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Original Research Article

A comparison of fentanyl and clonidine as adjuvants to intrathecal levobupivacaine for spinal anaesthesia and postoperative analgesia in patients undergoing for lower limb surgery

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Abstract

Objective: Analgesic adjuvants, clonidine and fentanyl have decreased the requirements the local anaesthesia and prolonged the effects of the analgesia. The purpose of this study was compare the intrathecal clonidine and fentanyl as adjuvant to levobupivacaine in terms of efficacy, safety and postoperative analgesia in patients undergoing lower limb surgeries.

Methods: This prospective study is conducted is sixty lower limb surgery patients, divided into two group C: 2.5ml of 0.5% levobupivacaine with either 30μg of clonidine and group F: 2.5ml of 0.5% levobupivacaine with either 15μg of fentanyl intrathecally. The hemodynamic parameters, onset and duration of sensory and motor block, total analgesia time and side effects were statistically analyzed using unpaired *t*-tests and Chi-square test.

Results: The onset of sensory and motor was statistically similar in both group F and group C. The duration of sensory and motor block were significantly higher ($p < 0.001$) in group C as compared to group F. The highest level sensory block was comparable in both group ($p=0.918$). Time reach max level and rescue analgesia were higher in group C (146.33 ± 10.44 and 513.33 ± 22.18 respectively) as compared to group F (139.17 ± 7.09 and 428.50 ± 25.53 respectively).

Conclusions: Intrathecal clonidine and fentanyl as adjuvant to levobupivacaine provide adequate anaesthesia for lower limb surgeries. Clonidine as an adjuvant provided prolonged postoperative analgesia as compared to fentanyl.

Keywords: Clonidine, Fentanyl, Intrathecal Levobupivacaine, Local Anaesthesia.

1. Introduction

Effective spinal anaesthesia is possible with the correct choice of local anaesthetic. Suitable local anaesthetics should provide effective anaesthesia and analgesia during the operation and should have no side effects. Levobupivacaine is a local anaesthetic that is relatively new to clinical practice [1-3]. Levobupivacaine is an S(-) enantiomer of bupivacaine and both agents have similar pharmacokinetic properties (1-3). The effects of spinal anaesthesia and postoperative analgesia can be prolonged by using adjuvants such as adrenaline, neostigmine, clonidine, midazolam, and opioids [4-9]. Wang *et al*. (1979) were the first to shows the successful intrathecal administration of morphine and since then

opioids were used as a local anaesthetic adjuvants [10]. Fentanyl became a first choice of the adjuvant among all opioids, because of its potency, rapid onset and short duration of action with lower incidence of respiratory depression [6,11]. However, in the adding of opioids as adjuvant to local anesthetic agent is related with adverse effects such as nausea, vomiting, pruritus, herpes labialis activation, respiratory depression and urinary retention. Moreover the recent study shows that the nonopioid such as clonidine is used as an adjuvant to local anesthetic agent [12]. Intrathecal clonidine is established to increase the effect of subarachnoid block as well as decreased the requirement of local anesthetic agent [13]. Intrathecal

clonidine also prolonged the postoperative analgesia effects and reduced the adverse effects associated with intrathecal opioids [6-8,14,15]. In this study, we aim to compare the intrathecal clonidine and fentanyl as adjuvant to levobupivacaine in terms of efficacy, safety and postoperative analgesia in patients undergoing lower limb surgeries.

2. Materials and Methods

After approval from the Institutional Ethic Committee, this prospective study was conducted on 60 American Society of Anesthesiologists (ASA) I or II patients between 18 and 65 years of age planned for elective lower limb surgeries and patients were divided into two groups of 30 each. From all the patients, written informed consent were obtained. Exclusion criteria were patient refusal, any contraindication for spinal anesthesia, known drug allergy, severe systemic disorders such as diabetes mellitus, hypertension, heart disease with ASA grade more than II, allergy to study drugs, and all potential contraindications for spinal anesthesia, such as spine deformity, raised intracranial pressure, neurological disorders, bleeding disorders or infection at the puncture site. The patients were randomized into two groups of 30 each as following.

