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Original Research Article

Comparison of Effects of Neostigmine and Fentanyl as Adjuvants to Hyperbaric Bupivacaine (0.5%) in Spinal Anaesthesia for Lower Abdominal and Lower Extremity Surgery

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Abstract:

Introduction: Augustus Bier performed the first spinal anaesthesia using cocaine in 1889. Bupivacaine 0.5% heavy was the only drug used for spinal anaesthesia after the discontinuation of lidocaine's intrathecal use. Bradycardia and hypotension are the hemodynamic side effects of use of high dose of local anaesthetic agent to prolong the duration of analgesia. Neostigmine is a cholinesterase inhibitor which leads to an increase of the acetylcholine concentration. The present study was undertaken to compare the efficacy of fentanyl and neostigmine as adjuvants to hyperbaric bupivacaine (0.5%) in subarachnoid block for lower abdominal and lower extremity surgery.

Materials and Method: The present study was carried out as Analytical comparative study. The study was carried out at Department of Anaesthesiology, Era's Lucknow Medical College, Lucknow. Era's Lucknow Medical College is a tertiary care centre with state-of-the-art infrastructure catering primarily to socio-economically underprivileged suburban and rural population of Lucknow area for eighteen months (November 2017 to June 2019).

After obtaining approval from the Institutional Ethical Committee, 96 ASA I & II patients fulfilling the inclusion criteria were included in the study. Thereafter, these patients were randomly allocated into three equal groups of 32 patients each with the help of Computer Generated Randomization as under:

Group I (Experimental Group): 32 patients received Injection Fentanyl (25 mcg) in combination with hyperbaric Bupivacaine (0.5%) spinal anaesthesia.

Group II (Experimental Group): 32 patients received Injection Neostigmine (25 mcg) in combination with hyperbaric Bupivacaine (0.5%) in spinal anaesthesia.

Group III (Control Group): 32 patients received hyperbaric Bupivacaine (0.5%) in spinal anaesthesia in combination with 0.5 ml normal saline.

Results: Out of 96 patients, 32 patients received Injection Fentanyl (25 mcg) in combination with hyperbaric Bupivacaine (0.5%) spinal anaesthesia were classified as Group I, another 32 patients received Injection Neostigmine (25 mcg) in combination with hyperbaric Bupivacaine (0.5%) in spinal anaesthesia were classified as Group II and rest 32 patients received hyperbaric Bupivacaine (0.5%) in spinal anaesthesia were classified as Group III. In present study, following induction, mean pulse rate was found to be significantly higher in neostigmine group as compared to the other two groups for most of the intraoperative period. Bradycardia rates were higher in fentanyl supplemented and bupivacaine alone groups as compared to neostigmine supplemented group. The better efficacy of neostigmine in present study could be owing to a possible sedative effect of neostigmine that reduces the perception of pain. In a previous study, Kaya *et al*.[1] found that in patients posted for elective cesarean study under combined spinal-epidural using epidural neostigmine showed that total duration of post-operative analgesia and global pain satisfaction scores were reduced in the neostigmine group.

In present study, number of patients requiring rescue analgesia was significantly lower in bupivacaine + neostigmine (12.5%) as compared to bupivacaine + fentanyl (43.8%) and bupivacaine alone (93.1%) groups, thus showing that addition of both the drugs reduced the rescue analgesic need, however, addition of neostigmine was more effective as compared to fentanyl.

Conclusion: The present study was conducted in the Department of Anaesthesiology, Era's Lucknow to compare the effect of Neostigmine and Fentanyl as adjuvant to hyperbaric bupivacaine in spinal anaesthesia for lower abdominal and lower extremity surgery. Out of cases scheduled for lower abdominal or lower extremity surgery 96 ASA Grade I & II cases fulfilling the inclusion criteria were enrolled and randomly divided in three groups, all the cases were given hyperbaric bupivacaine (0.5%), of these 32 cases were given fentanyl (25 mcg) and another 32 cases were given neostigmine (25 mcg) as adjuvant, rest 32 cases were not given any adjuvant.
Pulse rate of cases of neostigmine adjuvant group was found to be significantly higher than that of fentanyl adjuvant and no-adjuvant group at all the periods of observation while that of fentanyl adjuvant and non-adjuvant groups was comparable. During first 10 minutes, systolic BP of neostigmine adjuvant group was found to be significantly higher than that of fentanyl adjuvant and non-adjuvant groups. Bradycardia was observed in higher proportion of non-adjuvant group, followed by fentanyl adjuvant and least in neostigmine adjuvant group (46.9%, 25.0% & 12.5%).

