

Intrathecal buprenorphine versus fentanyl as adjuvant to 0.75% ropivacaine in lower limb surgeries

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Abstract

Background and Aims: This study aims to compare the anesthesia characteristics between buprenorphine and fentanyl when added as an adjuvant to intrathecal ropivacaine in an attempt to prolong the duration of spinal anesthesia.

Material and Methods: The present prospective double-blind study was undertaken on ninety American Society of Anesthesiologist I and II patients between 18 and 60 years of age undergoing subarachnoid block for lower limb surgery. Group I ($n = 30$) patients were administered 3 ml of intrathecal solution (2.8 ml of 0.75% ropivacaine + 0.2 ml of isotonic sodium chloride), while Groups II and III patients ($n = 30$ each) received 2.8 ml 0.75% ropivacaine + 0.2 ml buprenorphine (60 μg) and 2.8 ml 0.75% ropivacaine + 0.2 ml fentanyl (10 μg), respectively. Following parameters were observed: Onset times and duration of sensory and motor block, time to first analgesic use, total dose of rescue analgesia, intra- and post-operative pain scores based on visual analog scale, sedation scores, hemodynamic parameters, and side effects if any. Data were analyzed by appropriate statistical tests and $P < 0.05$ were considered significant.

Results: Time to onset of sensory and motor block in all the three groups was comparable. However, duration of sensory block was significantly prolonged in Groups II and III in comparison to Group I ($P < 0.05$) and it was the longest in Group II ($P < 0.05$). The duration of motor blockade was similar in all the three groups. The time to first analgesic dose was also significantly prolonged in Groups II and III as compared to Group I ($P < 0.05$) but was comparable between Groups II and III. Intra- and post-operative hemodynamic parameters, as well as side effects, were comparable.

Conclusion: Addition of buprenorphine and fentanyl as adjuvants to intrathecal 0.75% ropivacaine prolongs postoperative pain relief without causing any increase in the duration of motor blockade but buprenorphine is better as compared to fentanyl in prolonging the duration of sensory block and achieving a better outcome in terms of pain relief.

Key words: Adjuvants, buprenorphine, fentanyl, intrathecal, ropivacaine

Introduction

Though subarachnoid block is widely used for lower limb surgeries, it has practical limitations in prolonged surgeries. Weaning of the effects of subarachnoid block is very embarrassing for the anesthesiologist, discomforting for the surgical team, and excruciatingly unbearable for the patients. From time to time, various methods including

the addition of adjuvants to local anesthetics (LAs) have been tried but with a varying success. Various drugs such as morphine, pethidine, phenylephrine, neostigmine, ketamine, buprenorphine, fentanyl, and many others have been used, but not a single adjuvant can be considered as an ideal drug for such purpose.^[1-4] Drugs such as fentanyl^[5] and buprenorphine have also been tried as adjuvants to LAs as they are known to prolong the anesthetic effects of LA's. On searching the literature, we did not come across any

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study comparing the effects of buprenorphine and fentanyl with intrathecal ropivacaine. The better adjuvant among these two agents still needs to be explored. Therefore, we designed the present prospective, double-blind, randomized, and placebo-controlled study so as to assess the effectiveness of buprenorphine versus fentanyl when used as adjuvants to intrathecal ropivacaine for prolongation of intra- and post-operative analgesia. The secondary outcomes included any variation in hemodynamic parameters and side effects if any associated with administration of these two drugs when used as intrathecal adjuvant with ropivacaine.

Material and Methods

After approval from the hospital ethical committee, written informed consent was taken from all 90 American Society of Anesthesiologist Physical Status I and II patients, aged between 18 and 60 years undergoing lower limb surgery under intrathecal block. Patients with local sepsis at the site of proposed puncture, any known hypersensitivity to study drug and patients being treated with anticoagulants and central nervous system (CNS) active drugs for any neurological disease were excluded from the study.

Patients were randomly allocated in this double-blind study (using 90 coded slips) into three groups. Considering the results of our pilot study, sample size was estimated on the basis of postoperative analgesia assuming the value of Type I error of 0.05 and a Type II error of 0.1 to detect 30 min difference in postoperative analgesia so as to yield a power of 80%, a sample size of 28 patients was calculated for each group. However, we enrolled 30 patients in each group for better validation of results and elimination of confounding biases.

