administered it. The anesthesiologist who was collecting the data was blinded to the contents of these study groups.

Onset of sensory and motor block was noted using pinprick method and Bromage scale (grade 0, able to raise the lower limbs straight; grade 1, able to perform knee joint movement but not hip joint movement; grade 2, able to perform movement at ankle joint but neither at hip joint nor at knee joint; grade 3, able to perform the movement but unable to move ankle, knee, and hip joints; grade 4, no movement in lower limbs). Onset of sensory block was defined as time of intrathecal drug injection to loss of pinprick sensation at T_8 level, and onset of motor block was defined as time of intrathecal drug injection to reach Bromage scale grade 4.

Parameters such as heart rate, BP, respiratory rate, and oxygen saturation were recorded immediately after spinal anesthesia at an interval of 5 min for first 1 h, thereafter every 10 min till the end of surgery. The patients were monitored for grade of sedation, hypotension, bradycardia, nausea, vomiting, respiratory depression, and pruritus (sedation scoring: 0, fully awake; 1, sleeping comfortable but responding to verbal command; 2, deep sleep but arousable; 3, deep sleep but not arousable). Hypotension was described as systolic BP < 30% from baseline. Hypotension was treated with fluid and incremental dose of ephedrine (6 mg intravenously). Pruritus was treated with nalbuphine (2.5 mg intravenously). Any episode of bradycardia (heart rate < 60/min) was treated with increments of 0.02 mg/kg of intravenous atropine. After 1 h of induction of anesthesia, level of sensory block was assessed every 15 min using pinprick method till the regression of sensory block.

Duration of surgical time and basic parameters were noted down before shifting the patient to the recovery room. Postoperative assessment of pain was done by patients themselves using visual analog scale (VAS), which is a graphical rating scale. [A 10 cm baseline is recommended for VAS scale. The VAS score rating: 0, no pain; 1–3, mild pain; 4–6, moderate pain; 7–9, severe pain (cry, uncomfortable); 10, very severe pain (unbearable).] Intravenous tramadol (100 mg) was given as rescue analgesia when VAS score was greater than 4.

In postoperative period when pain reaches VAS score 1, time is noted and this decides the duration of sensory block (time interval between time of intrathecal drug injection and commencement of pain). Duration of motor block was calculated by noticing the time interval between times of intrathecal drug injection and beginning of movements of toes in recovery room. These data were recorded by recovery room nurse. The patients were asked to mark on the scale the degree of pain that they were having after 2.5 h of induction of anesthesia. Degree of pain was taken as distance between 0 and 10 (VAS scale) and recorded as percentage severity of pain.

All data are statistically analyzed with Statistical Package of Social Sciences (SPSS) and MS office Excel 2007. Data were expressed as mean ± SD and number (percentile) for all determination. Group A was used as a control group. Quantitative data between groups were compared by unpaired *t*-test. A *P*-value of <0.05 was considered clinically significant.

Results

The three groups were comparable with respect to age, weight, duration of surgery, and parameters such as baseline of BP, pulse rate, respiratory rate, and oxygen saturation [Table 1].

Table 2 showed that onset of sensory block (in min) and maximum height of sensory block (i.e., T_8) was same in all the three groups. Time taken for regression of sensory block below T_{10}, and L_1 and duration of analgesia (total analgesia) was significantly more in group C than the group B ($P < 0.05$).

Table 1: Baseline parameters

Parameters	Group A	Group B	Group C
Age (years)	33.47 ± 10.35	34.07 ± 9.95	32.9 ± 8.33
Weight (kg)	52.4 ± 9.6	54.6 ± 6.2	55.2 ± 5.6
Duration of surgery (in min)	108.33 ± 16.76	110.83 ± 13.85	128 ± 52.73
Blood pressure (systolic) (in mmHg)	111.17 ± 9.2	119.64 ± 6.89	103.82 ± 3.63
Pulse rate/min	96.89 ± 6.97	97.66 ± 6.19	81.45 ± 11.06
SpO_2 (%)	98.69 ± 0.93	98.65 ± 0.88	99.57 ± 0.63
Respiratory rate/min	17.3 ± 1.77	17.45 ± 1.65	16.2 ± 1.02

SpO_2 = oxygen saturation.
Data are given as mean ± SD.

Table 2: Characteristics of sensory block

Sensory block	Group A	Group B	Group C	*P*-value
Onset of action (min)	7.37 ± 1.43	7.03 ± 1.45	7.07 ± 1.41	0.9141
Time taken to regression of sensory block below T_{10} (min)	148.33 ± 14.36	272.9 ± 15.6	362.2 ± 13.7	0.0000001
Time taken to regression of sensory block below L_1 (min)	153.7 ± 9.42	275.6 ± 10.4	365.9 ± 13.5	0.0000001
Duration of analgesia (from subarachnoid injection to first report of pain in min)	164 ± 14.59	289.83 ± 15.4	387.8 ± 13.56	0.0000001

Data are given as mean ± SD.
$P < 0.05$ is statistically significant.