Key words Neostigmine, hypercoagulable state, hyperbaric bupivacaine, cholinesterase inhibitor.

Introduction

Augustus Bier performed the first spinal anaesthesia using cocaine in 1889.[1] By injecting a little volume of hyperbaric local anaesthetic solution into the subarachnoid fluid through a lumbar puncture conduction block of nerve roots is achieved. It not only produces complete analgesia with profound muscle relaxation, quiet respiration and contracted small bowel [2] but also has advantages of decreased intra-operative blood loss, post-surgery early return of gastrointestinal function, suppression of neuroendocrine response to surgery, better analgesia than parenteral opioids in the postoperative period, reduction in perioperative morbidity and mortality among high-risk patients, reduction in hypercoagulable state associated with surgery[3].

Bupivacaine 0.5% heavy was the only drug used for spinal anaesthesia after the discontinuation of lidocaine's intrathecal use. Bradycardia and hypotension are the hemodynamic side effects of use of high dose of local anaesthetic agent to prolong the duration of analgesia [**Error! Bookmark not defined.**].

Various adjuvants like ketamine, clonidine, adrenaline, midazolam, epinephrine, neostigmine and opioids (morphine & fentanyl) have been used with intrathecal bupivacaine. [2,5,6,7,8,9,10].

Neostigmine is a cholinesterase inhibitor which leads to an increase of the acetylcholine concentration. It has been frequently added to local anaesthetics for caudal epidural analgesia. [11,12] As an adjuvant neostigmine can effectively prolong the duration of subarachnoid block and could provide better hemodynamic stability during spinal analgesia but incidence of motor weakness, nausea and vomiting might increase. [13,14]

Morphine and fentanyl are the most preferred opioids used as adjuvants in regional anaesthesia to prolong postoperative analgesic-sparing sympathetic action. Fentanyl citrate a μ_1- and μ_2-receptor agonist is the single most commonly used opioid in regional anaesthesia. It is a highly potent drug because of its high lipophilicity and is preferred as an adjuvant in spinal anaesthesia because of its rapid onset and short duration of action with minimal cephalic spread. [14,15]

The present study was undertaken to compare the efficacy of fentanyl and neostigmine as adjuvants to hyperbaric bupivacaine (0.5%) in subarachnoid block for lower abdominal and lower extremity surgery.

Aim and Objectives

Comparison of effects of Neostigmine and Fentanyl as adjuvants to Hyperbaric Bupivacaine (0.5%) in spinal anaesthesia for lower abdominal and lower extremity surgery.

Objectives

1. To evaluate the Onset and duration of sensory and motor blockade
2. To evaluate the hemodynamic variables (heart rate, blood pressure and oxygen saturation).
3. To evaluate the time of use of first rescue analgesia.
4. To identify and note the side effects and complications, if any due to addition of adjuvants namely Neostigmine and Fentanyl.

Materials and Method

Study Design: The present study was carried out as Analytical comparative study.

Settings: The study was carried out at Department of Anaesthesiology, Era's Lucknow Medical College, Lucknow. Era's Lucknow Medical College is a tertiary care centre with state-of-the-art infrastructure catering primarily to socio-economically underprivileged suburban and rural population of Lucknow area.

Duration of Study: Eighteen months (November 2017 to June 2019).

Sampling Frame: Patients scheduled for lower abdominal or lower limb surgery at Department of Surgery were included in the study. The sampling frame of the study was bound by the following inclusion and exclusion criteria:

Inclusion Criteria

- ASA Grade I & II.
- Age group 20-70 years.

