Original Article

A Comparative Study of Efficacy of Clonidine and Fentanyl as Adjuvant to Intrathecal 2- Chloroprocaine in Lower Limb Surgeries: A Randomized, Double-Blind Trial

Vaishno Devi[1], Mushtaq Wani[1], Heena Gupta[1*], Anju Jamwal[1]

Abstract

Background: Preservative-free, 1% 2-chloroprocaine, is a short-acting local anesthetic agent with a favorable profile for daycare surgical procedures. Various adjuvants can be added to local anesthetics to potentiate their action. In this study, we compared the effect of intrathecal clonidine and fentanyl as an adjuvant to 1% 2-chloroprocaine (2-CP) in patients undergoing elective lower limb surgeries.

Materials and Methods: Seventy patients of the American Society of Anesthesiologists (ASA) grade 1 and 2 (18-60 years) scheduled for lower limb surgeries with a duration of ≤60 minutes under spinal anesthesia were randomly divided into two groups (n= 35). Group CF received 1% 2-chloroprocaine 40 mg and fentanyl 20µg (4.5 ml). Group CC received 1% 2-chloroprocaine 40 mg and clonidine 15µg (4.5 ml). The onset and duration of sensory and motor blocks, time for the demand of rescue analgesia, hemodynamics, and side effects were observed.

Results: The onset and duration of sensory and motor blocks were significantly earlier in the CC group. Time to demand rescue analgesia was significantly prolonged in Group CC than in CF. Other side effects were comparable in the two groups.

Conclusion: Intrathecal clonidine (15 µg) is a better alternative to fentanyl (20 µg) used as an adjuvant to 1% 2-chloroprocaine for lower limb surgeries.

Keywords: 1% 2-chloroprocaine, Fentanyl, Clonidine, Spinal anesthesia

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Introduction

Chloroprocaine is a short-acting amino ester local anesthetic with a favorable safety profile that may be a suitable alternative in daycare ambulatory surgeries (1). It has a rapid onset, a predictable block height, and time to complete regression. Its new formulation has been released for use in which the pH of the solution has been adjusted and is preservative and antioxidant-free (2). Lipophilic opioid fentanyl is increasingly being administered intrathecally as an adjunct to local anesthetic. It is a µ receptor agonist and enhances the quality of sensory block and duration of analgesia without significantly prolonging motor recovery (3, 4). Clonidine, an α2 adrenergic agonist, is used as a spinal additive and is free of opioid-related side effects. It

accelerates the onset, prolongs sensory and motor blockade, produces postoperative analgesia, and reduces the amount or concentrations of local anesthetic required to make this effect (5).

Clinical research with other local anesthetics such as bupivacaine or ropivacaine is well studied. Still, it has been limited to 2-Chloroprocaine mainly to dose-comparison and evaluation of block characteristics in patients undergoing short procedures (6-9). The rationale for conducting the present study was that very few studies are available in the literature that compares specific adjuvants' efficacy with 2-chloroprocaine. Moreover, literature is divided regarding the effectiveness of both intrathecal clonidine and fentanyl in providing prolonged postoperative analgesia. Therefore, the objective of the present study was to compare the efficacy of fentanyl and clonidine as adjuvants to intrathecal 1% 2-Chloroprocaine in lower limb surgeries lasting <60 min concerning onset, duration, and recovery of sensory and motor block and time to first request for postoperative analgesia.

