Original Article

COMPARISON OF ADDITION OF FENTANYL OR CLONIDINE TO INTRATHECAL BUPIVACAINE VERSUS INTRATHECAL BUPIVACAINE ALONE FOR LOWER LIMB SURGERIES IN ELDERLY PATIENTS: A PROSPECTIVE, RANDOMISED STUDY

(Intrathecal Fentanyl/Clonidine ± Bupivacaine for surgery in elderly)

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Abstract

Introduction: *Orthopaedic long bone fracture surgeries in elderly patients have their own inherent risks during anaesthesia. We aimed to compare the effect of adding clonidine or fentanyl to low dose intrathecal bupivacaine as opposed to intrathecal bupivacaine alone.* ***Materials and methods:*** *A prospective, double-blind study was conducted in ninety elderly patients undergoing lower limb surgery under spinal anaesthesia. After randomly allocating the patients to three groups, Group BC [Bupivacaine + Clonidine]: 9 mg bupivacaine (0.5%) + clonidine 15 µg + saline, Group BF [Bupivacaine + Fentanyl] : 9 mg bupivacaine (0.5%) + fentanyl 20 µg, Group BS [Bupivacaine + Saline] : 9 mg bupivacaine (0.5%) + saline. The time for onset of sensory and motor block, highest sensory level achieved, time taken to achieve peak sensory and motor blockade, duration of analgesia and side-effects were compared between the three groups. The relevant statistical analyses were done.* ***Results:*** *The time taken for the sensory level and motor block to recede was the longest in group BC. The duration of analgesia was maximum in the group BC group and minimum in group BS. Incidence of hypotension and use of ephedrine was maximum in Group BC.* ***Conclusion:*** *Fentanyl or clonidine added to low dose intrathecal bupivacaine for lower limb surgery in the elderly significantly increases the duration of analgesia compared with intrathecal bupivacaine alone, clonidine more than fentanyl.*

Key words: *Intrathecal; fentanyl; clonidine; Bupivacaine; elderly patients; lower limb surgeries*

Introduction

Spinal anaesthesia is the most commonly used anaesthetic technique for surgeries of orthopaedic long bone fracture in elderly patients. The adjuvants used in spinal anaesthesia have gained popularity because they reduce the quantity of local anaesthetics (LA), increase the duration of action and enhance the quality of analgesia[1,2]. Opioids and local anaesthetics co-administered intrathecally have synergistic analgesic effect, increasing the sensory blockade while maintaining the haemodynamics[3]. Fentanyl is a synthetic lipophilic opioid with a fast onset of action, greater analgesic potency and unlike morphine has much less tendency to cause delayed respiratory depression[4]. Clonidine, a selective partial agonist for alpha-2 adrenoreceptors, is an attractive alternative to commonly used opioids and is known to prolong sensory and motor effects of LA[5,6]. Although both of these adjuvants have been individually studied, our research revealed limited literature comparing these spinal additives in the geriatric population for lower limb surgery.

Objective

Our study aimed at comparing the effects of combining clonidine or fentanyl to intrathecal bupivacaine versus bupivacaine alone in elderly patients posted for surgical repair of fracture neck

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femur or fracture hip. We aimed to compare the duration of analgesia, block characteristics and side-effects between the three groups.

Materials and Methods

A prospective, randomised double blind interventional clinical study was conducted in a tertiary care centre over a period of one year from January 2021 to December 2021 after approval of the hospital ethics committee. A total number of ninety patients of ASA class (American Society of Anaesthesiologists) I and II or III, were recruited for the study after obtaining informed consent. The inclusion criteria included patients between 65-80 years, scheduled for Richard's plate-screw internal fixation of femoral neck fractures and Austin–Moore hemiarthroplasty for subcapital fractures of the femoral neck.

Patients with impaired kidney or liver functions, patients with a history of spine surgery, infection at injection sites, coagulopathy, hypersensitivity to local anaesthetics or opioids, mental disturbance or neurological disease were excluded from the study. Also, cases were excluded if the sensory level was inadequate after 30 minutes of LA injection.

All patients were allocated into three groups (30 patients each) by simple randomization using sealed envelopes. All patients were given Tab. Alprazolam (0.25mg) and Tab. Ranitidine (150mg) the night before surgery.