Exclusion Criteria

- Refusal of patient for enrolment under study.
- Patients with history of respiratory, cardiac or hepatorenal disorder.
- Patients allergic to drugs or having severe neurological deficit.
- Patients with history of chronic alcoholism or drug abuse
- Patients on medication of adrenoreceptor agonist, digoxin, anticonvulsants or psychotropic substance.
- Patients with bradycardia, hypertension
- Patients in whom the study drugs are contraindicated.
- Clotting and bleeding disorder.

Ethical Committee Clearance

- Clearance for carrying out the study was obtained from the Institutional Ethical Committee, Era's Lucknow Medical College, Lucknow. An informed consent was obtained from all the patients (Appendix).

Sample Size Calculation

Sample size was calculated at the Department of Social & Preventive Medicine, Era's LucknowMedical College & Hospital, Lucknow based on maximum variation in VAS score among experimental and control group using the formula:

$n = (Z_\alpha+Z_\beta)^2 (\sigma1^2 +\sigma2^2) / d_{max}^2$

When $\sigma1 = 0.6$ (the maximum SD of control group), $\sigma2 = 0.8$ (the maximum SD of experimental group), and $d= \mu(\sigma1, \sigma2)$ the difference considered to be clinically significant

Type I α error = 5%

type II β error = 20% for detecting results with 80% power of study

data loss = 10%

The sample size came out to be n= 32 in each group

Methodology: After obtaining approval from the Institutional Ethical Committee, 96 ASA I & II .Patients fulfilling the inclusion criteria were included in the study. Thereafter, these patients were randomly allocated into three equal groups of 32 patients each with the help of computer generated Randomization as under:

Group I (Experimental Group): 32 patients received Injection Fentanyl (25 mcg) in combination with hyperbaric Bupivacaine (0.5%) spinal anaesthesia.

Group II (Experimental Group): 32 patients received Injection Neostigmine (25 mcg) in combination with hyperbaric Bupivacaine (0.5%) in spinal anaesthesia.

Group III (Control Group): 32 patients received hyperbaric Bupivacaine (0.5%) in spinal anaesthesia in combination with 0.5 ml normal saline.

All patients were assessed the night before surgery and standard preoperative advice was ensured. Patients were kept nil orally from midnight before surgery. Written and informed consent was obtained from the patient, for the study as well as for anaesthesia.

After shifting the patient to the operation theatre non-invasive blood pressure cuff, pulse oximeter probe and electrocardiographic leads and temperature probe was attached.

Under the strict aseptic precautions, a 25 G spinal needle was introduced between L_3-L_4 space intrathecally. After confirmation of free flow of CSF, 0.5% heavy bupivacaine with the study of the drug was administered.

Sensory blockade was assessed using pinprick and cold sensation using alcohol swabs in mid-axillary line bilaterally. Regression time to reach sensory level upto T12 was recorded.

Motor block was assessed immediately after sensory block assessment using Modified Bromage score.

Adverse effects Sedation, Nausea/vomiting, Respiratory depression and Urinary retention were noted.

Modified Bromage Scor

Grade	Criteria
Grade 0	Able to move the hip, knee and ankle.
Grade 1	Unable to move the hip but able to move knee and ankle.
Grade 2	Unable to move the hip and knee but able to move ankle
Grade 3	Unable to move the hip, knee and ankle.

Time taken to reach Bromage score 3 was calculated as onset of motor blocked and time taken to reach Bromage score 0 was duration of motor blockade.

Sensory and motor block was assessed at every 2 min for first 10 min and thereafter every 20 min during surgery and post-operatively till the duration of block.

The highest sensory block level and recovery time of both sensory and motor block was recorded. Hemodynamic variables were observed immediately after start of surgery (Baseline) and thereafter at an interval of 2 min upto 10 min, thereafter at 20 min interval upto 170 min.

Duration of complete analgesia was taken as the time until VAS pain scores remained "0" following intrathecal injection of the study drug. Duration of effective analgesia was the time until VAS pain scores were ≥3 or when the patient first requested for supplemental analgesia, whichever appeared first. Rescue analgesia was achieved with Inj. diclofenac 1.5 mg/kg IM or injection paracetamol 15 mg/kg IV. The total number of rescue analgesics administered in 24 h were noted. Averaged 24 h VAS score was obtained as a measurement of total pain experienced by the patient. Observations were recorded on a Case Record Form for each patient (Appendix).