Methods

After obtaining approval from the Ethical Committee (IEC/GMC/2019/837) of the hospital, this double-blinded, randomized study was conducted on 70 patients of either sex with ASA 1 and 2 physical statuses and aged between 18-60 years in a tertiary care center in North India over one year (1 December 2019 to 30 November 2020). These patients were scheduled for lower limb surgeries, including foot surgeries, ankle procedures, knee arthroscopy, tibia nail removal, etc., for ≤60 minutes. All patients enrolled completed the study (Figure1). The patients were randomly divided into two groups: Group CF–35 patients received 1% 2-chloroprocaine 40 mg and fentanyl 20µg (total volume 4.5 ml), and Group CC- 35 patients received 1% 2-chloroprocaine 40 mg and clonidine 15µg (total volume 4.5 ml). Patients refusing to participate, pregnant females, having contraindications to spinal anesthesia, spine deformity or history of spine surgery, and Body Mass Index > 36kg/m2 were excluded from the study. The primary outcome of our study was to compare the effect of adding intrathecal fentanyl 20µg or clonidine 15µg on the onset and duration of sensory and motor block using 40 mg 1% 2- chloroprocaine. Secondary outcomes were to compare the hemodynamic effects of these intrathecal adjuvants with 2- chloroprocaine, time to first request for postoperative analgesia, and evaluate the adverse effects of these drugs.

For randomization, a computer-based random number table was generated for the allocation sequence to ensure equal distribution of patients into treatment groups. The allocation concealment was done in sequentially numbered, sealed, opaque envelopes that included the group's code and were opened only when the patient's consent was obtained. The syringes containing 3 ml of 1% 2-chloroprocaine 40 mg with fentanyl 20µg or 3 ml of 1% 2-chloroprocaine 40 mg with clonidine 15µg were prepared by an anesthesiologist not involved in the study or data collection. Data was recorded by another observer who was blinded to the group allocation. The patients and the post-anesthesia care unit staff were unaware of the group assignment. The code was broken after the completion of the study and statistical analysis.

After obtaining informed written consent, the patient was kept fasting overnight. Tablet Ranitidine 150 mg was given at bedtime the night before surgery. The patient was familiarized with the Visual Analogue Score (VAS), and it was used for monitoring post-operative pain. The intravenous line was secured via an 18 G cannula, and Ringer's Lactate (RL) infusion was started at 10ml/kg 20 min before the surgery. After the arrival of the patient in Operation Theater, basic monitors like Non-Invasive Blood Pressure, electrocardiograph, and oxygen saturation probe were attached, and baseline parameters like heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), SpO2, respiratory rate (RR) were noted. Using all aseptic precautions, in the sitting position, L3-L4 interspace was identified. The skin and interspinous ligaments were infiltrated with 2ml of 2% lignocaine. Lumbar puncture was performed through a mid-line approach using 27 gauge Quincke needles. On ensuring the free CSF flow, study drug with total volume of 4.5ml [1% 2-chloroprocaine 4ml (40mg) + fentanyl 0.5ml (20µg)

or 1% 2- chloroprocaine 4ml (40mg) + clonidine 0.5ml (15µg)] was administered slowly. After administering the study drug, the patient was placed supine. Heart rate (HR); Systolic, diastolic, and mean blood pressure (SBP, DBP, MAP); SpO2 was recorded just after spinal anesthesia, 0 min. These parameters were recorded at 5, 10, 15, and 20 minutes, then every 10 minutes until the end of the surgery, and every 20 minutes to 3 hours postoperatively.

The sensory level was assessed by loss of sensation using a blunt 25G hypodermic needle in a caudal to cephalad direction in the midclavicular line bilaterally. The point C5-C6 dermatome was used as an unblocked reference point. The block was assessed every 1 minute until the level T10 was achieved and taken as onset time. The time of intrathecal injection was taken as zero. The time from intrathecal injection to two dermatomes sensory regression was noted and was labeled as the duration of sensory block time. The motor block was assessed every minute using a modified Bromage scale (0: able to move hip, knee, ankle; 1: able to move knee and ankle, not hip; 2: able to move ankle only, not hip and knee; 3: not able to move). The time interval between injection of the drug into subarachnoid space to the patient´s inability to lift an extended straight leg was taken as onset time (Bromage -2). The duration of the motor block was taken from the time of injection to the complete regression of the motor block (Bromage -0).

