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Evaluation of Safety and Efficacy of Hyperbaric Bupivacaine (0.5%) Versus Hyperbaric Bupivacaine (0.5%) with 25 µg Fentanyl in Subarachnoid Block in Participants Undergoing Lower Limb Orthopaedic Surgery: A Prospective Randomized Double Blind Clinical Trial

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Abstract

Introduction: Intrathecal opioids potentiate the analgesic property of local anaesthetics. Hence, this study was conducted to evaluate the efficacy and safety of intrathecal Fentanyl (25µg) with hyperbaric Bupivacaine in lower limb orthopaedic surgery. *Methods:* 100 participants, aged 18 to 60 years, of ASA Physical status I and II, scheduled for lower limb orthopaedic surgery under subarachnoid block, were randomly divided into two groups (n=50 each); Group C received 3.0 ml (15 mg) 0.5% hyperbaric Bupivacaine + 0.5 ml Normal Saline (0.9%) and Group F received 3.0 ml (15 mg) 0.5% hyperbaric Bupivacaine + 0.5ml Fentanyl (25µg). Degree of sensory and motor block, quality of intraoperative anaesthesia, postoperative analgesia (VAS score), time of 1st rescue analgesia (effective analgesia), hemodynamic variables and side effects were evaluated and compared. At VAS ≥ 4, rescue analgesic Inj. Diclofenac Sodium intravenous was given. *Results:* Participants in Group F had faster onset and peak, with prolonged duration of sensory block ($p<0.0001$). Motor characteristics were comparable in both groups. Duration of analgesia was longer in Group F (179±12.08 min) than Group C (135±12.57 min) ($p<0.0001$). Effective analgesia was longer in Group F (350.1±34.02 min) than in Group C (292.5±31.94 min) ($p<0.0001$). Incidence of side effects was less in Group F. *Conclusion:* It is concluded that addition of 25µg Fentanyl with 0.5% hyperbaric Bupivacaine, in subarachnoid block, fastens and prolongs sensory block; also improves postoperative analgesia, with fewer side effects.

Keywords: Subarachnoid Block; Fentanyl; Hyperbaric Bupivacaine; Orthopaedic Surgery.

Introduction

Alleviation of pain is one of the most fundamental goals in anaesthesiology. Postoperative pain, apart from patient's sufferings, has many other adverse physiological and psychological effects like respiratory depression, circulatory disturbances and metabolic stress responses induced by anaesthesia and surgery. Good postoperative analgesia produces early patient mobilization, lesser respiratory complications and morbidity as well as improves patient's outcome and satisfaction [1]. Subarachnoid block was introduced in 1885 by J. Leonard Corning [2] and the advantages of simplicity of technique, rapid onset of action, reliability in producing uniform sensory and motor blockade, preservation of consciousness, thereby preventing the risk of aspiration, good postoperative analgesia, with minimal drug cost and side effects made this method a viable alternative to general anaesthesia for a variety of infra umbilical, perineal and lower limb surgical procedures: the lack of long lasting postoperative analgesia being the only drawback. Therefore, many adjuvants have been used along with local anaesthetic agents to relieve postoperative pain as well as improve the sensory and motor characteristics of subarachnoid block.

Neuraxial opioids when administered with local anaesthetics, improve the quality of intraoperative analgesia and prolongs the duration of postoperative

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analgesia [3,4,5,6]. Intrathecal opioids are synergistic with local anaesthetics and intensify the sensory block without increasing the sympathetic block with minimal hemodynamic instability. It is associated with improved tolerance power and reduced analgesic requirement in postoperative period [7,8]. As intrathecal morphine is associated with higher incidence of side effects, newer opioids (fentanyl, sufentanil, remifentanil) are combined with local anaesthetics which have minimal side effects [9].

In contrast to lipophobic drugs, the lipophilic drugs are more logical choice. Morphine, a lipophobic drug can easily migrate rostrally to the fourth ventricle in sufficient concentration to cause delayed respiratory depression whereas Fentanyl, a synthetic lipophilic opioid group of drug has fewer tendencies to cause such complicatons [10]. When administered with bupivacaine in subarachnoid block, fentanyl, by virtue of its lipophilic property (like faster onset of action and recovery, prolonged duration), reduces the need for supplements during surgery and produces improved perioperative analgesia which prompted us to evaluate the potential of fentanyl in participants undergoing lower limb orthopaedic surgery.

