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Comparison of Effect of Clonidine Added to Bupivacaine-Fentanyl Mixture on the Quality of Spinal Anaesthesia and Peri-Op Analgesia with Bupivacaine-Fentanyl or Bupivacaine-Clonidine Mixture in Major Orthopaedic Lower Limb Surgeries

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Abstract

Introduction: With side effects of central neuroaxial opioids or of high dose intrathecal clonidine in combination with bupivacaine in spinal anaesthesia, my study is to ascertain if small dose of clonidine when added to bupivacaine-fentanyl mixture improves spinal anaesthesia, without producing side effects, as compared to bupivacaine-fentanyl or bupivacaine-clonidine mixture. **Methods:** It's a prospective, double blinded randomised study of 90 ASA grade I-II patients, aged between 20-60 yrs, of either sex, weighing between 40-70 kgs, scheduled for major orthopaedic surgeries. Patients were randomly divided into 3 groups of 30 patients each as Group I (BCF): Bupivacaine 0.5%H 2.6ml + Fentanyl 20mcg + Clonidine 30mcg Group II (BC): Bupivacaine 0.5%H 2.6ml + Clonidine 30mcg Group III (BF): Bupivacaine 0.5%H 2.6ml + Fentanyl 20mcg Duration of sensory and motor blockade and effective analgesia mean time till two segment regression, haemodynamic profile, post-op pain and analgesia requirement were recorded. **Results:** The duration of sensory and motor blockade, effective analgesia and mean time till two segment regression were significantly longer in group BCF as compared to group BC (P – 0.002) and in group BC as compared to group BF (P – 0.01). The incidence of intra-op pain and requirement of post-op analgesia in the first 24 hours was significantly more in group BF as compared to other groups (P-0.01). **Conclusion:** Low dose Clonidine when added to Bupivacaine-Fentanyl mixture improves the quality of peri-op analgesia without significant side effects.

Keywords: Analgesia, Bupivacaine, Clonidine, Fentanyl

1. Introduction

Spinal anaesthesia is preferred over general anaesthesia for lower limb orthopaedic surgeries as it offers the advantages of reduced incidence of deep venous thrombosis, decreased intraoperative blood loss, and continued postoperative analgesia[1]. In the quest for an ideal adjuvant, various additives have been evaluated, to enhance the quality and duration of anaesthesia with minimal adverse effects. However, success with many additives has been variable, especially with regards to side-effects such as nausea, vomiting, urinary retention, hypotension, bradycardia, pruritus and respiratory depression[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. Most of these adverse effects are observed when clonidine is

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used in higher doses of 150-300 mcg[4]. It is possible that the combination of small doses of clonidine with fentanyl will prolong both motor and sensory block and decrease 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 anaesthesia.

2. Material and Methods

After institutional Ethics Committee approval and written informed consent, 90-adult patients, American Society of Anaesthesiologists grades I and II, aged between 20-60yrs, of either sex, weighing between 40-70kgs, scheduled for major orthopaedic lower limb surgery under spinal anaesthesia, were included in the study. Exclusion criteria included any patients on α-blockers and contraindication to regional anaesthesia, 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 anaesthetics and morbidly obese patients. A detailed preanesthetic check-up 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 Three-study groups of 30 patients each as per computer-generated random number list. The name of the drug to be given was sealed in envelopes numbered 1-90, which was opened by an anaesthesiologist not involved in the intraoperative and postoperative care of the patient and prepared in an unlabelled 5 ml syringe. This was then handed over to the attending anaesthesiologist in a coded form who was blind to the nature of drug given. The intrathecal solutions administered were as below:

Group I (BCF): Bupivacaine 0.5%H 2.6ml + Fentanyl 20mcg + Clonidine 30mcg

Group II (BC): Bupivacaine 0.5%H 2.6ml + Clonidine 30mcg

Group III (BF): Bupivacaine 0.5%H 2.6ml + Fentanyl 20mcg

After shifting the patient to the operation theatre, 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 25 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.

Duration of sensory and motor blockade and effective analgesia mean time till two segment regression, haemodynamic profile, post-op pain and analgesia requirement 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 highest dermatome, as assessed by pin-prick sensation. The highest level of sensory block was evaluated by pin-prick sensation 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 from maximum level of sensory block till regression of the block to L1. Motor blockwas defined according to modified Bromage score[5]. The duration of motor blockade was taken from the time of intra-thecal injection till no motor weakness could be detected. The duration of effective spinal anaesthesia 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.