The adverse effects of hypotension, bradycardia, respiratory depression, nausea and vomiting, pruritis, shivering, and sedation were assessed during the whole observation period, from intrathecal injection to 3 hours postoperatively. Hypotension (defined as a decrease in systolic arterial pressure ≥30% from baseline) was initially treated with a rapid infusion of 200ml of RL solution. A 3 mg ephedrine intravenously increment was administered if this was not effective. Bradycardia (defined as HR <50 beats/min) was treated with 0.3 mg atropine iv increments. If SpO2 fell below 90%, oxygen (2-4 liters/min) was administered via face mask. Duration of pain relief was defined as the time from spinal injection to the first request for rescue analgesia or VAS<4 or whichever is earlier. Intramuscular injection of diclofenac sodium 75 mg was used as rescue analgesia. In the postoperative period, nausea and pruritis were assessed on an ordinal scale, i.e. (0=no symptoms; 1=symptom present but not requesting treatment; 2=symptom present and requesting treatment). Nausea with an ordinal scale two and vomiting was treated with an ondansetron 4mg IV injection. Shivering was treated with warm drapes and warm fluid. If still not controlled, an injection of tramadol 30mg IV was given. The pain was assessed by VAS, i.e., 0-10 horizontal line (1-4 mild pain, 5-6 moderate pain, 7-10 severe pain). Sedation was assessed according to Ramsay sedation score, i.e. (1- anxious and agitated; 2- co-operative, oriented, and tranquil; 3- respond to command only; 4-brisk response to a light glabellar tap or loud auditory stimulus; 5- sluggish response to a light glabellar tap or loud auditory stimulus; 6 –no response to a light glabellar tap or loud auditory stimulus). If any, transient neurological symptoms (TNS), paresthesias, or dysesthesias in lower limbs or buttocks were also noted.

Based on a pilot study on 20 subjects conducted at our institute, the onset of sensory and motor block in Group CC was 5.39±1.4 minutes and 4±0.7 minutes, whereas, for Group CF, it was 6.00±0.50 minutes and 4.50±1.2 minutes, respectively. Based on these data, we calculated that at least 26 patients would be required per group for an experimental design incorporating two equal-sized groups, with α=0.05 and β=0.2. However, to minimize any effect of possible dropouts, we elected to recruit 35 patients per group for the study.

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov- Smirnov test. If the normality was rejected, then a non-parametric test was used. Quantitative variables were compared using the independent t-test or Mann- Whitney Test (when the data sets were not normally distributed) between the groups. Qualitative variables were correlated using the Chi-Square test/ Fisher's Exact test. A p- the value of < 0.05 was considered statistically significant. The data was entered in the MS EXCEL spreadsheet, and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