Materials and Methods

After approval from the Institutional Review Board (IRB No.517/2015), thorough pre anaesthetic check-up was done and 100 participants belonging to ASA grade I and II scheduled to undergo lower limb orthopaedic surgery were enrolled in this study with informed written consent. Participants having contraindications to subarachnoid block like congenital spinal anomalies, altered coagulation profile, local site skin infection, severe psychiatric disorders, neurological diseases, spinal cord and peripheral nerve diseases, hypersensitivity to local anaesthetic drug or study drug, participants refusal or any pregnant lady were excluded. Participants were randomly divided into 2 groups of 50 each by computer generated random software sequence.

Group C received 3.0ml (15mg) 0.5% hyperbaric Bupivacaine + 0.5ml Normal Saline (0.9%) and *Group F* received 3.0ml (15mg) 0.5% hyperbaric Bupivacaine + 0.5ml Fentanyl (25µg).

Preoperative preparation: All patients were kept nil by mouth (NBM) for 6 hrs. Baseline vital parameters [heart rate (ECG), blood pressure (systolic, diastolic and mean), respiratory rate and oxygen saturation] were recorded by standard monitoring. Intravenous access was secured using 18G venous catheter and the participants were premedicated with Inj. Ondansetron 0.08mg/kg intravenously 15 minutes prior to procedure. Preloading was done with Inj. Ringer Lactate 10ml/kg. Under all aseptic and antiseptic precautions, with the participant placed in left lateral position, subarachnoid block was performed with 25G (Quincke) spinal needle in L_{3-4} intervertebral space with midline approach and the drug was injected after obtaining free and clear flow of CSF, as per the group assigned. The study solution was prepared by the investigator of the team and the anaesthesiologist performing the block remained blinded to the content of the solution.

Immediately after the block, participants were turned supine. The time of injection was noted as time "0" and blockade characteristics were assessed as per the grading at every 30 seconds interval till peak effect was achieved. The degree of sensory block was assessed by pin prick method using the sterile 23G hypodermic needle. The degree of motor block was assessed with Modified Bromage Scale [11]. All participants were given supplemental oxygen by transparent face mask at the flow rate of 5L/min.

Pulse rate, respiratory rate, blood pressure and oxygen saturation monitoring was done at every 5 minutes for first 30 minutes and every 10 minutes thereafter throughout the surgery. Intra operatively, bradycardia (HR< 60) was treated with bolus inj. Atropine (0.02mg/kg) intravenously and hypotension (decrease in SBP more than 30% of baseline value) was treated with leg elevation, IV crystalloids (200mL bolus) or inj. Mephentermine 3mg IV as needed. Adverse effects like nausea and vomiting, pruritus, shivering and respiratory depression were recorded if any.

In PACU, sensory and motor block were assessed at every 30 minutes interval till complete regression. Thereafter, participants were monitored at 4 hourly intervals for next 24 hours for complications and adverse events if any. Time of analgesia request (TAR) was noted in post- operative period and participants were asked to point out the intensity of pain on 'Visual Analog Scale' (VAS) as explained preoperatively. Rescue analgesia- Inj. Diclofenac Sodium (1.5mg/kg) intravenous was given at VAS ≥ 4. The duration of complete analgesia termed as time from subarachnoid injection to first complaint of pain (pain score > 0) and effective analgesia termed as the time from subarachnoid injection to first dose of rescue analgesic were recorded respectively.

Statistical Analysis

The null hypothesis [HO] stating, there is no difference in the duration of analgesia following addition of 25µg of fentanyl intrathecally to 15mg of 0.5% hyperbaric bupivacaine with saline in participants undergoing lower limb orthopaedic surgery was tested. Data were calculated as Mean±Standard Deviation (SD) by statistical software (graph pad Instat 3.0 software) and presented in tabular or graphical form. Comparison between two groups was done using Mann-Whitney test (for non-parametric data) or unpaired Student's t-test (for parametric data) for Quantitative data; and Chi square test for Qualitative data. p value < 0.05 was considered statistically significant.