Group BC (Bupivacaine - Clonidine group) was administered 9 mg (1.8 ml) 0.5% heavy bupivacaine + clonidine 15 µg (0.1ml) + saline (0.3 ml).

Group BF (Bupivacaine - Fentanyl group) was administered 9 mg (1.8 ml) 0.5% heavy bupivacaine + fentanyl 20 µg (0.4ml).

Group BS (Bupivacaine - Saline group) was administered 9 mg (1.8 ml) 0.5% heavy bupivacaine + saline (0.4ml).

Total volume in all the three groups was 2.2 ml.

An anaesthesiologist not included in any other aspect of the study prepared the test drug solution and another anaesthesiologist blinded to the test drug performed the subarachnoid block and recorded the observations.

After securing an 18-gauge intravenous access with Ringer lactate on flow, standard monitoring according to ASA guidelines was initiated. Spinal puncture was performed at L3–4 or L4–5 level using a 25 G Quincke needle with the patient in a seated position. After ensuring free flow of clear CSF, the drugs were administered in separate syringes. The additive or saline was injected via a 1ml syringe and bupivacaine via a 2 ml syringe. The injection of the local anaesthetic (1.8 ml) was made over 30 seconds, that is 0.06 ml/sec. The patients were then made supine with support for head and shoulders.

The time of completion of spinal injection was designated as time 0 and other time points were measured from this time. As a routine oxygen was administered via nasal prongs to all patients.

The level of sensory block, defined as the dermatomal segment with loss of temperature sense to cold on each side of the midthoracic line, was measured every 5 minutes, until it reached the peak level with four consecutive tests. The following parameters were recorded:

   a) onset of sensory block

   b) peak sensory block time that is from time 0 to peak block level

   c) onset of motor blockade

   d) time taken to achieve maximum degree of motor block

Motor block was scored using a modified Bromage scale

   1: complete motor block

   2: almost complete motor block: able only to move the feet

   3: partial motor block: is able to move the knees

   4: detectable weakness of hip flexion: able to raise the leg but is unable to keep it raised

   5: no detectable weakness of hip flexion: able to keep the leg raised for 10 s at least

   6: no weakness at all

   e) time for sensory level to regress to level L1 from time 0

   f) time of recovery from motor block to modified Bromage 0

   g) use of supplemental analgesics perioperatively

   h) time to the first analgesic request after operation

The pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), respiratory rate (RR), sedation score (SS) were monitored, pre-operatively, every 5 minutes after the subarachnoid block for

45 minutes and then every 15 minutes till the end of surgery, every hour in the recovery room till the sensory level reached L1 and thereafter in the ward until the demand for rescue analgesic by staff who were also unaware of study group allocation. Any episode of hypotension after spinal anaesthesia was recorded. Hypotension was defined as a SBP less than 110 mmHg or mean arterial pressure of less than or equal to 65 mmHg and was managed with fluid bolus or 3 mg ephedrine intravenously. Clinically, relevant bradycardia was defined as heart rate less than 50 beats/min and was treated with atropine 0.6 mg intravenously.

Intraoperative sedation score was graded 0: Wide awake; 1: Sleeping comfortably but responding to verbal commands; 2: Deep sleep but arousable; 3: Not arousable[7]. Adverse effects such as pruritus, dryness of mouth, dizziness, nausea vomiting and hypoxemia (SpO2 ≤ 90%) were recorded during the surgery and recovery period and treated if required.

Any other intraoperative complication was recorded and managed appropriately. Post-operatively, time for demand of analgesic was recorded. The intensity of pain was assessed using a 10-point VAS. Duration of analgesia was defined as the duration between time 0 to VAS score of 4 or more. Slow intravenous tramadol 50 mg followed by 1 gram paracetamol infusion (if needed) were administered as a rescue analgesic.