On shifting the patients to operation theater, a large bore venous cannula was secured, and baseline parameters such as heart rate; noninvasive arterial systolic blood pressure and diastolic blood pressure; and peripheral oxygen saturation were observed and recorded. A senior resident of anesthesiology well experienced in administering subarachnoid block and who was unaware of the study design performed the procedures and carried out all the observations. The drug solution was prepared in two separate syringes by an anesthesia technician who was also unaware of the study design. These syringes were partially covered and coded as per study protocols. After all aseptic preparation, subarachnoid block was given at the L2-3/L3-4 interspace using a Quincke needle (25-gauge) with the patient in lateral position. After confirming free flow of clear cerebrospinal fluid, the study drug was injected and the patient was turned supine. Group I patients were administered 3 ml of intrathecal solution (2.8 ml of 0.75% ropivacaine + 0.2 ml of isotonic sodium

chloride), while Groups II and III patients received 2.8 ml 0.75% ropivacaine + 0.2 ml buprenorphine (60 µg) and 2.8 ml 0.75% ropivacaine + 0.2 ml fentanyl (10 µg), respectively. All the patients received oxygen 3-4 L/min through a facemask during perioperative period. The following parameters were observed and recorded. Onset of sensory block was taken as the time from injection of the study drug in the subarachnoid space until the time when maximum sensory level was achieved. The sensory blockade was assessed with bilateral pin prick method. The highest dermatome showing sensory analgesia was taken as the upper segmental level of block when it remained same even after 5 min. Total duration of sensory block was taken as an interval from intrathecal administration of the study drug to regression of sensory block to S-1 level.

The degree of motor block was assessed by the modified Bromage Scoring System. Motor blockade was assessed every 5 min until maximum motor block was achieved and then every 30 min until the return of normal motor function. The time to maximum motor block and complete recovery were also observed and recorded.

Postoperatively, pain was assessed using visual analog scale (VAS) every 15 min in postanesthesia care unit during first 2 h and then regularly at an interval of 4 h till the next 24 h in the ward. Whenever VAS score reached >4, rescue analgesia was given in the form of intramuscular diclofenac (75 mg). Time to the first dose of diclofenac and the total dose required for postoperative analgesia during first 24 h was observed and recorded. Occurrence of any side effects including hypotension, bradycardia, sedation, nausea, vomiting, respiratory depression, pruritis, and dry mouth were observed, recorded and appropriately treated.

After completion of the study, the results were compiled and statistically analyzed using Chi-square test for categorical data and the intergroup comparison was analyzed using ANOVA with *post hoc* significance for validation of the results. SPSS for Windows (SPSS Inc., Chicago, IL, USA) version 16, was used for statistical analysis. $P < 0.05$ was considered as significant.

Results

The demographic data were comparable in the three groups [Table 1]. The mean duration of sensory blockade was significantly higher in patients receiving 0.75% ropivacaine with buprenorphine and 0.75% ropivacaine with fentanyl when compared with 0.75% ropivacaine alone [Table 2] ($P < 0.001$). The duration of analgesia was significantly longer in Groups II and III as compared to Group I ($P < 0.001$) [Table 2]. However, the time to first rescue analgesic dose

when compared statistically between Groups II and III was nonsignificant [Table 2]. The total doses of rescue analgesia required were significantly less in Groups II and III when compared to Group I ($P < 0.001$) [Table 2]. However, there was no statistically significant difference in the doses of rescue analgesia in Groups II and III [Table 2]. Motor block characteristics followed a similar pattern as sensory block parameters. The time to establishment of motor blockade to Bromage 3 was earliest in Group II as compared to Groups III and I. Similarly, the fading of motor blockade to Bromage 0 was earliest in Group I and longest in Group II which was significant statistically on intergroup comparison ($P < 0.001$) [Table 3]. There was no significant difference during the intraoperative as well as postoperative period concerning any side effects such as hypotension, bradycardia, severe sedation, shivering, pruritis, dizziness, urinary retention, nausea, and vomiting among the patients of all the three groups [Table 4].

Discussion

The quest for safer anesthesia procedure with reduction of LA dose by addition of adjuvants seems to be never ending. The results of current study have established that the addition of buprenorphine and fentanyl to this newer LA ropivacaine

produced better anesthetic and analgesic effects with minimal side effects when compared to administration of ropivacaine alone for lower limb surgeries.

Ropivacaine, a newer amino-amide LA agent is similar to bupivacaine in chemical structure, but 30-40% less potent than bupivacaine and is found to be safe, having shorter duration of action than bupivacaine, and lesser incidence of transient neurological symptoms.^[6] Ropivacaine is a pure S (-) enantiomer structurally related to bupivacaine and thereby less cardiovascular and CNS toxic.^[7] These properties of ropivacaine encouraged us to undertake this study.