Table 3: Characteristics of motor block

Motor block	Group A	Group B	Group C	*P*-value
Onset of action (min)	5.9 ± 1.18	5.87 ± 1.25	5.8 ± 1.21	0.8263
Duration of action (min)	166.5 ± 11.61	177 ± 23.69	305.11 ± 14.14	0.0000001

Data are given as mean ± SD.
$P < 0.05$ is statistically significant.

This proves that clonidine significantly prolongs the duration of sensory block as compared to the fentanyl.

The characteristics of motor block, such as onset of action and duration (in min), are shown in Table 3, showing all patients had a grade 3 motor blockade and the duration of motor block was significantly prolonged in group C as compared to group B.

The incidence of side effects such as hypotension, bradycardia, nausea/vomiting, shivering, pruritus, and sedation is shown in Table 4. From the table, it is evident that larger number of patients in group C required treatment for hypotension (60%) as compared to group A (46.66%) and group B (16.66%). The incidence of bradycardia and sedation was significantly higher in the group C ($P < 0.05$). Sedation score was grade 2 in all the patients of group C. It is evident from the table that nausea and vomiting were more pronounced in group A ($P < 0.05$). The incidence of pruritus was significantly higher in group B ($P < 0.05$). Table 5 shows the postoperative pain scoring chart (VAS chart), in which patients in group C had significantly low VAS score ($P < 0.05$) as compared to group B.

Table 4: Side effects

Incidence of side effects	Group A (*n* = 30)	Group B (*n* = 30)	Group C (*n* = 30)	*P*-value
Hypotension	10.8 ± 0.8	0.6 ± 0.9	18.5 ± 3.6	<0.05
Nausea/vomiting	18	11	5	<0.05
Shivering	4	5	6	>0.05
Pruritus	0	11	0	<0.05
Bradycardia	0	0	5	<0.05
Sedation	0	0	8	<0.05

The incidences of hypotension were written as mean ± SD.

Table 5: Postoperative pain scoring chart (VAS chart)

VAS chart	Group A	Group B	Group C	*P*-value
VAS score	3.44 ± 0.57	3.27 ± 0.67	1.07 ± 0.87	0.000000144

VAS, visual analog scale.
VAS score values were mean value of VAS scores of 30 patients after 2.5 h of SAB.

Discussion

The spinal anesthesia is preferred for lower limb orthopedic surgeries as it is simple, easy to perform, and economical with rapid onset of anesthesia and complete muscle relaxation. In our study, we used 15 mg (3 ml) hyperbaric bupivacaine to create subarachnoid block because hyperbaric bupivacaine at 10 mg or less has been shown to carry a risk of inadequate block as proven by Pederson et al.[15] Therefore generous doses (12.5–15 mg) have been shown to guarantee effective anesthesia for surgery as followed by Belzarena.[2]

In group B we have used fentanyl as an adjuvant to 0.5% hyperbaric bupivacaine. Fentanyl is a lipophilic μ-receptor agonist opioid. Intrathecally fentanyl exerts its effect by combining with opioid receptors in the dorsal horn of spinal cord and may have a supraspinal spread and action. The effectiveness of intrathecal opioids depends on the bioavailability.[16] So opioids can provide good perioperative analgesia. Reuben et al.[17] used same dose (50 μg) of fentanyl as used in our study). He used various doses (0, 5, 10, 20, 40, or 50 μg) of fentanyl in combination with 0.5% bupivacaine and concluded that minimal analgesia was derived from the 0, 5, and 10 μg doses whereas all patients in the 40 and 50 μg groups had excellent analgesia (VAS<1) within 10 min. None of the patients experienced respiratory depression or other side effects. The results of these studies correlate well with results of our study.