SPSS 20.0 software was used for the statistical analysis. The sample size was calculated based on the assumption that a difference of 50 min in the duration of analgesia between the groups was significant. Minimum of 28 patients were required in each group to produce a significant difference assuming a type-1 error of 0.05 and power of 0.95.
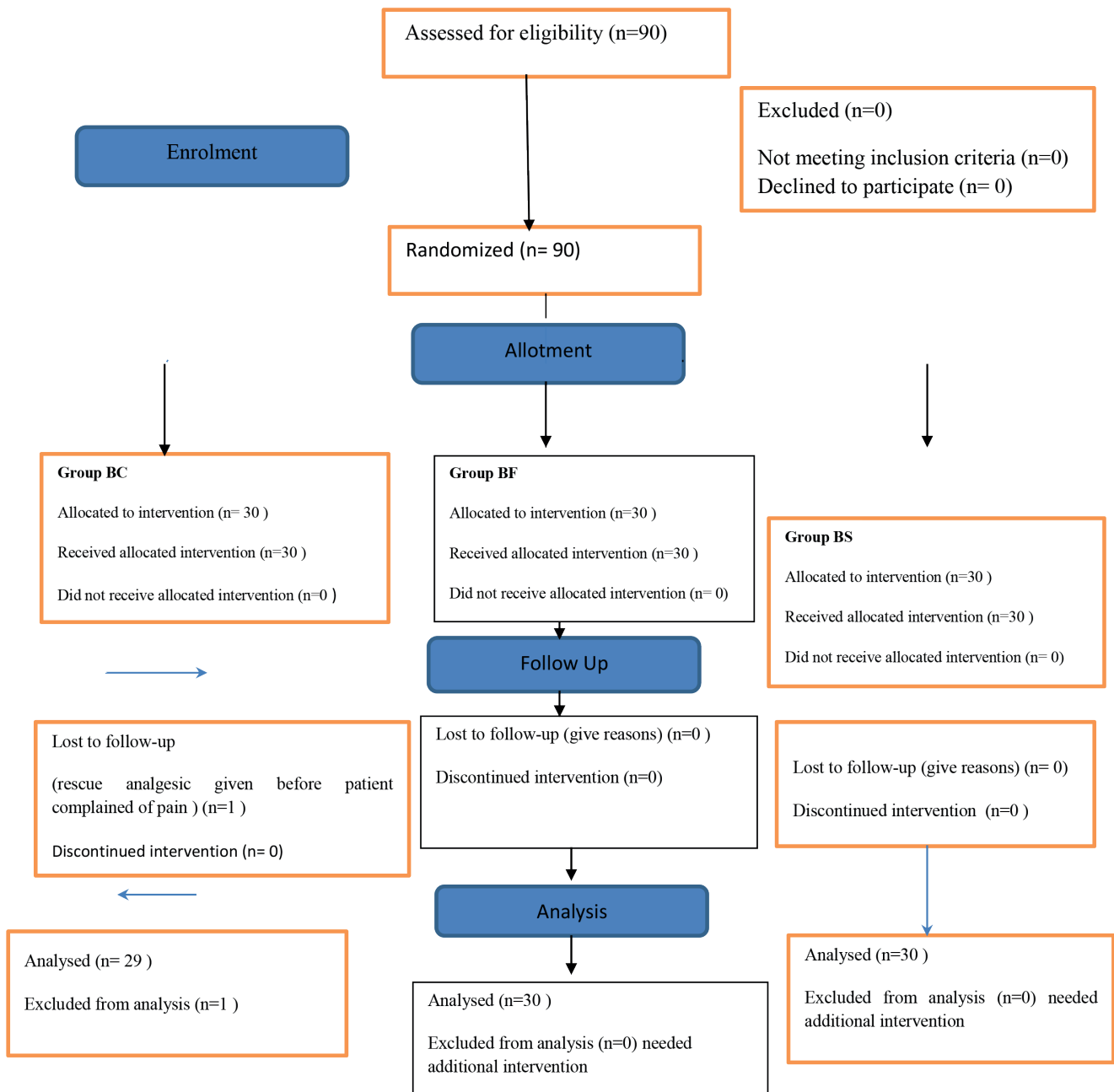
Continuous data and frequency (percentage) was represented as mean ± standard deviation and nonparametric (categorical) data was written as median (range). The groups were compared using analysis of variance (ANOVA). Comparison between the groups was done using the post hoc Tukey test. Intra group comparisons were done using repeated measures ANOVA and post hoc Bonferroni's test. P < 0.05 was considered statistically significant. P < 0.001 was considered highly statistically significant.

Results

Among the 90 patients enrolled in the study, 89 patients completed the study and were included in the data analysis (Figure 1). The Group BF, Group BC and Group BS included 30, 29 and 30 patients respectively. These groups did not differ with respect to the demographic variables. The surgical time was also comparable between the three groups (Table 1).