Fentanyl is a synthetic opioid and is a strong agonist at μ receptors. As off-label use, it is preferred because of its rapid onset and short duration of action with lesser incidence of respiratory depression when used as an adjuvant in spinal anesthesia.^[8]

Buprenorphine is an opioid of the phenanthrene morphine class with extremely high binding affinity at the μ - and kappa receptor. It has partial agonist activity at the μ - and kappa opioid receptor, partial or full agonist activity at the opioid receptor-like 1/nociception and delta opioid receptor and

Table 1: Demographic data

Variables	Group I	Group II	Group III
Age (years)	36.17±13.83	40.67±12.67	36±12.72
Sex (male/female)	19/11	19/11	21/9
ASA physical status (I/II)	22/8	23/7	23/7
Weight (kg)	66.70±7.491	69.60±8.444	68.95±6.219
Height (cm)	157.50±2.819	158.55±3.379	157.35±4.017
Duration of surgery (min)	79.25±15.600	82.75±10.062	81.00±15.694

Data: Mean ± Standard deviation or number of patients, ASA = American Society of Anesthesiologist

Table 2: Sensory blockade characteristics

Sensory blockade characteristics	Group I	Group II	Group III	Group I versus Group II	Group I versus Group III	Group II versus Group III
Total duration of sensory blockade (min)	161.80±19.34	215.8±24.36	196.00±29.48	<0.000	<0.000	<0.009
Duration of analgesia/time to first rescue analgesic (h)	3.50±1.102	7.44±1.69	5.68±1.19	S	S	S
Number of rescue analgesic doses	3.00±0.746	1.28±0.678	1.72±0.678	<0.000	<0.009	>00.56
Total analgesic dosage (mg)	175.00±74.56	105.00±37.370	112.50±38.141	<0.000	<0.001	>0.45

Data: Mean ± SD, S = Significant, SD = Standard deviation

Table 3: Characteristics of motor blockade

Motor block characteristics				Intergroup significance		
	Group I	Group II	Group III	I-II	I-III	II-II
Time to reach Bromage 3 (min)	3.30±1.031	2.75±1.020	3.10±0.852	NS	NS	NS
Regression to Bromage scale 0						
Time (min)	243.8±22.0	387.0±39.4	305.4±35.8	S	S	S

Data: Mean ± SD, NS = Nonsignificant ($P > 0.05$). SD = Standard deviation, S = Significant

Table 4: Incidence of adverse effects in all the three groups

Adverse effects	Number of patients			Statistical analysis
	Group I	Group II	Group III	
Hypotension	3	4	1	NS
Bradycardia	2	2	0	NS
Sedation	0	6	7	S
Dry mouth	0	2	0	NS
Others (shivering)	1	0	0	NS
Urinary retention	1	0	0	NS
Nausea	0	0	0	—
Vomiting	0	0	0	—
Respiratory depression	0	0	0	—
Pruritis	0	0	0	—

NS = Nonsignificant ($P > 0.05$), S = Significant ($P < 0.05$)

competitive antagonist activity at the κ -opioid receptor. These multifaceted properties of buprenorphine formed the basis for comparison with the traditionally established fentanyl for use as an adjuvant in subarachnoid block with ropivacaine.

From the results of previous studies which added 50 μg buprenorphine intrathecally to 0.5% bupivacaine showed significantly prolonged sensory recovery time, the dose equivalence of buprenorphine to fentanyl was estimated.^[9]

The finding appropriate dose of buprenorphine equivalent to fentanyl was further augmented by the results of more studies in which the researchers used different doses of buprenorphine but with varying results. There was prolongation of effects up to 8 h. with 30 μg and to 12 h. with 45 μg . However, increasing the dose up to 60 μg led to a prolonged duration of 8 h only.^[10,11] This could probably be due to ceiling effect of buprenorphine. However, the variable results were observed by the study of Lalla,^[12] in which the mean analgesia was 11 h for 44 μg intrathecal buprenorphine and lignocaine. Since we used ropivacaine, which is considered to be 30-40% less potent than bupivacaine when used as regional anesthetic, we chose a higher dose of buprenorphine (60 μg) to augment the anesthetic effects of ropivacaine. Our results of sensory duration of approximately 8 h with addition of buprenorphine to ropivacaine corroborate the clinical effects of this mixture. However, the motor blockade characteristics of our study are comparable to the results of all these studies. These results can be termed more significant in the light of facts that ropivacaine is a safer option than bupivacaine and lignocaine and at the same time achieving similar clinical effects as have been demonstrated by earlier studies.^[10-12] Chung *et al.* showed that adding a small dose of fentanyl (10 μg) to 0.5% hyperbaric ropivacaine increased the duration of effective analgesia to a mean duration of 207

min.^[13] Whereas Biswas *et al.* found in their study that addition of 12.5 μg fentanyl to hyperbaric bupivacaine 0.5% increased the duration from time to subarachnoid injection to administration of first rescue analgesia to a mean of 248 min.^[14] Similar results have been shown in study conducted by Thomas *et al.* and Chan *et al.*^[15,16] We also used fentanyl in dose of 10 μg , and our results are almost similar to all the above studies.