In our study, we used 150 μg clonidine in group C. We chose clonidine because it is the most studied drug used for human neuraxial analgesia.[18] It is moderately lipid soluble and easily penetrates the blood–brain barrier leading to spinal and supraspinal receptor binding and thus provides effective and long-lasting postoperative analgesia. The mechanism by which intrathecal α_2 adrenoceptor agonists prolong the motor and sensory block of local anesthetics is not well known. They act by binding to presynaptic C-fibers and postsynaptic dorsal horn neurons.[11] Their analgesic action is a result of depression of the release of C-fiber transmitters and hyperpolarization of postsynaptic dorsal horn neurons. The prolongation of effect may result from synergism between local anesthetics and α_2-adrenergic agonists to motor neurons in the dorsal horn.[19] Intrathecal α_2-receptor agonists are found to have antinociceptive action for both somatic and visceral pain.[20]

We have chosen 150 μg clonidine dose, which favored the study of Bonnet et al.,[21] who have used 150 μg dose along with 0.5% bupivacaine and found that this dose significantly prolonged the duration of sensory and motor block as compared to bupivacaine alone with minimal side effects. This is also supported by the study carried out by Strebel et al.,[22] in contrast Chiari et al.[23] reported that the risk of hypotension is more with higher doses (≈150 μg).

In our study, the mean time of onset of sensory block at T_8 level and level of sensory block achieved was same (T_8 level) in both groups B and C. In a comparative study, Singh et al.[24] concluded that fentanyl as well as clonidine does not alter the onset of sensory block which is supported by the study of Strebel et al.[22] In our study, the time taken for regression of sensory block from T_8 level to T_{10} level was statistically higher in group C ($P < 0.05$). This is similar to the study by Elia et al.,[25] who concluded that the time taken for two-segment regression was prolonged with the 150 μg dose of clonidine.

Similarly, in our study, the time taken for regression of sensory block below L_1 level was significantly higher in the group C ($P < 0.05$). Similar results were found by Strebel et al.[22]

In our study, time for onset of motor block was same in groups B and C. The study of Singh et al.[24] proved that fentanyl did not alter the onset of motor block and the study of Strebel et al.[22] supported that clonidine does not alter the onset of motor block.

In our study, the duration of motor block was significantly higher in group C as compared to group B ($P < 0.05$). This shows that fentanyl does not prolong the duration of motor block as supported by the study of Singh et al.[24] However, clonidine significantly prolongs the duration of motor block and it is supported by the studies of Elia et al.[25] and Jain et al.[26]. They concluded that duration of motor block was significantly more in the clonidine group as compared to group A, which was in contrast to the study of Kaabachi et al.,[27] who concluded that the addition of 2 μg/kg (≈100μg) clonidine to hyperbaric 0.5% bupivacaine does not prolong the duration of motor block.

In our study, the duration of total analgesia (from subarachnoid block to first report of pain in minutes) was statistically significant ($P < 0.05$) in group C as compared to group B, which was supported by the study of Strebel et al. [22]

In our study, in patients of group B there was a moderate decrease of BP (10–15% drop from baseline value), which gradually returned to baseline value within an hour, whereas in group C, there was a significant decrease of BP (>20–30% decrease from the baseline value) after 5 min of spinal block, but BP does not raise to baseline value after treatment with vasopressors but then sustains to the accepted limit throughout the intraoperative and postoperative period. This decrease in BP in group C was supported by the study of Elia et al.[25] that reported there were more episodes of hypotensions with 150 μg dose of clonidine. This is in contrast to the study of Strebel et al.,[22] that the relative hemodynamic stability was maintained with 150 μg of clonidine in combination to 0.5% hyperbaric bupivacaine.

The incidences of nausea and vomiting were higher in group A (control group) (about 60% of patients) as compared to groups B and C. This was similar to the conclusion of Cohen et al.[28] Pruritus significantly occurred in about 36.66% patients in group B as compared to other two groups. The other side effects were bradycardia (found in 16.66% in group C), sedation (26.66% in group C), and shivering. Sedation was also found in the study of Jain et al.[26]

Contrast to this was the study of Grandhe et al.,[29] where 75 μg clonidine was used with 0.5% hyperbaric bupivacaine, found no significant sedation or respiratory depression in clonidine combination group. In our study, significant change was not observed in the respiratory rate and oxygen saturation in all the groups.

In our study, the VAS chart for postoperative pain was significantly lower in group C (clonidine group) as compared to group B (fentanyl group). This was supported by the study

of Jain et al.[26] who found that pain score remained 0 in clonidine + bupivacaine group as compared to 0.5% bupivacaine alone group. VAS scores for pain were also least in the 75 μg clonidine group in the study carried out by Grandhe et al.[29]

Conclusion

The effective relief of pain during the intra- and postoperative period is of principal importance for anesthesiologist as it has significant physiological benefit by means of smoother postoperative course and earlier discharge from hospital, and it may also reduce the onset of chronic pain syndromes. In our study, we added two different adjuvants to bupivacaine in lower limb surgeries and found 150 μg clonidine significantly prolonged sensory and motor block as compared to 50 μg fentanyl without any significant side effects and maintaining hemodynamics. Thus we concluded that clonidine is a better adjuvant to bupivacaine than compared to fentanyl for lower limb surgeries.

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