Comparison of mean onset of sensory block showed no significant difference between the three groups. Group BC needed the longest time to reach peak sensory level 9.76 ± 2.97 min and Group BF needed at least 9.6 ±5.14 min. The highest sensory level attained was T4: 2,3 and 2 patients in BF, BC, BS groups respectively. Time taken for the onset of the motor block was longest in Group BS group 5.8 ± 1.38 min and fastest in Group BC, 5.17 ± 1.31 min. Peak motor block (min) was achieved slowest in Group BS 10.93 ± 2.59 min and fastest in Group BF 10.4 ± 3.32 min. 2 patients in group BS group, 1 in group BF and 1 in group BC had a modified Bromage score of 2, rest of the patients had complete motor blockade. Time taken for the sensory level to recede to L1 was the longest in the BC group and shortest in the BS group, 177.41 ± 32.83 min in the BC group, 147 ± 27.97 min in the BF group and 115.17 ± 43 in the BS group. The intergroup difference was statistically significant. Comparison of the mean motor block duration (min) between the three groups showed significant difference between the three groups. The highest mean values were seen in Group BC (127.28 ± 16.98) followed by Group BF (113.57 ± 16.84) and Group B (89.43 ± 28.5). The duration of effective analgesia was maximum in the BC group, 371.38 ± 91.21 min and minimum in BS group, 181.5 ± 61.58 min. This difference was statistically significant. Group BF had duration of analgesia for 306.33 ± 100.35 min, and this was significantly less compared to the BC group (Table 2).

There was a decrease in the pulse rate as compared to the baseline in all the three groups, but it was not significant and none of the patients needed atropine. Comparison of pulse rate between the three groups did not show any significant difference between the groups.

Enrolment

Assessed for eligibility (n=90)

Excluded (n=0)

Not meeting inclusion criteria (n=0)
Declined to participate (n= 0)

Randomized (n= 90)

Allotment

Group BC

Allocated to intervention (n= 30)

Received allocated intervention (n=30)

Did not receive allocated intervention (n=0)

Group BF

Allocated to intervention (n=30)

Received allocated intervention (n=30)

Did not receive allocated intervention (n= 0)

Group BS

Allocated to intervention (n=30)

Received allocated intervention (n=30)

Did not receive allocated intervention (n= 0)

Follow Up

Lost to follow-up

(rescue analgesic given before patient complained of pain) (n=1)

Discontinued intervention (n= 0)

Lost to follow-up (give reasons) (n=0)

Discontinued intervention (n=0)

Lost to follow-up (give reasons) (n= 0)

Discontinued intervention (n=0)

Analysis

Analysed (n= 29)

Excluded from analysis (n=1)

Analysed (n=30)

Excluded from analysis (n=0) needed additional intervention

Analysed (n=30)

Excluded from analysis (n=0) needed additional intervention

Figure 1: Consort Chart

Group BC (Bupivacaine-Clonidine group), Group BF(Bupivacaine – Fentanyl group), Group BS (Bupivacaine – Saline group)

Table 1: Demographic variables

	Group BF (n=30)	Group BC (n=29)	Group BS (n=30)	P VALUE
Age (years)	72.8±9.08	71.59±6.58	72.93±6.91	0.717
Weight (kg)	52.53±9.33	51±7.44	52.97±8.93	0.657
Height (cm)	151.9±7.41	149.45±5.49	153.43±8.64	0.114
Gender F/M	19/11	20/9	20/10	
ASA I/II/III	4/19/7	3/18/8	3/19/8	
Surgical time (min)	93.67±20.59	92.59±18.4	90±19.7	0.759