Statistical Tools Employed

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The values were represented in Number (%) and Mean ±SD.

The following Statistical formulas were used:

Mean: To obtain the mean, the individual observations were first added together and then divided by thnumber of observation. The operation of adding together or summation is denoted by the sign Σ.

The individual observation is denoted by the sign X, number of observation denoted by n, and the mean by $\overline{X}$.

$$\overline{X} = \frac{\Sigma X}{No.of\ observations\,(n)}$$

Where O = Observed frequency

E = Expected frequency

Analysis of Variance: Analysis of Variance (ANOVA): The ANOVA test was used to compare the within group and between group variances amongst the study groups *i.e.* the three different sealers. Analysis of variance of these three sealers at a particular time interval revealed the differences amongst them. ANOVA provided "F" ratio, where a higher "F" value depicted a higher inter-group difference.

$$F = \frac{\text{Mean of Sum of Between Group Differences}}{\text{Mean of Sum of within Group Differences}}$$

2. **Standard Deviation**: It is denoted by the Greek letter σ. If a sample is more than 30 then.

$$\sigma = \sqrt{\frac{\Sigma (X - \overline{X})^2}{n}}$$

When sample in less than 30 then.

$$\sigma = \sqrt{\frac{\Sigma (X - \overline{X})^2}{n-1}}$$

3. **Chi square test:**

$$\chi^2 = \sum \frac{(O-E)^2}{E}$$

Differences	Sum of Squares	df	Mean Square	F
Between Groups	A	N_1	$X=A/N_1$	X/Y
Within Groups	B	N_2	$Y=B/N_2$	

5. **Paired "t" test**: To compare the change in a parameter at two different time intervals paired "t" test was used.

$$t = \frac{d_{av}}{SD/\sqrt{N}}$$

where:
d_{av} is the mean difference, i.e. the sum of the differences of all the datapoints (set 1 point 1 - set 2 point 2, ...) divided by the number of pairs **SD** is the standard deviation of the differences between all the pairs **N** is the number of pairs.

6. **Kruskal Wallis H Test**:

$$K = (N-1)\frac{\sum_{i=1}^{g} n_i(\bar{r}_{i\cdot} - \bar{r})^2}{\sum_{i=1}^{g}\sum_{j=1}^{n_i}(r_{ij} - \bar{r})^2},$$

Where

- n_i is the number of observations in group i
- r_{ij} is the rank (among all observations) of observation j from group i
- N is the total number of observations across all groups

$$\bar{r}_{i\cdot} = \frac{\sum_{j=1}^{n_i} r_{ij}}{n_i},$$

$\bar{r} = \frac{1}{2}(N+1)$ is the average of all the r_{ij}.

7. **Mann-Whitney U test**: The value of U in this test is calculated in following manner:

$$U_a = n_a n_b + \frac{n_a(n_a+1)}{2} - \sum R_a$$

and

$$U_b = n_a n_b + \frac{n_b(n_b+1)}{2} - \sum R_b$$

8. **The Wilcoxon signed rank statistic** W+ is computed by ordering the absolute values |Z1|, ..., |Zn|, the rank of each ordered |Zi| is given a rank of Ri. Denote where I(.) is an indicator function. The Wilcoxon signed ranked statistic W+ is defined as

$$W_+ = \sum_{i=1}^{n} \phi_i R_i$$

$$Z = \frac{(W - \mu_W) \pm 5}{\sigma_W}$$

$$\sigma_W = \sqrt{\frac{[N(N+1)(2N+1)]}{6}}$$

where μ_w is the mean of population.

9. Level of significance: "p" is level of significance

p >0.05 Not significant

p <0.05 Significant

p <0.01 Highly significant

p <0.001 Very highly significant.