Group C: 2.5ml of 0.5% levobupivacaine with either 30μg of clonidine intrathecally

Group F: 2.5ml of 0.5% levobupivacaine with either 15μg of fentanyl intrathecally

All Patients were nil per orally for 6 h, pre-medicated with ondansetron 4 mg IV and glycopyrrolate 0.2 mg intravenous (IV). Sedatives were avoided as premedication, as well as during operative procedure. Patients were preloaded with 10-15 ml/kg body of ringer lactate. Under all aseptic precautions, subarachnoid block were given with 25 gauge Quincke needle in sitting position and depending upon the groups, either 15μg fentanyl or 30μg clonidine admixed with 2.5ml of 0.5% levobupivacaine resulting in total volume of 3 ml were injected intrathecally. Baseline standard monitoring included continuous electrocardiogram, pulse oximetry, non-invasive blood pressures and urine output. Before the start of anesthesia, sensory and motor assessment methods were described in all patients. The drug solution was prepared aseptically by the anesthetist. Noninvasive heart rate, blood pressure and oxygen saturation were measured every 5 min first 25 min and thereafter every 15 min. oxygen saturation was maintained ($\leq 92\%$) with the help of supplementary O_2. Sensory block was tested by touch, pinprick or cold Motor block by using a modified Bromage Scale (0=no block, 1=inability to raise extended leg, 2=inability to flex knee, and 3=inability to flex ankle and foot) [16,17]. The onset of analgesia, highest level of sensory block, duration of sensory and motor block, time to reach maximum level and first request for analgesic were recorded. Any possible side effects such as nausea, vomiting, shivering, pruritus, sedation, hypotension, bradycardia, and respiratory discomfort were recorded. Patients were monitored for degree of pain with the visual analogue scale (VAS). Postoperative rescue analgesia was given when the VAS score was >5 and the time of injection of first analgesic drug were noted.

2.1. Statistical analysis

The collected data were analyzed by using SPSS statistical software 21. The sample size determination was based on α error (0.05) and β error (0.10). Data are presented as Data are represented as mean, ±SD, n (%) and ratio. SD=Standard deviation. Student "t" tests were used for statistical calculations. Categorical data were analyzed using Chi-square test. A *P* value <0.05 was considered statistically significant.

3. Results

The demographic variables in both groups were statistically similar with respect to mean age, mean height, mean weight, sex, duration of surgery and ASA grade were shown in Table 1. Age of patients included in the study ranged from 16-65years of age as per inclusion criteria. Difference in mean age of patients of group F (43.37±22.45) and group C (40.93±5.37) were not found to be statistically significant (p=0.566). Out of 60 patients, 30% females and 70% male in group F whereas 27% female and 73% male in group C but differences in gender was not found to be statistically significant in between groups. The mean height, mean weight, sex, duration of surgery and ASA grade were comparable in between group F and group C.

At all the periods of observation the heart rate was more stable in group C. The mean difference in heart rate was not found to be statistically significant at all periods of observation except at 20 min., 25 min. and 40 min (Fig. 1). The mean systolic blood pressure (SBP) was also comparable in both groups except at 15 min., in which the SBP was significantly changed in group C from baseline (Fig. 2). The mean diastolic blood pressure (DBP) was also statistical similar in both groups from base line to 55 min. perioperative (Fig. 3).

The onset of sensory and motor were statistically similar in both group F (6.17±1.08, 9.20±1.19) and group C (6.60±1.13, 9.80±1.52), respectively. The duration of sensory and motor block were significantly higher (p <0.001) in group C (182.00±13.75, 197.60±19.23) as compared to group F (140.83±9.0, 167.83±11.94), respectively. The highest level sensory block was comparable in both group (p=0.918). Time reach max level and rescue analgesia were also higher in group C (146.33±10.44, 513.33±22.18) as compared to group F

(139.17±7.09, 428.50±25.53), respectively as shows in Table 2.

Sedation score was non-significant in between groups intraoperatively. Side effects such as nausea, bradycardia, shivering and itching were slightly higher in fentanyl group whereas vomiting and hypotension were higher in group C. Moreover, the side effects were not significantly different in between group F and group C (Table 3).