Table 2: Comparison of subarachnoid block characteristics

	Group BF (n=30)	Group BC (n=29)	Group BS (n=30)	P value	Group BF vs Group BC difference (P value)	Group BF vs Group BS difference (P value)	Group BC vs Group BS difference (P value)
Sensory onset (min)	4.77±1.61	4.34±1.7	5.1±1.27	0.173	0.42 (0.544)	-0.33 (0.679)	-0.76 (0.148)
Time for max sensory level (min)	9.6±5.14	9.76±2.97	9.73±2.41	0.989	-0.16 (0.985)	-0.13 (0.989)	0.03 (1)
Maximum sensory level	T10:4; T8:17; T6:7; T4:2	T10:3; T8:14; T6:9; T4:3	T10:3; T8:18; T6:7; T4:2				
Motor onset (min)	5.33±1.42	5.17±1.31	5.8±1.38	0.193	0.16 (0.894)	-0.47 (0.389)	-0.63 (0.19)
Time for peak motor block (min)	10.4±3.32	10.79±3.16	10.93±2.59	0.78	-0.39 (0.873)	-0.53 (0.775)	-0.14 (0.983)
Time taken for sensory level to recede to L1 (min)	147±27.97	177.41±32.83	115.17±43	**<0.001**	**-30.41 (0.004)**	**31.83 (0.002)**	**62.25 (<0.001)**
Motor block duration (min)	113.57 ± 16.84	127.28 ± 16.98	89.43 ± 28.5	**<0.001**	-13.71 (0.043)	24.13 (<0.001)	37.84 (<0.001)
Duration of analgesia (min)	306.33±100.35	371.38±91.21	181.5±61.58	**<0.001**	**-65.05 (0.013)**	**124.83 (<0.001)**	**189.88 (<0.001)**
Ephedrine use (mg)	4.1 ± 6.47	7.14 ± 6.18	4.4 ± 4	0.082	-3.04 (0.103)	-0.3 (0.977)	2.74 (0.157)

Intragroup analysis showed a significant decrease in SBP from 10 minutes till 180 minutes post SAB in all the groups. There was a significant difference in the systolic blood pressure between the three groups after 10 minutes of the subarachnoid block. The BF group had the highest mean systolic pressures until 180 minutes. After that the difference was insignificant. 21 patients in the BC group, 14 patients in BF and 15 patients in the BS group needed fluid boluses or ephedrine to maintain SBP >/= 110 mmHg or MAP >/= 65 mmHg . The mean arterial pressure in the BF group was significantly higher than the BC and BS group from 10 minutes after SAB (Figure 2). But the MAP in all the groups remained above 65 mmHg throughout the duration of the study.

Consumption of ephedrine use between the three groups showed no significant difference between the three groups (test value of 2.573 and p value of 0.082). The highest mean values were seen in Group BC (7.14 ± 6.18) followed by Group B (4.4 ± 4) and Group BF (4.1 ± 6.47) (Table 2).

The sedation score was significantly more in the BF and BC group compared to the BS group. The patients in the BF group were significantly more sedated compared to the BC group. But the above differences were seen only from 15 minutes to 1 hour of SAB

Pruritus was seen in 4 patients in the BF group. No other side effects were recorded in any of the groups.
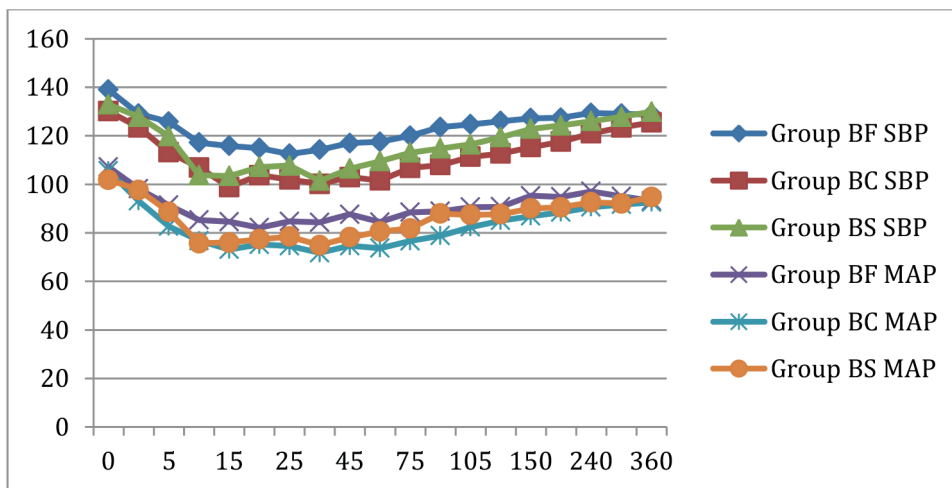
Figure 2: Comparison of Systolic Blood pressure (SBP) and Mean Arterial Pressure (MAP) between the three groups (Mean+/- SD)
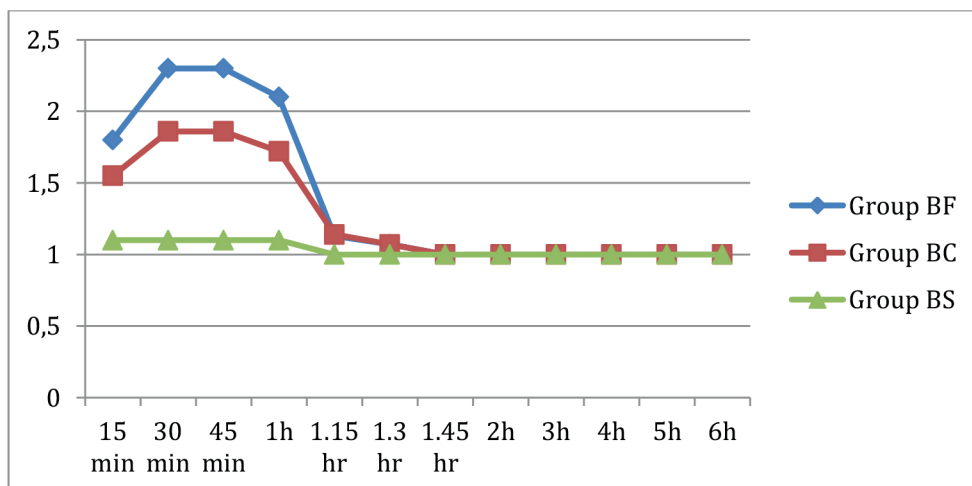
Figure 3: Comparison of Sedation Score between the three groups (Mean +/-SD)

