Original Article

Effect of clonidine and/or fentanyl in combination with intrathecal bupivacaine for lower limb surgery

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Abstract

Background and Aims: Various adjuncts to local anesthetics have been used with the purpose of improving the quality of subarachnoid block. This randomized double-blind study was conducted to evaluate the efficacy of adding clonidine to bupivacaine and bupivacaine-fentanyl combination.

Material and Methods: A total of 100 patients scheduled for surgery under spinal anesthesia were randomly allocated into four groups (n = 25 each) to receive intrathecal bupivacaine 7.5 mg plus normal saline 0.5 ml (group BS), intrathecal bupivacaine 7.5 mg, and fentanyl 25 μg (group BF), intrathecal bupivacaine 7.5 mg and clonidine 75 μg (group BC), intrathecal bupivacaine 7.5 mg, clonidine 37.5 μg, and fentanyl 12.5 μg (group BCF). The time of onset and duration of sensory block, highest dermatome level of sensory block, time of onset of motor block, time to complete motor block recovery and duration of spinal anesthesia, intraoperative and postoperative hemodynamics and side effects if any were recorded. VAS, total number of patients who were administered supplemental analgesic in each group and the total amount of supplemental analgesic administered in the next 24 h was quantified and documented in all the groups.

Results: The time of onset of sensory block (min) in groups BS, BC, BCF, and BF was 10.80 ± 2.26, 10.20 ± 1.00, 10.00 ± 0.00, and 13.80 ± 2.61 respectively, thus onset of sensory block was significantly earlier in groups BC and BCF. Similarly, onset of motor block was also quicker in groups BC and BCF. Time of requirement of supplemental analgesia was 135.20 ± 12.70 min, 199.2 ± 21.92 min, 209.80 ± 26.32 min, and 208.00 ± 26.58 min in groups BS, BF, BC, and BCF respectively. Intraoperative and postoperative changes in heart rate, mean arterial blood pressure, oxygen saturation, and respiratory rate were comparable. Sedation scores were significantly higher in group BC. Pruritus was only observed in groups BF and BCF. Mean nausea vomiting scores were comparable in all groups.

Conclusion: We conclude that the addition of clonidine in doses of 75 μg and 37.5 μg to low-dose bupivacaine and bupivacaine-fentanyl prolongs the sensory and motor block while increasing the duration of postoperative analgesia without significant side-effects.

Key words: Intrathecal clonidine, spinal adjuvants, subarachnoid fentanyl

Introduction

Spinal anesthesia is preferred over general anesthesia for lower limb surgeries due to its advantages such as decreased intraoperative blood loss, reduced incidence of deep venous thrombosis, and continued postoperative analgesia.[1] Various additives have been evaluated in the quest for an ideal adjuvant, which can enhance the quality of analgesia and prolong the duration of spinal anesthesia with minimal adverse effects. However, success with many additives has been variable, especially with regards to side-effects such as hypotension, bradycardia, pruritus, respiratory depression, nausea, vomiting, and urinary retention.[2]

Fentanyl has been used as a spinal additive to lower the dose of bupivacaine and prolong postoperative analgesia though at the expense of side effects such as pruritus and respiratory depression.[3] In recent times, clonidine has been attempted as a spinal additive. However, the most common adverse effects reported with the use of intrathecal clonidine are sedation and hypotension.[4] Most of these adverse effects are observed when clonidine is used in higher doses of 150-300 mcg.[5] It is possible that the combination of small doses of clonidine with fentanyl will prolong both motor and sensory block and decrease

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the incidence of adverse effects. Hence, the present study was designed to evaluate the effect of a combination of a small dose of clonidine and fentanyl on the quality of spinal anesthesia.