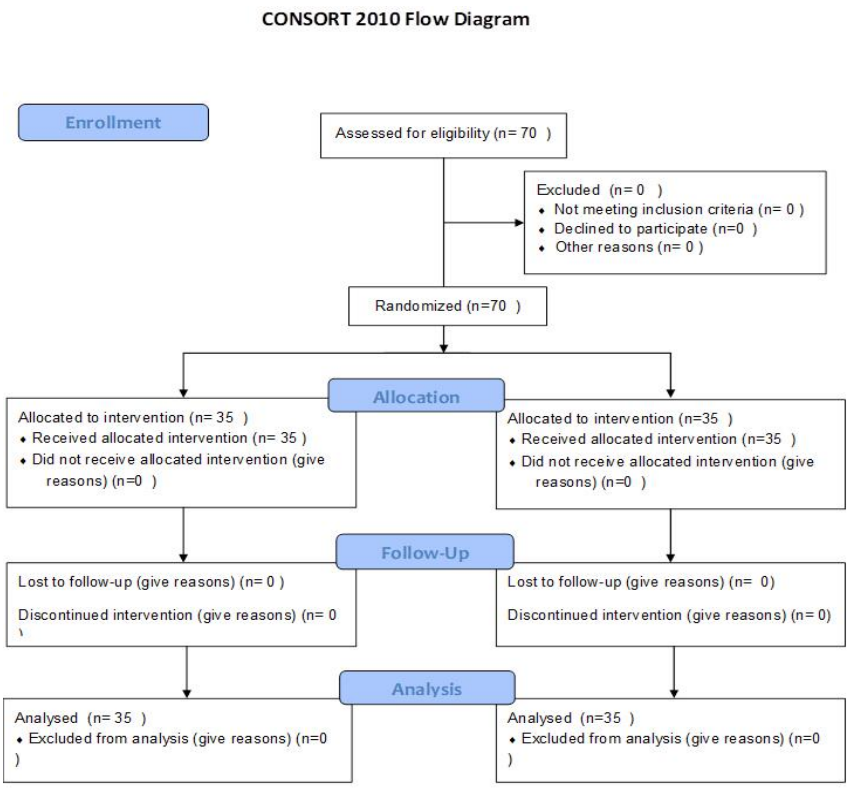

Figure 1. Consort Flow Diagram.

Table 1: Demographic variables.

Group	Age(years)	Sex (male:female)	Weight (kg)	Height (cm)
Group CC (n=35)	33.14 ± 9.24	27:8	57.43 ±5.39	156.43 ± 6.26
Group CF (n=35)	34.77 ± 10.37	32:3	56.71 ± 6.24	156.09 ± 6.13
P Value	0.490	0.188	0.510	0.818

Results

All the subjects enrolled completed the study (Figure 1). Both the groups were comparable in age, sex, height, and weight (Table 1). The onset of sensory block (time to reach the T 10 sensory blockade) and the time to get the peak sensory level was significantly earlier in Group CC than in Group CF (6.34±1.39 vs.

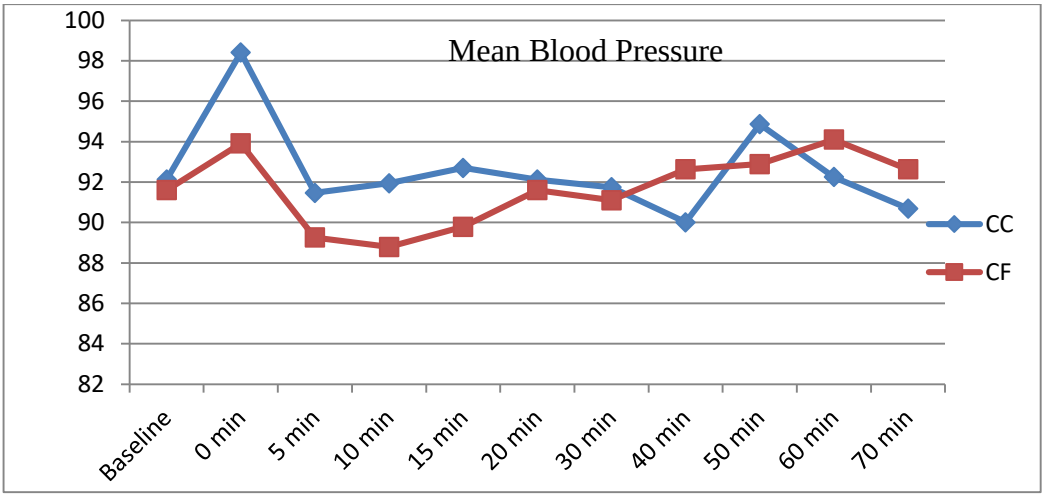

Figure 2. Mean Blood Pressure (mmHg).

7.83±0.79 minutes; P<0.001) (Table 2). The onset of motor block (time to reach Bromage 2) was earlier in clonidine than in fentanyl (3.34±1 vs. 5.11±1.51 minutes; P<0.001). Duration of sensory block group (136.17±12.98 vs. 99.86±10.55; P<0.001) and motor block (113.14±12.95 vs. 81.66±9.55 minutes) was prolonged in CC than CF group.

The two groups remained statistically comparable concerning systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) measurements taken at various time intervals (Figure 2). The mean time taken to first request for analgesia was significantly prolonged in the CC group (97.86±11.59 vs. 75.51±8.94 minutes, P<0.001) (Figure 3). Postoperative nausea and pruritis were seen in 2 patients who received fentanyl but none in the clonidine group (Table 3). No patient experienced TNS with either of the drugs. Incidence of other side effects like shivering, sedation, and respiratory depression were comparable in both groups.