Discussion

In the present study, the addition of clonidine or fentanyl to intrathecal bupivacaine in the elderly increased the duration of analgesia compared to placebo, clonidine significantly more effective than fentanyl.

With rising life expectancy worldwide, the number of elderly individuals is increasing and it is estimated that the incidence of hip fracture will rise from 1.66 million in 1990 to 6.26 million by 2050[8]. A higher mortality is seen in the elderly trauma patients as compared to young patients due to pre-existing comorbidities, decreased physiologic response after traumatic injury, poor response from the cardiovascular reserve, diminished cardiac output and poor functional capacity during periods of stress that impair their ability to tolerate injury[9]. With respect to the type of anaesthesia, no significant differences have been found in the postoperative complications or 30-day mortality of patients who received general anaesthesia versus spinal anaesthesia for the surgical repair of a hip fracture.[1] However spinal anaesthesia decreased early mortality, reduced the cases of deep vein thrombosis, acute postoperative confusion, myocardial infarction, pneumonia, fatal pulmonary embolism, postoperative hypoxia, hospital stay and also reduced the incidence of Postoperative Cognitive Dysfunction (POCD) in the first postoperative week[11,12,13].

Surgery for fracture femur or hip lasts for 75-90 minutes and can be managed with single shot spinal anaesthesia. But providing adequate anaesthesia and analgesia while maintaining stable haemodynamics with minimal side effects in the senior citizens remains a challenge. This can be overcome with addition of adjuvants to local anaesthetics. Alpha 2 agonists and opioids are arguably the most commonly used additives.

Haemodynamic stability is much better in patients who receive a low dose (5-10 mg) of intrathecal 0.5% bupivacaine in combination with opioids due to minimal potential effects on sympathetic pathways[14].

Fentanyl is the most often used intrathecal lipophilic opioid. Addition of fentanyl to local anaesthetics prolongs the duration of sensory block/ effective analgesia possibly due to the residual analgesic effect of the fentanyl that manifests after the sensory block due to the effect of the intrathecal local anaesthetic (0.5% hyperbaric bupivacaine) has been dissipated[15]. It has minimal cephalic spread thus reducing the risk of delayed respiratory depression and aiding in early ambulation[14].

Clonidine is also often used as an adjuvant because it has several advantages and is considered safe. It causes hyperpolarization of postsynaptic dorsal horn neurons and depression of the release of C-fiber transmitters. Binding of clonidine to motor neurons in the dorsal horn may prolong motor block[16]. Clonidine in small doses of 15 μg or 30 μg was seen to prolong duration of analgesia and potentiate sensory block levels produced by 9 mg hyperbaric bupivacaine in elderly patients[15,16].

It has been demonstrated that addition of fentanyl combined with minidose (4 mg) isobaric bupivacaine prolongs the sensory block with dramatically less hypotension as compared with conventional dose of isobaric bupivacaine[17]. But the use of minidose hyperbaric bupivacaine alone will not provide sufficient sensory or motor level[18].