Material and Methods

After institutional Ethics Committee approval and written informed consent, 100-adult patients, American Society of Anesthesiologists grades I and II, scheduled for lower limb surgery under spinal anesthesia, were included in the study. Exclusion criteria included any patients on α-blockers and contraindication to regional anesthesia, history of significant coexisting diseases like ischemic heart disease, hepatic or renal diseases, hypertension, diabetes mellitus, neuropathies, rheumatoid arthritis, spinal deformities like kyphoscoliosis, history of allergy or anaphylaxis to local anesthetics and morbidly obese patients. A detailed preanesthetic checkup was conducted one day prior to surgery. Patients were instructed about the use of visual analogue scale (VAS) preoperatively as a tool for measuring postoperative pain. Investigations such as complete hemogram, urine routine, renal function tests, random blood sugar, chest X-ray, and electrocardiogram (ECG) were done prior to surgery as and when indicated. Patients were allowed light meals 6 h before surgery and clear liquids such as water and clear juice till 2 h prior to surgery. All patients were premedicated with tablet ranitidine 150 mg and tablet alprazolam 0.5 mg at night prior to surgery and 2 h before surgery.

Patients were randomly allocated into either of four-study groups of 25 patients each as per computer-generated random number list. The name of the drug to be given was sealed in envelopes numbered 1-100, which was opened by an anesthesiologist not involved in the intraoperative and postoperative care of the patient and prepared in an unlabeled 2 ml syringe. This was then handed over to the attending anesthesiologist in a coded form who was blind to the nature of drug given. The intrathecal solutions administered were as below:

- Group BS: Hyperbaric bupivacaine 7.5 mg (1.5 ml) + normal saline (0.5 ml).
- Group BF: Hyperbaric bupivacaine 7.5 mg (1.5 ml) + fentanyl 25 μg (0.5 ml).
- Group BC: Hyperbaric bupivacaine 7.5 mg (1.5 ml) + clonidine 75 μg (0.5 ml).
- Group BCF: Hyperbaric bupivacaine 7.5 mg (1.5 ml) + clonidine 37.5 μg (0.25 ml) + fentanyl 12.5 μg (0.25 ml).

After shifting the patient to the operation theater, before insertion of intravenous (IV) cannula, baseline parameters such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), peripheral oxygen saturation (SpO_2), and ECG were recorded. After achieving an IV access, preloading was done with 10 ml/kg of lactated ringer's solution over 15-20 min. Under all aseptic precautions, a midline spinal puncture was performed at the L3-L4 or L2-L3 level in sitting a position using a 26 gauge Quincke spinal needle after prior local infiltration with 2 ml of 0.5% lignocaine. All injections were given at a rate of 1 ml over 4-5 s and intrathecal solutions were at room temperature. Thereafter, the patients were placed in the supine position for surgery.

The time of onset and duration of sensory block, highest dermatome level of sensory block, time of onset of motor block, time to complete motor block recovery and duration of spinal anesthesia were recorded. At the end of the procedure, patients were shifted to postanesthesia care unit (PACU) where monitoring was continued.

The onset of sensory block was defined as the time between intrathecal injection to the absence of sensation at the T_{8-9} dermatome, as assessed by light touch using cotton wool. The highest level of sensory block was evaluated by light touch at mid clavicular line anteriorly every 5 min for 20 min after injection, thereafter every 15 min. The duration of sensory block was defined as the time of regression of two segments in the maximum block height. Time for motor block onset was defined as when modified Bromage score was three or lesser.[6] The duration of spinal anesthesia was defined as the period from the spinal injection to the first occasion when the patient complained of pain in the postoperative period. Surgery was allowed to commence on achieving adequate sensory block height (T_{8-9}). Sensory block was recorded 5, 10, 15, and 20 min after intrathecal injection and subsequently every 15 min. In the postoperative period, motor block recovery, and sensory block regression were assessed till 3 h every 15 min after completion of surgery.

Systolic blood pressure, DBP, HR, RR, and SpO_2 were recorded 5 min before intrathecal injection, 5, 10, 15, 20, and 25 min after intrathecal injection and subsequently every 15 min for the duration of surgery. In the PACU, HR, SBP, DBP, RR, and SpO_2 were recorded every 15 min for 1st h, and then half hourly till 4th h and then every 4 h till completion of 24 h.