Results

Table 1: Groupwise Distribution of Study Population

SN	Group	Description	No. of patients	Percentage
1-	Group I	Inj. Fentanyl (25 mcg) with hyperbaric Bupivacaine (0.5%)	32	33.3
2-	Group II	Inj. Neostigmine (25 mcg) with hyperbaric Bupivacaine (0.5%)	32	33.3
3-	Group III (Control)	Hyperbaric Bupivacaine (0.5%)	32	33.3

Out of 96 patients, 32 patients received Injection Fentanyl (25 mcg) in combination with hyperbaric Bupivacaine (0.5%) spinal anaesthesia were classified as Group I, another 32 patients received Injection Neostigmine (25 mcg) in combination with hyperbaric Bupivacaine (0.5%) in spinal anaesthesia were classified as Group II and rest 32 patients received hyperbaric Bupivacaine (0.5%) in spinal anaesthesia were classified as Group III.

Table 2(a): Intergroup Comparison of Pulse rate at different time intervals

Time Interval	Group I (n=32)		Group II (n=32)		Group III (n=32)		ANOVA	
	Mn	SD	Mn	SD	Mn	SD	F	p
BL	80.44	5.13	81.75	2.72	81.19	4.37	0.788	0.458
2m	74.50	6.12	80.25	4.15	75.81	4.32	11.888	<0.001
4m	70.94	5.72	79.88	4.74	72.25	4.70	28.912	<0.001

6m	67.38	5.43	79.94	5.12	68.38	4.53	61.401	<0.001
8m	65.69	4.74	79.50	6.03	65.44	4.69	76.891	<0.001
10m	67.06	7.00	77.75	5.17	67.00	4.87	36.935	<0.001
30m	68.19	7.56	78.00	5.95	66.19	5.71	30.675	<0.001
50m	69.94	6.81	78.63	6.49	65.69	6.84	30.870	<0.001
70m	69.69	6.45	79.13	4.40	66.38	6.45	40.961	<0.001
90m	68.50	7.53	79.75	4.89	67.56	6.30	36.680	<0.001
110m	70.56	5.62	81.06	5.23	68.31	6.53	43.801	<0.001
130m	70.03	5.01	81.00	4.16	68.88	5.25	61.453	<0.001
150m	70.13	5.20	80.75	4.06	71.69	5.21	44.714	<0.001
170m	69.69	4.93	81.19	3.29	75.50	5.90	45.392	<0.001

At all the periods of observations after baseline, pulse rate of patients of Group II was found to be higher as compared to Group I and Group III. Difference in mean Pulse rate among patients of above three groups was found to be statistically significant at all the periods of observation.

Table 2(b): Between Group Comparison of Pulse rate at different time intervals

Time interval	Group I vs. II			Group I vs. III			Group II vs. III		
	Mn diff.	SE	'p'	Mn diff.	SE	'p'	Mn diff.	SE	'p'
BL	-1.31	1.05	0.426	-0.75	1.05	0.755	0.56	1.05	0.854
2m	-5.75	1.24	<0.001	-1.31	1.24	0.540	4.44	1.24	0.002
4m	-8.94	1.27	<0.001	-1.31	1.27	0.557	7.63	1.27	<0.001
6m	-12.56	1.26	<0.001	-1.00	1.26	0.708	11.56	1.26	<0.001
8m	-13.81	1.30	<0.001	0.25	1.30	0.980	14.06	1.30	<0.001
10m	-10.69	1.44	<0.001	0.06	1.44	0.999	10.75	1.44	<0.001
30m	-9.81	1.61	<0.001	2.00	1.61	0.433	11.81	1.61	<0.001
50m	-8.69	1.68	<0.001	4.25	1.68	0.034	12.94	1.68	<0.001
70m	-9.44	1.46	<0.001	3.31	1.46	0.066	12.75	1.46	<0.001
90m	-11.25	1.58	<0.001	0.94	1.58	0.825	12.19	1.58	<0.001
110m	-10.50	1.45	<0.001	2.25	1.45	0.274	12.75	1.45	<0.001
130m	-10.97	1.21	<0.001	1.16	1.21	0.605	12.13	1.21	<0.001
150m	-10.63	1.21	<0.001	-1.56	1.21	0.406	9.06	1.21	<0.001
170m	-11.50	1.21	<0.001	-5.81	1.21	<0.001	5.69	1.21	<0.001

At all the periods of observations, pulse rate of patients of Group II was found to be higher as compared to Group I and Group III, and these differences were found to be statistically significant except at baseline between Group II and Group III. Difference in Pulse rate of patients of Group II and Group III were found to be statistically significant only at 50 m and 170 m.