Sample Size

Sample size calculation assuming α error being 0.05 and β error being 0.20 with a power of study 80% showed that 50 patients were required per study group to compare hemodynamic effects and subarachnoid blockade characteristics.

Observation and Result

Participants' characteristics in terms of age, sex, weight, height, ASA physical status and duration of surgery were comparable in two groups (Table 1). As shown in Table 2, there was statistically significant difference in mean time for onset, peak and duration of sensory block in two groups (p<0.0001). The onset and peak of sensory block was achieved earlier in group F than in group C. Duration of sensory block was prolonged in group F in comparison to group C. There was statistically significant difference in mean time for onset, peak and duration of motor block in two groups, but clinically it was not significant.

Addition of 25µg of Fentanyl to hyperbaric Bupivacaine (Group F) produced statistically significant prolonged duration of effective blockade than addition of Normal Saline to hyperbaric Bupivacaine (Group C) (p<0.0001). Decreased VAS scores were observed Group F than Group C up to 6 hours postoperatively (p<0.0001).

As shown in figure 1, majority of the participants in group C required rescue analgesics between 4-5 hours, 10 participants between 5-6 hours and 4 participants between 6-7 hours of subarachnoid blockade. In group F, majority of the participants required rescue analgesics between 5-6 hours, 3 participants between 4-5 hours and 7 participants between 6-7 hours of subarachnoid blockade. The analgesic requirement was significantly reduced in group F when compared with group C. Three participants (6%) required three injections of rescue analgesic and 47 participants (94%) required only two injections in 24 hours in group F while, one

Table 1: Demografic profile of patients

Demographic Profile	Group C (n=50)	Group F (n=50)	*p* Value
Age (Years)	34.54 ± 11.11	35.02 ± 11.94	0.83
Gender (M/F)	38/12	44/06	0.19
Weight (Kg)	57.64 ±6.31	58.48 ± 7.18	0.53
Height (m)	1.63 ± 0.05	1.64 ± 0.05	0.39
ASA Physical Status (I/II)	21/29	30/20	0.10
Duration of Surgery (min)	107 ± 17.78	111.2 ±22.46	0.30

Values are mean ± SD or absolute numbers (percentage). p>0.05 Non significant, p<0.05 Significant, p<0.001 Highly significant

Table 2: Sensory and motor characteristics of subarachnoid block

	Minutes	Group C (n=50)	Group F (n=50)	p Value
Sensory	Onset (from Time "0" to L_1 level)	2.33 ± 0.78	1.8 ± 0.82	<0.0001
	Peak (from Time "0" to maximum level achieved)	5.3 ± 0.87	4.38 ± 1.29	<0.0001
	Duration (regression from Time "0" to L_1 level)	135 ± 12.57	179 ± 12.08	<0.0001
Motor	Onset (from Time "0" to Modified Bromage Scale I of motor block)	2.56 ± 0.71	2.25 ± 0.86	0.007
	Peak (from Time "0" to Modified Bromage Scale III of motor block)	5.72 ± 0.77	5.25 ± 1.08	0.003
	Duration (from Time "0" to Modified Bromage Scale 0 of motor block)	157 ± 6.85	159.5 ± 5.73	0.05
	Effective analgesia	292.5 ± 31.94	350.1 ± 34.02	<0.0001

participant (2%) required two injections of rescue analgesic and 49 participants (98%) required three injections (Figure 2).

Hence, there was significant reduction in total dose of rescue analgesic required in group F in comparison to group C.

There was statistically significant decrease in HR in group F after 30 minutes of subarachnoid block. ($p<0.05$) One participant in group F developed bradycardia (HR<60bpm) which responded to bolus inj. Atropine 0.6mg intravenously. Changes observed in systolic, diastolic and mean blood pressure were comparable in both the groups at different time points ($p>0.05$). (Figure 3) Three participants in group F and nine participants (18%) in group C developed hypotension (statistically and clinically not significant) which responded to intravenous fluid therapy. All other participants in both the groups were hemodynamically stable. SpO_2 remained stable and comparable in both the groups throughout the study period ($p>0.05$).