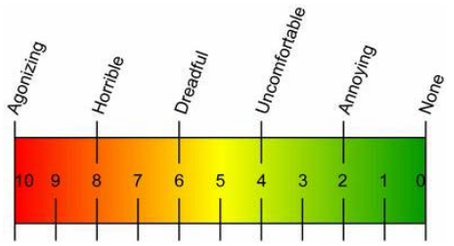
Systolic blood pressure, DBP, HR, RR, and SpO_2 was recorded 5 min before intrathecal injection, 5, 10, 15, 20, and 25 min after intrathecal injection and subsequently every 15 min for the duration of surgery. In the PACU, HR, SBP, DBP, RR, and SpO_2 were recorded every 15 min for 1st h, and then half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

200ml Ringer's lactate and IV ephedrine 10 mg, repeated every 5 min if necessary. Bradycardia was defined as HR less than 50 beats/min for which 0.6 mg of atropine sulfate was administered intravenously. Sedation was evaluated using a 4-point sedation scale:[6] 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:[7] 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 anaesthesiologist 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 was 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 anaesthetic or patient complaining of pain in the intraoperative period, which required administration of general anaesthesia, was excluded from the study.

2.1 Visual Analogue Scale (VAS)



2.2 Modified Bromage Scale

Grade	Definition
0	No motor block
1	Inability to raise extended leg; able to move knees and feet
2	Inability to raise extended leg and move knee; able to move feet
3	Complete block of motor limb

3. Statistical Analysis

The sample size was based on the power analysis calculated by previous study[8],

Taking alpha 0.05 and sample size of 30 in each group, Power of the study was 70%.

The results were tabulated and analysed 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 anaesthesia, and demographic variables were analysed by one-way Analysis of Variance (ANOVA). 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. $P< 0.05$ was considered as statistically significant.

4. Results

A total number of 90 patients were studied. No patient was excluded from the study.

Comment: The treatment groups were comparable with respect to age, weight, height, sex distribution, and duration of surgery (Table 1).

Comment: The onset of sensory block was faster in groups BCF and BC as compared to group BF and this was found to be statistically significant (P ~ 0.002) (Table2).

The mean time till two-segment regression, duration of sensory and motor block, and duration of effective analgesia were significantly longer in group BCF, as

Table 1. Patients demographic variables and duration of surgery

Variables	Group BCF (n-30)	Group BC (n-30)	Group BF (n-30)	P Value
Age (years)	35.64 +/- 14.87	38.42 +/- 16.66	43.21 +/- 13.54	>0.05
Male/Female	22/8	25/5	24/6	>0.05
Height (cms)	155 +/- 4	154 +/- 5	157 +/- 5	>0.05
Weight (kgs)	49.8 +/- 4.1	55.3 +/- 7.5	52.2 +/- 5.7	>0.05
ASA I/II	18/12	22/8	17/13	>0.05
Duration of surgery (minutes)	129.2 +/- 21.5	117.1 +/- 25.7	111.8 +/- 18.4	>0.05

Values in the table are mean +/- SD or absolute numbers (percentage). SD= standard deviation. ASA=American Society of Anaesthesiologist.

Table 2. Characteristics of spinal anaesthesia

Variables	Group BCF (n-30)	Group BC (n-30)	Group BF (n-30)
Onset of sensory block(minutes)	12.67 +/- 3.7	13.5 +/- 4.4	16.4 +/- 4.8
Highest sensory block achieved (spinal segment)	T8	T8	T8
Duration of sensory blockade(minutes)	208.5 +/- 22.1	176.7 +/- 29.6	144 +/- 12.3
Duration of motor blockade(minutes)	236.7 +/- 21.7	201.2 +/- 30.2	165.5 +/- 12.9
Mean time till two-segment regression(minutes)	104.25 +/- 25	94.35 +/- 52.4	74.88 +/- 27.9
Duration of effective analgesia(minutes)	407 +/- 131.5	320 +/- 96.2	180 +/- 45.6

Values in the table are mean +/- SD or absolute numbers (percentage). SD= standard deviation. All time are calculated from time of intra-thecal injection.

compared to groups BC and BF (P value ~ 0.001) and in group BC (P ~ 0.02) as compared to group BF (Table 2).