Table 3a): Intergroup Comparison of Systolic BP at different time intervals

Time Interval	Group I (n=32)		Group II (n=32)		Group III (n=32)		ANOVA	
	Mn	SD	Mn	SD	Mn	SD	F	p
BL	131.81	6.30	132.22	3.96	130.13	5.25	1.426	0.245
2m	122.50	11.06	128.63	4.23	125.06	10.12	3.743	0.027
4m	123.13	10.86	127.25	5.20	121.81	11.54	2.779	0.067
6m	118.13	8.48	124.88	4.71	117.97	10.42	7.363	0.001
8m	120.88	8.23	124.81	5.05	118.78	10.11	4.607	0.012
10m	116.25	10.63	121.31	6.32	116.16	9.47	3.444	0.036
30m	118.63	9.82	120.06	5.89	115.59	8.73	2.410	0.095
50m	120.56	11.55	123.06	6.20	117.22	11.61	2.691	0.073
70m	120.88	10.64	120.38	6.00	117.31	8.95	1.558	0.216
90m	122.63	11.92	120.63	5.98	118.22	9.32	1.766	0.177
110m	119.25	13.18	120.53	6.57	118.25	14.12	0.301	0.740
130m	119.09	12.32	120.31	5.79	120.72	12.51	0.201	0.818
150m	119.44	10.96	120.81	5.88	118.66	11.93	0.385	0.681
170m	121.06	8.09	125.63	9.00	118.75	13.23	3.654	0.030

Difference in systolic BP of patients of above three groups was found to be statistically significant at 2m, 6m, 8m, 10m and 170m. At rest of the periods of observation SBP of patients of above three groups was found to be comparable.

Table 3(b): Between Group Comparison of Systolic BP at different time intervals

Time interval	Group I vs. II			Group I vs. III			Group II vs. III		
	Mn diff.	SE	'p'	Mn diff.	SE	'p'	Mn diff.	SE	'p'
BL	-0.41	1.31	0.949	1.69	1.31	0.408	2.09	1.31	0.254
2m	-6.13	2.25	0.021	-2.56	2.25	0.492	3.56	2.25	0.257
4m	-4.13	2.41	0.206	1.31	2.41	0.849	5.44	2.41	0.067
6m	-6.75	2.06	0.004	0.16	2.06	0.997	6.91	2.06	0.003
8m	-3.94	2.02	0.130	2.09	2.02	0.555	6.03	2.02	0.010
10m	-5.06	2.25	0.068	0.09	2.25	0.999	5.16	2.25	0.062
30m	-1.44	2.08	0.769	3.03	2.08	0.316	4.47	2.08	0.085
50m	-2.50	2.53	0.586	3.34	2.53	0.386	5.84	2.53	0.059
70m	0.50	2.19	0.972	3.56	2.19	0.238	3.06	2.19	0.344
90m	2.00	2.35	0.672	4.41	2.35	0.151	2.41	2.35	0.563
110m	-1.28	2.95	0.901	1.00	2.95	0.938	2.28	2.95	0.720
130m	-1.22	2.67	0.892	-1.63	2.67	0.816	-0.41	2.67	0.987
150m	-1.38	2.49	0.845	0.78	2.49	0.947	2.16	2.49	0.662
170m	-4.56	2.59	0.188	2.31	2.59	0.646	6.88	2.59	0.025

At all the periods of observation except at 70m and 90m SBP of Group II was found to be higher as compared to Group I but difference was found to be significant only at 2m and 6m. SBP of patients of Group I was found to be higher as compared to Group II at all the periods of observation except at 2m and 100m but difference was found to be statistically significant only at baseline. SBP of patients of Group II was found to be higher as compared to Group III at all the periods of observation except at 100m, difference was found to be statistically significant only at baseline, 6m, 8m and 130m.