Hypotension was defined as SBP of less than 20% below baseline. Hypotension was treated with IV ephedrine 10 mg, repeated every 5 min if necessary. Bradycardia was defined as HR less than 50 beats/min for which 0.5 mg of atropine sulfate was administered intravenously. Sedation was evaluated using a 4-point sedation scale:[7] 0 = awake and alert, 1 = drowsy, but responding to verbal commands, 2 = not responding to verbal command, but responding to manual stimulation, 3 = difficult to awaken. Nausea was evaluated using a 5-point scale:[8] 1 = no nausea and vomiting, 2 = mild nausea, 3 = moderate nausea,

4 = severe nausea, treatment is necessary, 5 = intractable nausea, patient complains despite treatment. A rescue antiemetic in the form of IV injection ondansetron hydrochloride, 4 mg stat, was given when the nausea vomiting score ≥3. Adverse effects such as pruritus, dryness of mouth, dizziness, and hypoxemia (SpO_2 ≤90%) were recorded and treated if required. All observations were recorded by an anesthesiologist who was blinded to the group allocation of the patient.

Pain scores using VAS were assessed in the PACU at 0, $^1/_2$, 1, $1^1/_2$, 2, 3, 4, 8, 12, 18, and 24 h. Patients had been informed before surgery that they could request an analgesic when they felt pain in the postoperative period. Any patient reporting VAS ≥3 was administered a supplemental dose of an analgesic injection tramadol 50 mg IV. Total number of patients who were administered supplemental analgesic were noted in each group. The amount of supplemental analgesic administered in the next 24 h was quantified and documented in all the groups. Any patient with failed spinal anesthetic or patient complaining of pain in the intraoperative period, which required administration of general anesthesia, was excluded from the study.

Statistical analysis

The sample size was based on the power analysis calculated by previous study,[9] so that 25 patients in each group would provide a power >0.8 (α = 0.5) to detect an increase of 30 min in the duration of spinal anesthesia and an increase of 30% in the time interval from intrathecal injection to first analgesic request.

The results were tabulated and analyzed using appropriate statistical techniques. Unless otherwise stated, results are expressed as mean ± standard deviation. All normally distributed continuous variables such as the duration of sensory block, motor block, spinal anesthesia, and demographic variables were analyzed by one-way analysis of variance (ANOVA). Motor block, the highest level of sensory block, and sedation scores were analyzed by Kruskal-Wallis test. Group means (HR, mean arterial pressure [MAP], and VAS) were tested by using Tukey's test. Student's *t*-test was used to compare different groups among themselves and ANOVA for repetitive observations. For determining the significance of the difference between different groups, ANOVA was applied. *Posthoc* Tukey multi-comparison test was applied for pair-wise comparison. $P < 0.05$ was considered as statistically significant.

Results

The treatment groups were similar respect to age, weight, height, sex distribution, and duration of surgery [Table 1]. No patient was excluded from the study.

The mean time of onset of sensory block in groups BS, BF, BC, and BCF were 10.80 ± 2.26 min, 13.80 ± 2.61 min, 10.20 ± 1.00 min, and 10.00 ± 0.00 min respectively. The time of onset of sensory block in group BF was delayed significantly as compared to groups BS, BC, and BCF. In addition, it was significantly shorter in group BCF as compared to group BS and BF ($P < 0.05$). No, statistically significant differences were observed between group BC and BCF [Table 2].

The mean time of onset of motor block in groups BS, BF, BC, and BCF was 14.60 ± 1.38 min, 15.40 ± 2.86 min, 14.00 ± 2.04 min, and 14.40 ± 1.66 min respectively. The time of onset of motor block was significantly delayed

Table 1: Patient's demographic characteristics

Variables	Group BS (*n* = 25)	Group BF (*n* = 25)	Group BC (*n* = 25)	Group BCF (*n* = 25)
Age (years)	34.16±16.26	31.84±14.11	37.48±14.90	42.12±17.98
Height (cm)	163.30±4.25	163.50±5.00	165.30±5.22	166.40±5.06
Weight (kg)	70.28±7.35	67.76±11.99	69.40±6.34	68.52±10.90
ASA grade I/II	16/9	11/14	12/13	17/8
Male/female	23/2	18/7	23/2	22/3
Duration of surgery (min)	69.00±26.93	72.60±26.81	77.80±42.08	74.20±32.94