Chart 1. P~0.002 for Group BCF as compared to Group BF, P~0.04 for Group BC as compared to Group BF, both of which were significant.

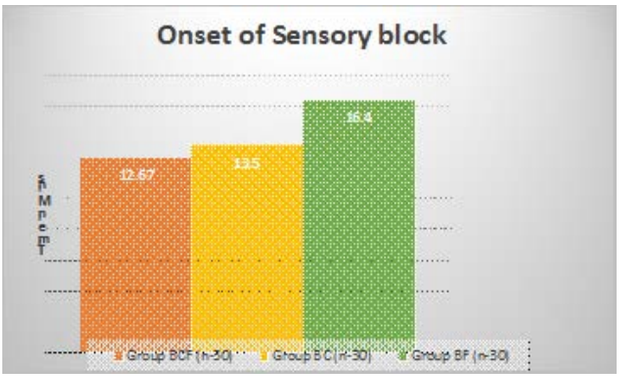


Chart 2. P~0.001 for Group BCF as compared to Group BF, P~0.02 for Group BCF as compared to Group BC, both of which were found to be significant.

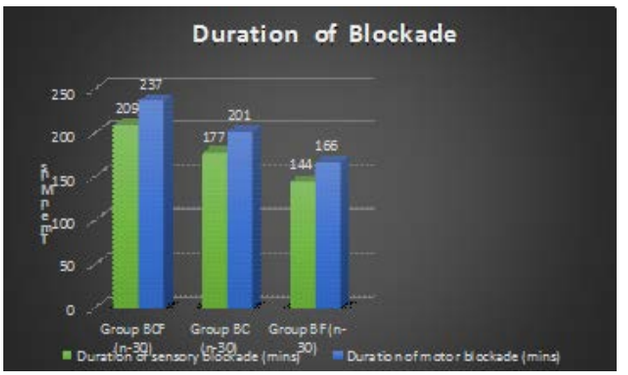
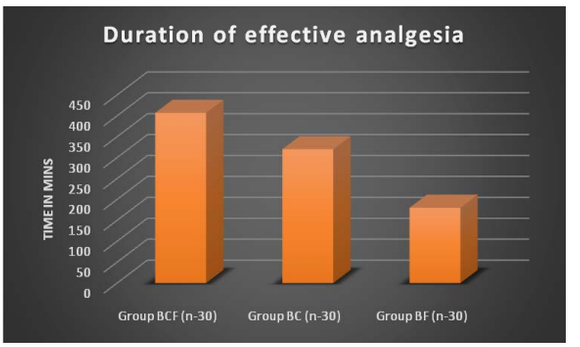


Chart 3. P~0.005 for Group BCF as compared to Group BF, P~0.02 for Group BCF as compared to Group BC, both of which were found to be significant.



Comment: All the patients, however, required a rescue analgesic in the postoperative period during first 24 hours which was significantly higher in group BF (2.36) as compared to the group BCF n group BC (P ~ 0.01) (Tables 3). However, there was no intra-op supplemental analgesia requirement.

Chart 4. P<0.05 for Group BCF n Group BC as compared to Group BF which was significant.

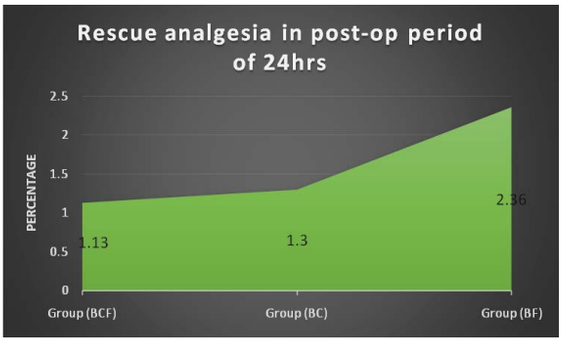
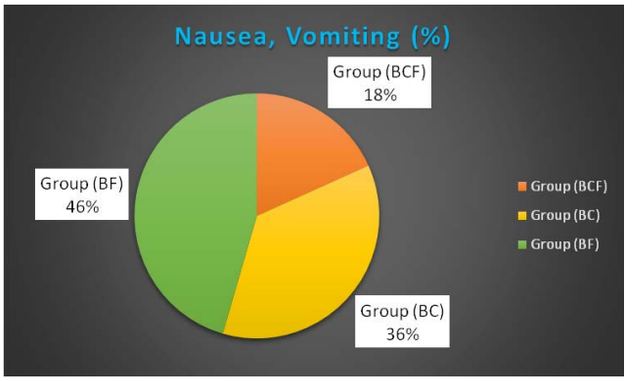