Table 4(a): Intergroup Comparison of Level of Sensory Block

	Group	T4	T6	T8	T10	T12	KruskallWalis Test
2m	Gp I	0.0	0.0	6.3	50.0	43.8	H=9.399; p=0.009
	Gp II	0.0	0.0	37.5	40.6	21.9	
	Gp III	0.0	0.0	34.4	40.6	25.0	
4m	Gp I	0.0	6.3	40.6	46.9	6.3	H=5.765; p=0.056
	Gp II	0.0	21.9	46.9	25.0	6.3	
	Gp III	0.0	18.8	53.1	25.0	3.1	
6m	Gp I	0.0	75.0	25.0	0.0	0.0	H=0.500; p=0.779
	Gp II	0.0	81.3	18.8	0.0	0.0	
	Gp III	0.0	81.3	18.8	0.0	0.0	
8m	Gp I	0.0	100.0	0.0	0.0	0.0	H=0.000; p=1.000
	Gp II	0.0	100.0	0.0	0.0	0.0	
	Gp III	0.0	100.0	0.0	0.0	0.0	
10m	Gp I	0.0	100.0	0.0	0.0	0.0	H=0.000; p=1.000
	Gp II	0.0	100.0	0.0	0.0	0.0	
	Gp III	0.0	100.0	0.0	0.0	0.0	
30m	Gp I	0.0	100.0	0.0	0.0	0.0	H=0.000; p=1.000
	Gp II	0.0	100.0	0.0	0.0	0.0	
	Gp III	0.0	100.0	0.0	0.0	0.0	
50m	Gp I	0.0	100.0	0.0	0.0	0.0	H=0.000; p=1.000
	Gp II	0.0	100.0	0.0	0.0	0.0	
	Gp III	0.0	100.0	0.0	0.0	0.0	
70m	Gp I	0.0	100.0	0.0	0.0	0.0	H=0.000; p=1.000
	Gp II	0.0	100.0	0.0	0.0	0.0	
	Gp III	0.0	100.0	0.0	0.0	0.0	
90m	Gp I	0.0	100.0	0.0	0.0	0.0	H=0.000; p=1.000
	Gp II	0.0	100.0	0.0	0.0	0.0	

	Gp III	0.0	100.0	0.0	0.0	0.0	
110m	Gp I	0.0	100.0	0.0	0.0	0.0	H=0.000; p=1.000
	Gp II	0.0	100.0	0.0	0.0	0.0	
	Gp III	0.0	100.0	0.0	0.0	0.0	
130m	Gp I	0.0	100.0	0.0	0.0	0.0	H=0.000; p=1.000
	Gp II	0.0	100.0	0.0	0.0	0.0	
	Gp III	0.0	100.0	0.0	0.0	0.0	
150m	Gp I	0.0	100.0	0.0	0.0	0.0	H=0.000; p=1.000
	Gp II	0.0	100.0	0.0	0.0	0.0	
	Gp III	0.0	100.0	0.0	0.0	0.0	
170m	Gp I	0.0	100.0	0.0	0.0	0.0	H=0.000; p=1.000
	Gp II	0.0	100.0	0.0	0.0	0.0	
	Gp III	0.0	100.0	0.0	0.0	0.0	

% Row-wise Significant differences in level of sensory block was found among patients of above three groups at 2m only. Level of sensory block was T6 of all the patients at 10m and all the periods of observation after 10m.

Table 4(b): Between Group Comparison of Level of Sensory Block (Mann-Whitney U test)

Time interval	Group I vs. Group II		Group I vs. Group III		Group II vs. Group III	
	Z	'p'	Z	'p'	Z	'p'
2m	2.821	0.005	2.479	0.013	0.323	0.747
4m	1.954	0.051	2.193	0.028	0.080	0.936
6m	0.600	0.549	0.600	0.549	0.000	1.000
8m	0.000	1.000	0.000	1.000	0.000	1.000
10m	0.000	1.000	0.000	1.000	0.000	1.000
30m	0.000	1.000	0.000	1.000	0.000	1.000
50m	0.000	1.000	0.000	1.000	0.000	1.000
70m	0.000	1.000	0.000	1.000	0.000	1.000
90m	0.000	1.000	0.000	1.000	0.000	1.000
110m	0.000	1.000	0.000	1.000	0.000	1.000
130m	0.000	1.000	0.000	1.000	0.000	1.000
150m	0.000	1.000	0.000	1.000	0.000	1.000
170m	0.000	1.000	0.000	1.000	0.000	1.000