Values in the table are mean ± SD or absolute numbers (percentage). SD = Standard deviation, ASA = American Society of Anesthesiologists

Table 2: Characteristics of spinal block

Variables	Group BS (*n* = 25)	Group BF (*n* = 25)	Group BC (*n* = 25)	Group BCF (*n* = 25)
Time of onset of sensory block (min)	10.80±2.26	13.80±2.61	10.20±1.00	10.00±0.0
Time of onset of motor block (min)	14.60±1.38	15.40±2.86	14.00±2.04	14.40±1.66
Duration of sensory block (min)	80.00±11.55	89.00±9.68	128.20±14.85	137.80±11.09
Duration of motor block (min)	72.80±11.37	88.20±7.48	111.60±9.80	112.40±10.32
Highest dermatome level of sensory block	T7	T7	T7	T7
Time of first analgesic request (min)	135.20±12.70	199.20±21.92	209.80±26.32	208.00±26.58

Values in the table are mean ± SD or absolute numbers (percentage). All times are in calculated from time of intrathecal injection. SD = Standard deviation

in group BF as compared to groups BS, BC, and BCF ($P = 0.0001$). Intergroup comparison did not reveal any statistically significant difference between the groups BS, BC, and BCF [Table 2].

The duration of sensory block in groups BS, BF, BC, and BCF was 80.00 ± 11.55 min, 89.00 ± 9.68 min, 128.20 ± 14.85 min, and 137.80 ± 11.09 min respectively. Whereas, the duration of motor block in groups BS, BF, BC, and BCF were 72.80 ± 11.37 min, 88.20 ± 7.48 min, 111.60 ± 9.80 min, and 112.40 ± 10.32 min respectively. The duration of both sensory and motor block was significantly prolonged in groups BC and BCF as compared to groups BS and BF ($P = 0.0001$). However, there was no statistically significant difference between group BC and BCF with respect to duration of motor and sensory block [Table 2].

Visual analogue scale scores were significantly higher in group BS at 3 h and 12 h when compared to groups BF, BC, and BCF ($P = 0.009$). At 4 h and 8 h, groups BC and BCF had significantly lower VAS compared to groups BS and BF ($P = 0.004$ and 0.008) [Figure 1].

The requirement of rescue analgesic was significantly higher in group BS as compared to all other groups at 2 h and 3 h postoperatively ($P = 0.04$ and $P = 0.007$). At 4 h postoperatively, groups BS and BF required more analgesic when compared to groups BC and BCF and the difference was statistically significant.[Figure 2] Group BF patients required significantly more amount of analgesic consumption as compared to group BCF at 12 h. Mean 24 h analgesic consumption was significantly more in group BS followed by groups BF, BC, and BCF ($P = 0.005$). Group BC had the lowest amount of mean dose of analgesic consumption [Figure 3].

Intraoperative and postoperative changes in HR, MAP, SpO_2, and RR were statistically insignificant and comparable among all the groups at all-time intervals.

Sedation scores at 10 min, 1.5 h and 2.5 h were higher in group BC as compared to other groups, and the difference was statistically significant ($P = 0.032$ and $P = 0.010$). At 3.5 h and 4 h, statistical difference was observed between group BCF and rest of the groups ($P = 0.024$). Overall, group BC had higher sedation scores as compared to groups BS and BF [Figure 4].

Pruritus was observed in groups BF and BCF. Statistically significant incidence of pruritus was observed among group BF at 25 min postoperatively ($P = 0.047$). None of the