Table 2: Sensory and Motor Block Characteristics.

Time to reach (minutes)	Group CC (n=35)	Group CF (n=35)	P value
T_{10} level (sensory blockade onset time)	6.34 ± 1.39	7.83 ± 0.79	<0.001
Bromage 2 motor blockade	3.34 ± 1.00	5.11 ± 1.51	<0.001
Sensory regression to S_2 segment	136.17 ± 12.98	99.86 ± 10.55	<0.001
Bromage 0 motor blockade	113.14 ± 12.95	81.66 ± 9.55	<0.001

Table 3: Postoperative complications.

Postoperative complication	Group CC (n=35)	Group CF (n=35)	P value
Nausea	1 (2.86%)	2 (5.71%)	0. 78
Pruritis	0	2 (5.71%)	0.64
Shivering	3 (8.57%)	4 (11.4%)	0.89
Sedation	4 (11.4%)	3 (8.57%)	0.89
Respiratory depression	0	2 (5.71%)	0.64
Transient Neurological Symptoms	0	0	

Discussion

The principal finding of our study was that the addition of 15µg of clonidine to 40 mg of 2-chloroprocaine shortened the onset and prolonged the duration of sensory and motor block compared to 20 µg of fentanyl in 40 mg 1% 2- chloroprocaine. Since there is no recommendation on the appropriate intrathecal dose of 2-CP, therefore we used the amount of 40 mg based on the study by Ghisi D et al. (8).

Our study observed that the onset of sensory block onset was 6.34 ± 1.39 minutes in CC and 7.83±0.79 minutes in CF. Thus, it was significantly earlier in the CC group than CF group ($p<0.001$). Casati et al. evaluated the dose-response relationship of 2-chloroprocaine at three different doses of 30 mg, 40 mg, and 50 mg (10). They found that the onset time of sensory block was similar in all three groups. Therefore, in our study, the difference in the onset of sensory block was due to the addition of fentanyl or clonidine with 2-chloroprocaine. A previous study done by Saporito A et al. has shown preservative-free 2-CP to be an excellent alternative to low-dose bupivacaine for a subarachnoid block with a similar onset time (11). Clonidine in different doses was found to have an earlier sensory block onset time effect in various other studies (12-14)**.** The possible mechanisms involved in potentiating spinal block in group CC is because clonidine suppresses the activity of a wide dynamic range of neurons and releases substance p, norepinephrine, and acetylcholine in the spinal cord dorsal horn and direct inhibition of impulse conduction in especially C-fibers and Aδ delta, possible by increasing potassium conductance. Our findings were in contrast to the study by Khare et al., who found no difference in the onset of the sensory block using clonidine and fentanyl as adjuvants to 2-chloroprocaine (15). Tandan M et al., in their study, compared 2- chloroprocaine with bupivacaine and concluded that the meantime of onset in both groups was 6 min. Our study also showed group CC's sensory block onset of 6.34 ± 1.39 min (16).

Our study observed that motor block onset was earlier in the CC group than in the time in the CF group. This was in contrast to the earlier findings by Routray et al., Khare et al., and Bajwa et al., who found no statistical difference in the motor block onset using fentanyl and clonidine as adjuvants to the local anesthetic (6, 15, 17). Arora R et al. compared bupivacaine with different doses of clonidine. They found that the meantime to achieve onset of motor block was 12±2.50 minutes in bupivacaine 12.5mg and 5.60±1.65 minutes in bupivacaine 12.5mg, clonidine 15µg (13). This difference between them was statistically highly significant ($P<0.001$). Their results were similar to the results of the current study. The faster onset of motor block in group CC is mainly due to vasoconstriction caused by clonidine and

subsequently decreased systemic absorption of local anesthetic (18).