Table 1: Demographic Details

	Group F (n=30)	Group C (n=30)	p-Value
Age (years)	43.37±22.45	40.93±5.37	0.566
Height (cm)	165.77±5.06	166.40±4.51	0.611
Weight	63.37±7.19	64.37±6.43	0.572
Sex (Male/Female)	21/9	22/8	0.779
Surgery Duration	99.13±5.96	102.27±9.69	0.137
ASA Grade (I/II)	18/12	16/14	0.795

Data are represented as mean and ±SD (Standard deviation)

Table 2:

	Group F (n=30)	Group C (n=30)	p-Value
Onset sensory (min)	6.17±1.08	6.60±1.13	0.136
Onset motor (min)	9.20±1.19	9.80±1.52	0.093
Duration sensory (min)	140.83±9.0	182.00±13.75	<0.001[**]
Duration motor (min)	167.83±11.94	197.60±19.23	<0.001[**]
Highest level sensory block (min)	9.67±1.18	9.70±1.32	0.918
Time reach max level (min)	139.17±7.09	146.33±10.44	0.003[*]
Rescue analgesia (min)	428.50±25.53	513.33±22.18	<0.001[**]

[*]=Significant (p=<0.05), [*]=Significant (p=<0.001)

Table 3: Side Effects

Side Effects	Group F (n=30)	Group C (n=30)	p-Value
Nausea	1	0	0.321
Vomiting	0	1	0.321
Hypotension	2	4	0.647
Bradycardia	4	3	0.394
Respiratory Depression	0	0	-
Shivering	4	3	0.694
Itching	3	1	0.309
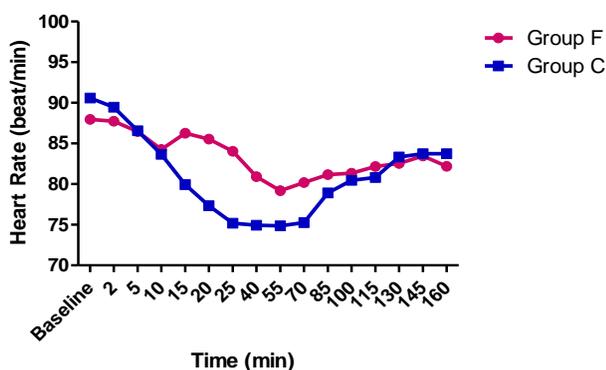
Fig. 1 : Heart Rate (beat/min)
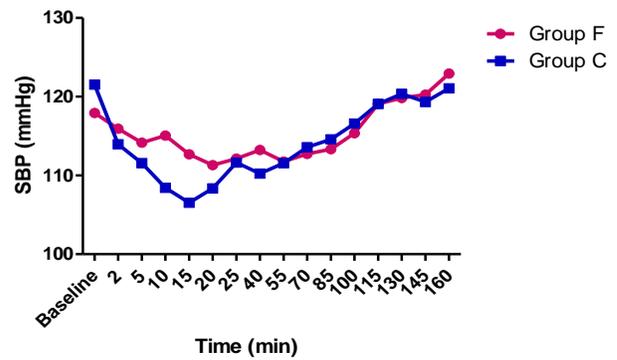
Fig. 2: Systolic blood pressure (SBP) mmHg
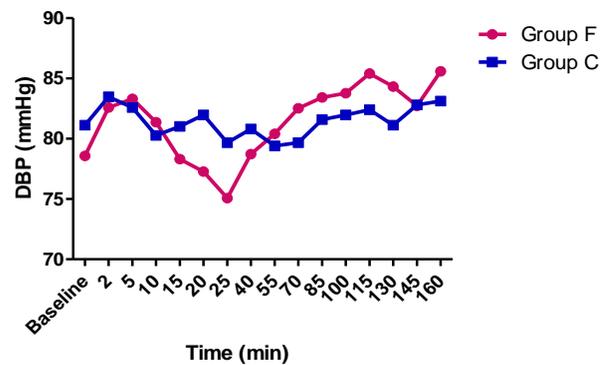
Fig. 3: Mean diastolic blood pressure (DBP) mmHg