Mean time for spontaneous voiding of urine was 276.9±29.4 min in Group C and 273.7±33.92 min in group F. ($p>0.05$) Two participants (4%) in group C experienced nausea and vomiting, which was statistically not significant (Table 3). No other complications were noted in either group.

Table 3: Complications (intra and post operative)

Complications	Group C (n=50)		Group F (n=50)	
	No.	%	No.	%
Nausea/vomiting	2	4%	0	0
Hypotension	9	18%	3	6%
Bradycardia	0	0	1	2%
Shivering	0	0	0	0
Pruritis	0	0	0	0
Respiratory depression	0	0	0	0
Anaphylaxis	0	0	0	0

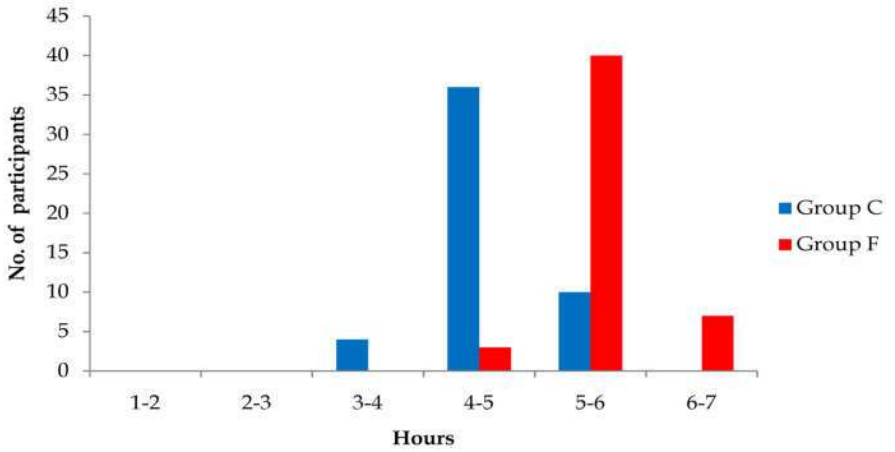

Fig. 1: Time of first rescue analgesia

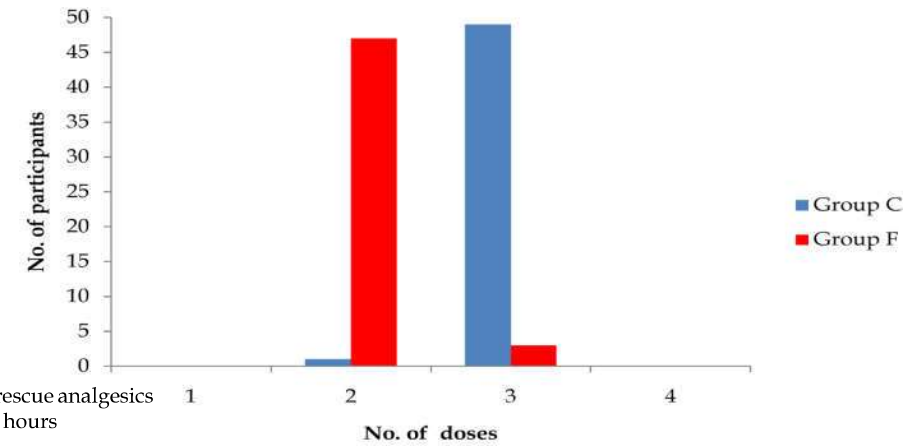

Fig. 2: Total no. of rescue analgesics required within 24 hours

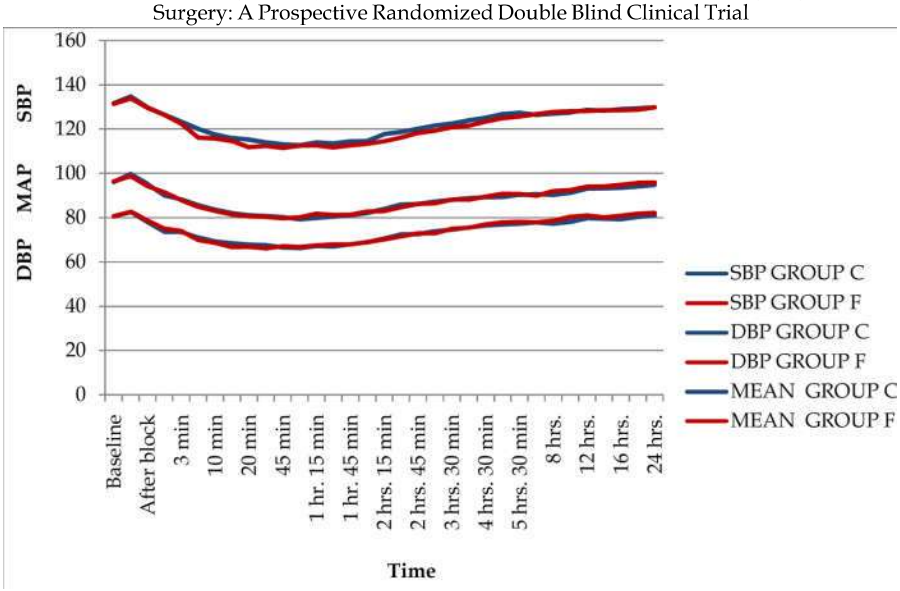

Fig. 3: Changes in systolic, diastolic and mean blood pressure in both the groups

Discussion

Fentanyl citrate, a synthetic amine opioid from the class of pure µ opioid receptor agonist, is structurally related to the phenylpiperidine nucleus and 100 times more potent than morphine [12] as an analgesic in equivalent doses. Fentanyl is a very important drug in anaesthetic practice because of its relatively shorter time to peak analgesic effect [13], rapid termination of effect after small bolus doses, minimal direct depressant effects on the myocardium, and their ability to significantly reduce the dosing requirement for the volatile action.

Morphine is a forerunner as an opioid adjuvant added to local anaesthetic for spinal anaesthesia and causes delayed respiratory depression (>2 hours after administration) which is to some extent dose-related [9] and believed to be a result of the cephalad spread of opioids to the medulla within the cerebrospinal fluid (CSF), seen more commonly with hydrophilic opioids. Hence, the lipophilic drugs like fentanyl, sufentanil, remifentanil, alfentanil, methadone are more logical choice. The safety of fentanyl regarding neurotoxicity has been demonstrated in animal studies and it has been proved safest among all opioids [14,15].