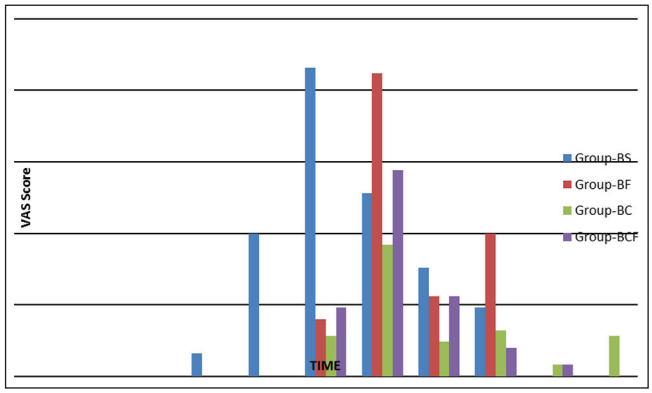

Figure 1: Trends in postoperative visual analogue scale scoring

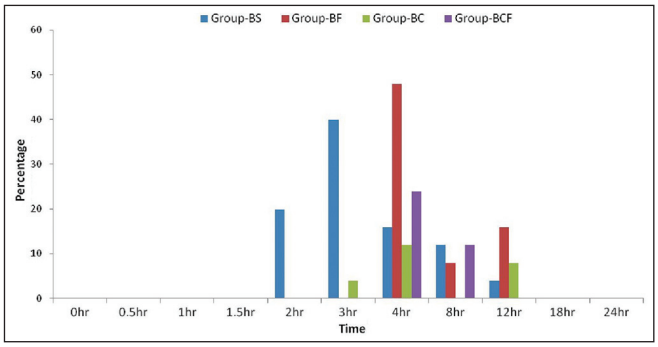

Figure 2: Requirement of rescue analgesic in each group for 24 h

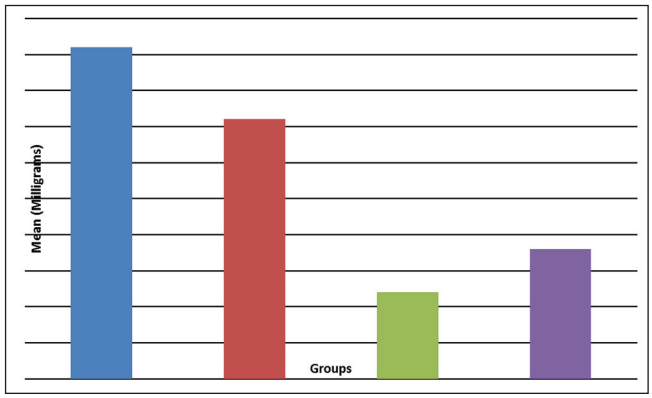

Figure 3: Twenty-four hours mean analgesic consumption

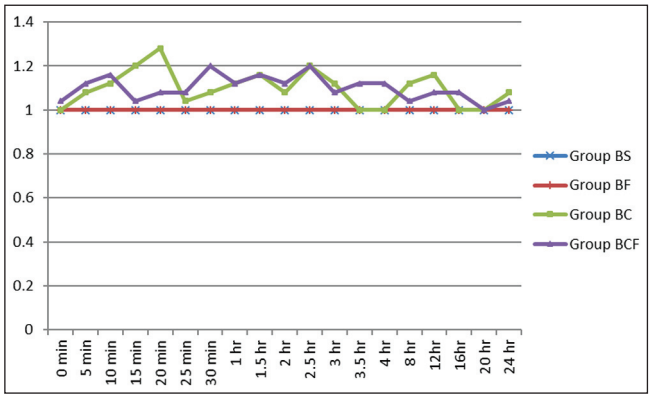

Figure 4: Trends in postoperative sedation scores

patients in groups BS and BC complained of pruritus. Mean nausea vomiting scores were comparable among all the groups. None of the patients reported the dryness of mouth.

Discussion

Clonidine is a selective partial agonist for alpha-2-adrenoreceptors. It is known to potentiate both sensory and motor block of local anesthetics.[8] The possible mechanisms involved in potentiating spinal block include: Suppression of the activity of wide dynamic range neurons and release of substance P, norepinephrine and acetylcholine in spinal cord dorsal horn and direct inhibition of impulse conduction in Aδ and especially C fibers, possibly by increasing potassium conductance.[4] Clonidine, thus complements the action of local anesthetics in stabilizing neurons and accounts for enhancement of effect of local anesthetics and opioids by modulating the transmission of painful stimuli thereby preventing the state of central sensitization.[9]