4. Discussion

Levobupivacaine, the S-(-)-enantiomer of bupivacaine was shown to be similarly effective in both spinal and epidural anaesthesia with less neurotoxic and cardiac adverse effects [18]. In epidural, the levobupivacaine have shown sensory-motor dissociation and maybe in spinal route [19-21]. Lee *et al.* (2003) firstly evaluated the efficacy of the spinal route of levobupivacaine (2.6 mL 0.5%). They reported that the onset time, sensory and motor block and hemodynamic stabilities were similar to bupivacaine at same racemic [18]. Spinal anaesthesia and analgesia can be prolonged the effect of local anaesthetics by added the adjuvants to like opioids, clonidine, midazolam, neostigmine and adrenaline [4-8]. Fentanyl is a lipophilic μ-receptor agonist opioid, preferred adjuvant for rapid onset and short duration of action in spinal anaesthesia with no major complications [6,11,12,19]. Previous various clinical studies reported that the intrathecal clonidine prolongs the effects of sensory and motor block of spinal anaesthesia and decreases the requirement of dose of local anaesthetics [13], and prolonged the effects of the analgesia postoperatively [2-8,14].

Lower dose of clonidine and fentanyl are safe and prolongs the postoperative analgesia of intrathecal levobupivacaine and there is a very few studies on comparing of efficacy and safety of these drugs. In this study, we observed that the clonidine and fentanyl groups

were similar regarding onset sensory/motor and time to highest level sensory block, but the duration of sensory/motor, time reach max level and rescue analgesia are significantly higher in clonidine group than in fentanyl group. Our findings are supported by the studies of Bajwa *et al.* (2017) and Routray *et al.* (2017), who reported that intrathecal clonidine as adjuvant to hyperbaric bupivacaine provided the better postoperative analgesia with more sedation as compared to fentanyl [22,23].

In the present study, we evaluated the safety and efficacy of intrathecal clonidine and fentanyl as adjuvant to levobupivacaine and postoperative analgesia in patients undergoing lower limb surgeries. We found that the both clonidine and fentanyl are effective as adjuvants to intrathecal levobupivacaine in prolonging the analgesia duration. The first time requirement of analgesia was significantly higher in clonidine group as compared to fentanyl group. Our results are supported by similar findings of previous studies [22-28]. Our findings are supported by the studies of Sharan *et al.* (2016) and Ogun *et al.* (2006) reported that the onset of sensory, motor and time to highest level sensory block were comparable in ropivacaine (15 mg) and clonidine (30 μg) with ropivacaine (17.5 mg) in women undergoing cesarean deliveries [29,30]. A previous study by Chaudhary *et al.* (2014), who also found similar reported in sixty transurethral resection patients [31]. Similarly, Yegin *et al.* (2005) also demonstrated the similar effect onset of sensory block of intrathecally 0.5 ml of fentanyl (25 μg) or 0.5 ml of normal saline to 6 mg/ml hyperbaric ropivacaine (18 mg) for transurethral resection [32].

In this study, the side effects such as nausea, bradycardia, shivering, itching or sedation are not associated with small dose of intrathecal fentanyl or clonidine. Both groups are haemodynamic stable in this study. Our findings are supported by the studies of Sethi *et al.* (2007) and Shah *et al.* (2011), who observed that very few incidences of hypotension and bradycardia by using 1 mcg/kg of intrathecal clonidine for nonobstetric surgeries [33,34]. While Kothari *et al.* (2011) reported that the increased frequency of both bradycardia and hypotension in bupivacaine alone as compared with bupivacaine with clonidine [25]. Whereas Bajwa *et al.* (2012) did not observe bradycardia in with clonidine (45 μg in 9 mg) [26]. Similar Biswas *et al.* (35) and Agrawal *et al.* (2009) reported that the hemodynamic stability was observed in intrathecal fentanyl (12.5 μg and 25 μg) with bupivacaine [35, 31].

5. Conclusion

This study shows that the use of intrathecal clonidine as an adjuvant to levobupivacaine leads to a rapid onset and prolonged duration of sensory and motor block. Moreover, clonidine prolonged postoperative analgesia and stable hemodynamic as compared to fentanyl.

Conflict of interest

The author(s) confirm that this article content has no conflict of interest.

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