Yaksh et al. [16] in 1988, found that intrathecal administration of opioids can produce profound segmental analgesia without causing significant alteration of motor or sensory function or subjective effects.

The synergistic effect of opioid combined with local anaesthetic can be explained by virtue of their different mechanism of action. Intrathecal opioids inhibit nociceptive afferent synaptic transmission via Aδ and C fibers by opening presynaptic K^+ channels to inhibit transmitter release and thus reduce calcium influx. There is also a direct postsynaptic effect with hyperpolarization and reduced neuronal activity evoked by glutamate. Local anaesthetic, bupivacaine, works primarily by causing blockade of voltage-gated Na^+ channels in the axonal membrane and, possibly, a further effect on presynaptic inhibition of Ca^{2+} channels.

The results of our study are consistent with experimental evidence of synergistic interaction between spinal opioids and local anaesthetics, which are characterized by enhanced somatic analgesia without effect on the degree or level of the local anaesthetic induced sympathetic or motor blockade [8,17,18,19].

Bendavid B et al. [8] concluded that addition of 10µg fentanyl to spinal anaesthesia with diluted small dose bupivacaine intensifies the sensory blockade and increases the duration of sensory block whereas small dose bupivacaine alone is inadequate for ambulatory arthroscopy.

Chu et al. [20] found that 12.5µg or 15µg of fentanyl added to spinal bupivacaine provided analgesia superior to that when 7.5µg or 10µg was added.

Justins et al. [21] suggested that 80µg fentanyl added to 3ml of 0.5% bupivacaine provided faster onset and longer duration of analgesia than a similar volume and concentration of bupivacaine with saline. The association between bupivacaine or

lignocaine and sufentanil (5-7.5µg) or fentanyl (20-30µg) produces a faster blockade and better intraoperative and immediate postoperative analgesia with no increase in the degree of motor blockade or time until discharge.