Buprenorphine and fentanyl as adjuvant to intrathecal ropivacaine has been evaluated in animal models, and only one study in humans compared it's use in urological surgeries in elderly patients.^[17] Khan and Hamdani in their study used 0.75% hyperbaric bupivacaine and added a dose of buprenorphine 30 μg while fentanyl was used in the dose of 10 μg in elderly patients undergoing urological surgery. The time of onset of sensory anesthesia was lesser in the fentanyl group, but the duration of sensory anesthesia and motor blockade was prolonged in buprenorphine group. The results pertaining to duration of sensory and motor blockade are almost similar to our study, but the early onset of sensory anesthesia in fentanyl group can be explained on the basis of a lower dose of buprenorphine in their study. Moreover, their study had higher incidence of nausea and vomiting which is contradictory findings to our study. This could be related to higher dose of LA in their study as well as elderly population.

Conclusion

Fentanyl 10 μg and buprenorphine 60 μg when used as adjuvants to 0.75% isobaric ropivacaine intrathecally produces significantly longer duration and better quality of postoperative analgesia than ropivacaine alone. However, on comparing the two drugs buprenorphine appears to be superior in prolonging the duration of sensory blockade and has better outcome in terms of pain relief postoperatively.

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Conflicts of interest

There are no conflicts of interest.

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Conference Calendar April 2016

Name of conference	Dates	Venue	Name of organising Secretary with contact details
ISACON CENTRAL – 2016 Annual Central Zone Conference of ISA	October 15 th -16 th 2016	HIMS, Jolly Grant, Dehradun	Org Secretary: Dr. J. P. Sharma Mobile No.: +91-9411718466 Email: jpshims@gmail.com
ISACON MAHARASHTRA – 2016 (MISACON 2016) Bi Annual State Conference of ISA 2016 MAHARASHTRA State Chapter	October 15 th -16 th	M G M Medical College Aurangabad	Org Secretary: Dr. Balaji Asegaonkar Mobile No.: +91-9325078733 Email: b_asegaonkar@yahoo.com/misacon2016@yahoo.com Website: pwww.misacon2016.com
ISACON NORTH EAST 2016 4 th North East Zone Conference of ISA	October 22 nd -23 rd , 2016	Assam Medical College, Dibrugarh	Org Secretary: Dr. Dhruvajyoti Borgohain Mobile No.: +91-9435031489 Email: dhruva_borgohain@yahoo.co.in
American Society of Anesthesiologists (ASA) Annual Meeting ANESTHESIOLOGY® 2016	October 22 nd -26 th , 2016	McCormick Place Convention Center Chicago, Illinois 60616, United States	Email: annmtg@asahq.org URL: https://www.asahq.org/Annual%20Meeting/?utm_source=asahq&utm_medium=landing-page&utm_campaign=Annual-Meeting
Difficult Airway Society Annual Meeting 2016 (DAS 2016)	November 16-18 th , 2016	Riviera International Centre, Torquay	https://www.das.uk.com/meetings
64 th Annual National Conference of Indian Society of Anaesthesiologists ISACON 2016	November, 25 th -29 th , 2016	Punjab Agricultural University Campus, Ludhiana	Dr. Sunil Katyal, Organizing Secretary 19-H, Ashok Vihar, Rishi Nagar, Ludhiana -141001, Punjab, India Mobile: +91 9814030552, Email ID: katyalsunilmd@gmail.com Web: www.isacon2016.com
Anaesthesiology 69 th Postgraduate Assembly 2016 (NYSSA 2016)	December 9 th -13 th , 2016	Marriott Marquis, New York, USA	http://pganyc.weebly.com/ THE NEW YORK STATE SOCIETY OF ANESTHESIOLOGISTS, INC. 110 East 40th Street, Suite 300, New York, NY 10016 USA Telephone: 1-212-867-7140 Fax: 1-212-867-7153 International: +00 followed by number HQ@nyssa-pga.org