Table 3. Post-op analgesia and side effects

Variables	Group (BCF)	Group (BC)	Group (BF)
Average requirement of Rescue analgesia (Inj.Tramadol 50mg) in post-op period of 24hrsper patient	1.13 (1-2)	1.30 (1-2)	2.36 (2-3)
Sedation (%)	43.3 (13)	80 (24)	10 (3)
Nausea, Vomiting (%)	6.7 (2)	13.3 (4)	16.7 (5)

Values in the table are mean +/- SD or absolute numbers (percentage). SD = standard deviation.

Chart 5. The incidence of intraoperative nausea and vomiting was more in Group BF and Group BC as compared to Group BCF. Sedation was significantly more in Group BC as compared to Groups BF and BCF (P ~ 0.002), as well as in Group BCF compared to Group BF (BC > BCF > BF) (P ~ 0.001). However, sedation never exceeded grade 2 (drowsy). Requirement of mephentermine and additional fluids was similar in the three groups.



Comparison of serial measurement of Heart rate, SBP, DBP, MAP did not reveal any significant variation amongst the three groups.

There was no incidence of Pruritis, dryness of mouth or hypoxia.

5. Discussion

Our study indicates that addition of 30 μg of clonidine to a mixture of 0.5% hyperbaric bupivacaine + 15 μg of fentanyl significantly prolongs the duration of the sensory and motor blockand duration of effective analgesia as compared to the bupivacaine + clonidine and bupivacaine+ fentanyl combinations, without any significant side effects.

We found the time of onset of sensory and motor blockade to be significantly less in patients who were given intrathecal clonidine. Similar results were observed by Strebel *et al.*,[8] and Gecaj-Gashi *et al.*,[9] who reported shorter onset of sensory and motor block in patients receiving intrathecal clonidine.

In our study we found that the duration of effective analgesia and time to two-segment regression were significantly more when clonidine was added to bupivacaine and fentanyl. Gautier et al.,[10] found that patients receiving 30 μg clonidine to sufentanil significantly increased the duration of analgesia which is close to our study and better as compared to 15 μg clonidine with sufentanil. Benhamou et al.,[11] also found that the duration of analgesia was longer in the BCF group as compared to the BC group (P < 0.05) which also supports our study.

Postoperatively, lower VAS scores were observed for 24 hours and significantly reduced 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.*,[8] and Benhamou *et al.*,[11] 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[2,12]. However, we observed stable hemodynamic 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 (30 μg), and the mean level of anaesthesia achieved was $T_{8\text{-}9}$. Our results are similar to those of Singh *et al.* who observed no significant difference in HR and blood pressure in patients receiving 30 μg and 50 mcg of clonidine intrathecally undergoing cesarean section[13]. 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[15].

In our study we found the incidence of sedation is significant with bupivacaine + clonidine and bupivacaine+ clonidine + fentanyl group than in bupivacaine + fentanyl groups. Benhamou et al. and Liu et al., also found that clonidine caused sedation, and Filos et al., demonstrated a dose-dependent sedation in their patients[4,11,16]. Sedation represented an α2-adrenergic effect, as it had been seen that sedation from epidural clonidine could be reversed by a specific antagonist, yohimbine, in postoperative patients. Sedation did not exceed grade 2 in any of our patients and we feel that mild-to-moderate sedation might be a desirable effect in postoperative patients. We did not find pruritus in any of our patients, unlike other studies[12].

6. Conclusion

In conclusion we observed that 30 μg of clonidine added to bupivacaine and fentanyl increased the duration of

effective analgesia as well as the duration of sensory and motor block, as compared to bupivacaine + clonidine and bupivacaine + fentanyl combinations, without causing any significant hemodynamic side effects. The incidence of intraoperative pain and requirement of postoperative analgesics is significantly less with the addition of clonidine to the intrathecal mixture.

7. Limitations

- One of the limitations of our study was the small sample size. Although certain trends could be established in this pilot study, further controlled, large sample-sized studies are required to confirm the results.
- We did not attempt dose-response effect by using various doses of clonidine.

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