Clonidine has been used intrathecally in different doses. The dose of clonidine used in the present study corresponds to that of van Tuijl *et al*. who administered intrathecal clonidine in a dose of 75 mcg/kg.[8] The results of our study demonstrates that that the addition of clonidine in doses of 75 μg to bupivacaine (7.5 mg) and 37.5 μg to bupivacaine (7.5 mg) plus fentanyl (12.5 μg) truncates the time of onset of sensory and motor block. Similar results were observed by Strebel *et al*.[9] and Gecaj-Gashi *et al*.[10] who reported shorter onset of sensory and motor block in patients receiving intrathecal clonidine. Grace *et al*., however observed prolonged time to onset of motor block in pethidine-clonidine group which is in contrast to the results of our study.[11] The difference in the result could be due to the fact that higher doses of pethidine 0.75 mg/kg was used in this study. It is possible that the higher dose of intrathecal pethidine could mask the effect of intrathecal clonidine.

We also observed significant prolongation of the duration of motor block in the groups BC and BCF. Singh *et al*.[12] and Benhamou *et al*.[13] also reported significant prolongation of motor block when clonidine was used as an adjuvant for intrathecal use. The time of duration of motor block was similar in the group BC and BCF. Similar results were reported by Nazareth *et al*.[14] who obtained corresponding duration of motor block in the intrathecal clonidine group and in a group where combination of intrathecal clonidine and fentanyl were administered.

Postoperatively, lower VAS scores were observed for 12 h and significantly reduced cumulative 24 h supplemental analgesic consumption was noted in groups receiving intrathecal clonidine, indicating good postoperative analgesic effect. The results of our study are comparable to those of Strebel *et al*.,[9] Merivirta *et al*.,[15] and Benhamou *et al*.[13] where addition of clonidine intrathecally resulted in significantly reduced VAS scores and significant reduction in postoperative analgesic consumption.

Intrathecal clonidine has been reported to result in intraoperative hypotension.[2,4] However, we observed stable hemodynamics among all the groups without any incidence of respiratory depression. This could be explained by adequate preloading which was performed in all the patients prior to subarachnoid block. In addition, the dose used in our study was small, and the mean level of anesthesia achieved was T_{8-9}. Our results are similar to those of Singh *et al*. who observed no significant difference in HR and blood pressure in patients receiving 50 μg and 75 mcg of clonidine intrathecally undergoing cesarean section.[12] Similarly, Nazareth *et al*. also reported stable hemodynamic parameters in the groups receiving intrathecal clonidine and fentanyl combination.[14] However, Dobrydnjov *et al*. reported significant decreases in patients receiving clonidine and fentanyl intrathecally. The difference could be explained by the fact that they used 3.5 ml of hyperbaric bupivacaine and clonidine as compared to the present study, accounting for higher level of sensory blockade achieved and thus explaining hypotension.[16]

Patients in groups BC and BCF were sedated as evidenced by higher sedation scores. However, sedation never exceeded grade 2 and did not cause any problems in any of the patients. Singh *et al*.[12] and Nazareth *et al*.[14] also reported mild to moderate degree of sedation in the clonidine groups. Clonidine is known to cause sedation, and this hypnotic response is believed to be mediated via locus coeruleus where alpha-2-adrenergic receptors are abundant.[4]

A potential limitation of our study design relates to small sample size. Secondly, we did not attempt dose-response effect by using various doses of clonidine. Recently, there are few studies which report beneficial effects of using 30 or even 15 mcg of intrathecal clonidine with minimal adverse effects.[17,18] Possibly, further reducing the dose of clonidine could have elucidated dose-response relationship.

Conclusion

Our study demonstrates that the addition of intrathecal clonidine leads to a rapid onset and prolonged duration of sensory and motor block. In addition, we also observed prolonged adequate postoperative analgesia with moderate

sedation and stable hemodynamic profile. Side effects related to local anesthetics, opioids, and clonidine are minimized. The quality of analgesia as evidenced by VAS scores and total postoperative rescue analgesic consumption was comparable among 37.5 μg and 75 μg clonidine in combination with bupivacaine and bupivacaine-fentanyl. Therefore, our study validates the use of intrathecal clonidine in doses of 75 μg and 37.5 μg in prolonging postoperative anesthesia and analgesia in terms of benefits versus side effects in patients undergoing lower limb surgeries.

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