We noted the time taken for regression of the sensory blockade to the S2 dermatome, which was labeled as the duration of the sensory block. Our study found that Group CF showed a faster regression of the sensory block than Group CC. Our results match the findings of Davis BR et al. and Khare et al., who found that the mean time taken for regression to S2 dermatome was 131±15 minutes and 146.03±22.46 minutes in group 2-chloroprocaine with clonidine, respectively (9, 15). Our findings coincide with the results shown by Routray et al., Bathari et al., Bajwa et al., and Kaushik. They found that the duration of sensory block was more prolonged in the clonidine group than in the fentanyl group ($P<0.05$) (6, 7, 17-18). Clonidine enhances the time of sensory block by binding to presynaptic c-fibers and postsynaptic dorsal horn that may have an additive or synergetic effect on local anesthetic action (18-19).

Davis and Kopacz et al. and Khare et al. found that the duration of motor block was significantly prolonged in group 2-chloroprocaine with clonidine (138.5±15.4 minutes) as compared with group 2-chloroprocaine with fentanyl (122.66±13.91 minutes, $P=0.001$) (9, 15). In our study, we observed that patients of group CC took a longer time to reach modified Bromage scale 0, which was 113.14±12.95 minutes, compared to group CF, which was 81.66±9.55 minutes. Vath and Kopacz compared the time to go Bromage 0, i.e., duration of motor block in chloroprocaine (40mg) with fentanyl or saline. They found it 81±16 minutes and 67±13 minutes, respectively, and it was statistically significant3. Davis et al. also compared the effect of adding clonidine 15µg with chloroprocaine 40mg. They found that the time taken to reach Bromage 0 was 79±19 minutes in chloroprocaine 40mg with clonidine 15 µg, and it was also statistically significant, showing that both the adjuvants increase the duration of motor blockade when compared with chloroprocaine alone9. Our study also confers that fentanyl, as an adjuvant to chloroprocaine, has a more negligible effect on the prolongation of motor block (20)**.** This long time to reach Bromage 0 in group CC may be because intrathecal clonidine combined with local anesthetic significantly potentiates the intensity and duration of motor block. The explanation for this could be the α2 agonist-induced cellular modification in the ventral horn of the spinal cord (motor neuron hyperpolarization) which facilitates the local anesthetic action (14)**.**

There was no significant change in hemodynamic parameters of both the study groups at any time interval, as observed in other studies (5-7). This could be attributed to the lesser doses of adjuvants used in our study. However, Davis BR and Kopaz DJ observed significant side effects like hypotension and bradycardia with intrathecal clonidine (1-2µg/kg)9. 2-chloroprocaine antagonizes k and µ opioid receptors, which may interfere with neuraxial opioid administration (21). Our study studied the effect of clonidine and fentanyl on the duration of postoperative analgesia. We found that the time to first analgesic request was shorter in chloroprocaine with fentanyl group than in the 2-chloroprocaine with clonidine group. However, the duration of analgesia achieved with fentanyl was less than the study by Geeta S et al. (115.20±25.54 minutes) (4). In our study, intrathecal clonidine was a better drug than intrathecal fentanyl for prolonged analgesia, as observed in previous studies (20, 22). The analgesic effects of intrathecal clonidine are due to the interruption of nociceptive stimulus in the periphery, the spinal cord, and the supraspinal site. It blocks the conduction of C and Aδa fibers by increasing potassium conduction. Fentanyl depresses C-fibers reflexes alone and affects afferent nociceptive fibers without effects on sympathetic efferent fibers, which may facilitate its analgesic effects3. Incidence of other side effects like shivering, sedation, and respiratory depression were similar to previous studies (4, 13, 22).

It was a single-center trial. We did not compare different doses of clonidine and fentanyl with 2-chloroprocaine. More extensive randomized control trials with more patients would be required to establish the results.

Conclusion

Intrathecal clonidine (15 µg) is a better alternative to

fentanyl (20 µg), used as an adjuvant to 1% 2-chloroprocaine for lower limb surgeries.

Acknowledgment

None.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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