As the study group involved single shot spinal anaesthesia, 0.5% hyperbaric bupivacaine 1.8 ml (9 mg) was used in order to ensure that the sensory and motor blockade was adequate in all the groups. Although earlier studies have compared various doses of clonidine or fentanyl added to intrathecal bupivacaine in young adults, there are only a few studies comparing clonidine or fentanyl added to bupivacaine in the elderly[7,16,19,20,21].

In the present study, onset of sensory block and maximum sensory level achieved did not differ between the three groups. This was similar to the study in which 25 mg fentanyl added to 10 mg 0.5% bupivacaine was compared with 10 mg bupivacaine alone[15].

Contrary to this, addition of fentanyl hastened the onset of the sensory block and the peak sensory level achieved when 12.5mg 0.5% bupivacaine was compared with 7.5 mg 0.5% bupivacaine with fentanyl[3].

Our study did not find any significant difference between onset and degree of motor blockade between the three groups. However, other studies differed in their findings. Desai D. et al found that the maximum Bromage score of motor block was lesser in group BF compared with bupivacaine alone because fentanyl has differential synergism with local anaesthetic agents and acts on only Aδ & C

fibres so it cannot add to motor blockade of local anaesthetic agent[3]. However, Lalita Gauri Mitra et al, C Olofsson et al, did not observe any difference in motor blockade with addition of Fentanyl[22,23]. Similar to present study, clonidine 15 μg or 30 μg added to 9 mg bupivacaine, did not affect the onset of surgical anaesthesia as compared with bupivacaine alone[16].

This study found that the time taken for sensory regression to L1 and recovery from motor blockade were longest in the BC group followed by the BF group; the sensory level receded earliest in the BS group. Agarwal D. had found that the addition of clonidine had prolonged the mean time for sensory regression to T_{12} level and motor block regression[16]. In another study, regression time to L1 level was longer in the BF group in comparison to group B[3].

Addition of fentanyl or clonidine significantly increased the duration of analgesia as compared with the group receiving bupivacaine alone, clonidine more than fentanyl. One patient in the BF group and 3 patients in the BS group undergoing dynamic hip screw insertion grew restless and complained of pain during the final skin sutures. They were given intravenous fentanyl in 20 mcg instalments. Once the awkward surgical position was corrected and patients were made supine, they were comfortable in the immediate post-operative period.

A systematic review reported a 31.3% incidence of hypotension in patients receiving clonidine 15-150 μg without evidence of dose responsiveness versus a 20% incidence in controls[24]. On the contrary, haemodynamic stability was well-maintained in elderly patients when clonidine or fentanyl was used as adjuvant to bupivacaine during the transurethral resection of bladder tumour or prostate[21,25]. In another study, the addition of 15 or 30 μg clonidine to 9 mg 0.5% bupivacaine did not cause an increase in the incidence of hypotension when compared with 9 mg bupivacaine alone[16]. But in the present study, incidence of hypotension and the use of ephedrine was more in the BC group compared with the other two groups.

Desai D. et al found that the incidence of hypotension in the bupivacaine group was higher than the bupivacaine-fentanyl group[3]. But they had used 12 mg bupivacaine in group B and 7.5 mg bupivacaine in group BF. We used the same dose of bupivacaine (9 mg) in all the groups. Among the changes relevant for geriatric trauma care is that

the threshold for hypotension is suggested to be 110 mmHg, not 90 mmHg[9,26]. The increased incidence of hypotension in our study could be due to the higher threshold for hypotension; most of the previous studies have defined hypotension as SBP < 90 mmHg or 25% decrease from baseline.

Sedation score was comparable in all the three groups. Three patients in the BF group complained of pruritus. None of the patients in the BC or BS groups developed pruritus. No other side effect was recorded in any patient.

Limitations

The limitation of this study was the small sample size. Also the patients on different antihypertensives were not segregated and compared with regards to their hemodynamic characteristics.

Conclusion

Fentanyl or clonidine added to low dose intrathecal bupivacaine in the elderly for lower limb surgery significantly increase the duration of analgesia compared with intrathecal bupivacaine alone. The incidence of hypotension and use of ephedrine was highest in the clonidine group compared with the other two.

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