Celeski et al. [22] demonstrated that there is no real advantage of using doses of intrathecal fentanyl greater than 25µg, in quality and duration of effective labor analgesia.

Reuben SS et al. [23] suggested that 40µg intrathecal fentanyl provides satisfactory analgesia for approximately 5 hours in an elderly patient population, with a low incidence of side effects. In view of above findings, the dose of fentanyl 25µg had been chosen in our study to compare the quantity of dose and its effects on quality and duration of analgesia.

This study showed that addition of 25µg fentanyl as an adjuvant to bupivacaine in subarachnoid block provided earlier onset and peak with prolonged duration of sensory blockade, as compared to control group (plain bupivacaine alone) along with effective postoperative analgesia up to 6 hours.

Belzerena Sergio [24] concluded that time taken to regression below T_{12} dermatome was longer in treated group and increased with increasing dose of fentanyl.

Shende D et al. [25] found in their study that sensory block to T_4 was achieved after 6.5min in those who received fentanyl compared to 8min in the control group. Similar results were found with Dahlgren et al. [26] and Srivastava U et al. [27].

In this study, the mean time to onset, peak and duration of motor blockade were comparable clinically in both the groups which is consistent with previous studies [8,16,18].

Fentanyl provided prolonged duration of analgesia as compared to control group in our study. Kim et al. [28] reported the duration of analgesia of approximately 7 hours after the use of 4mg bupivacaine with 25µg fentanyl for TURP. Earlier studies report the duration of analgesia with intrathecal fentanyl ranging from one to four hours [29].

In our study, decreased pain scores and reduced analgesic requirement in the postoperative period was observed in group F. Results show that 98% participants in group C required three rescue analgesic doses while 96% participants in group F required two rescue analgesic doses in 24 hours postoperatively.

Shende D et al. [25] assessed intra operative comfort score using Visual Analog Scale. As fentanyl is more efficient in abolishing visceral pain providing better quality of surgical analgesia, good hemodynamic stability and fewer side effects; we observed improved quality of intra operative surgical anaesthesia in fentanyl group in our study.

Bogra J et al. [3] and Hunt CO et al. [5] found in their studies that duration of analgesia was prolonged and less analgesic requirement was needed in early postoperative period. All these results were consistent with our study.

Heart rate and mean arterial blood pressure were decreased from the baseline in both the groups but there was no statistical difference between the two groups. So, fentanyl provides stable haemodynamics. Side effects observed in our study were nausea, vomiting, hypotension, bradycardia and shivering. The total number of participants who experienced side effects were significantly less in group F. Nine participants (18%) in the group C and three participants (6%) in the group F had hypotension in our study, requiring treatment with intravenous Inj. Mephentermine (3mg) in addition to crystalloid bolus. Neuraxial administration of opioids has been reported to be associated with hypotension [14].

Two participants (4%) in group C experienced nausea and vomiting as compared to group F, which was statistically not significant. The decreased incidence of emetic effects after supplementation of spinal anaesthesia with intrathecal fentanyl in our study has also been reported by other investigators [63]. In present study where 25µg fentanyl was used, no participant in either group experienced respiratory depression.

Reuben SS et al. [23] and Varrasi G et al. [30] found that although no patient developed respiratory depression, respiratory rate changes increased with the dose of fentanyl and they suggested that larger doses probably will be associated with respiratory depression. Late rostral spread with small dose intrathecal fentanyl is less and studied by Neil Roy et al. [31], Echevarriaet al. [32], Singh H et al. [33], Dalhgren G et al. [26] and Olofssonet al. [34] and they concluded that 25µg fentanyl is the safest dose. The mean time for spontaneous voiding of urine was comparable among both the groups. Previous studies have reported that intrathecal bupivacaine is associated with a clinically significant disturbance of bladder function and spontaneous voiding may not be expected until the sensory blockade has regressed to the S_3 level [35].

Conclusion

From present study, it is concluded that addition of 25µg Fentanyl as an adjuvant with 0.5% hyperbaric Bupivacaine in subarachnoid block for lower limb orthopaedic surgery, has faster onset and prolongs sensory block without influencing motor blockade; also improves postoperative analgesia with less requirement of rescue analgesic dose, and with minimal side effects.

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