Table 5(a): Intergroup Comparison of Level of Motor Block

	Group	B/S-0	B/S-1	B/S-2	B/S-3	Kruskal Walis Test
2m	Gp I	34.4	65.6	0.0	0.0	H=264; p=0.876
	Gp II	37.5	62.5	0.0	0.0	
	Gp III	40.6	59.4	0.0	0.0	
4m	Gp I	0.0	34.4	65.6	0.0	H=1.461; p=0.482
	Gp II	3.1	34.4	62.5	0.0	
	Gp III	6.3	40.6	53.1	0.0	
6m	Gp I	0.0	0.0	34.4	65.6	H=2.188; p=0.335
	Gp II	0.0	3.1	34.4	62.5	
	Gp III	0.0	6.3	43.8	50.0	
8m	Gp I	0.0	0.0	0.0	100.0	H=5.429; p=0.066
	Gp II	0.0	0.0	3.1	96.9	
	Gp III	0.0	0.0	12.5	87.5	
10m	Gp I	0.0	0.0	0.0	100.0	H=0.000; p=1.000
	Gp II	0.0	0.0	0.0	100.0	
	Gp III	0.0	0.0	0.0	100.0	
30m	Gp I	0.0	0.0	0.0	100.0	H=0.000; p=1.000
	Gp II	0.0	0.0	0.0	100.0	
	Gp III	0.0	0.0	0.0	100.0	
50m	Gp I	0.0	0.0	0.0	100.0	H=0.000; p=1.000
	Gp II	0.0	0.0	0.0	100.0	
	Gp III	0.0	0.0	0.0	100.0	

70m	Gp I	0.0	0.0	0.0	100.0	H=0.000; p=1.000
	Gp II	0.0	0.0	0.0	100.0	
	Gp III	0.0	0.0	0.0	100.0	
90m	Gp I	0.0	0.0	0.0	100.0	H=0.000; p=1.000
	Gp II	0.0	0.0	0.0	100.0	
	Gp III	0.0	0.0	0.0	100.0	
110m	Gp I	0.0	0.0	0.0	100.0	H=0.000; p=1.000
	Gp II	0.0	0.0	0.0	100.0	
	Gp III	0.0	0.0	0.0	100.0	
130m	Gp I	0.0	0.0	0.0	100.0	H=0.000; p=1.000
	Gp II	0.0	0.0	0.0	100.0	
	Gp III	0.0	0.0	0.0	100.0	
150m	Gp I	0.0	0.0	0.0	100.0	H=0.000; p=1.000
	Gp II	0.0	0.0	0.0	100.0	
	Gp III	0.0	0.0	0.0	100.0	
170m	Gp I	0.0	0.0	0.0	100.0	H=0.000; p=1.000
	Gp II	0.0	0.0	0.0	100.0	
	Gp III	0.0	0.0	0.0	100.0	

% Row-wise Motor block of all the groups was found to be comparable at all the periods of observation.

Table 5(b): Between Group Comparison of Level of Motor Block (Mann-Whitney U test)

Time interval	Group I vs. Group II		Group I vs. Group III		Group II vs. Group III	
	Z	'p'	Z	'p'	Z	'p'
2m	0.258	0.796	0.512	0.608	0.254	0.799
4m	0.346	0.729	1.172	0.241	0.812	0.417
6m	0.346	0.729	1.413	0.158	1.046	0.296
8m	1.000	0.317	2.049	0.040	1.386	0.166
10m	0.000	1.000	0.000	1.000	0.000	1.000
30m	0.000	1.000	0.000	1.000	0.000	1.000
50m	0.000	1.000	0.000	1.000	0.000	1.000
70m	0.000	1.000	0.000	1.000	0.000	1.000
90m	0.000	1.000	0.000	1.000	0.000	1.000
110m	0.000	1.000	0.000	1.000	0.000	1.000
130m	0.000	1.000	0.000	1.000	0.000	1.000
150m	0.000	1.000	0.000	1.000	0.000	1.000
170m	0.000	1.000	0.000	1.000	0.000	1.000

Table 4(c): Comparison of Time to achieve peak Motor block level (B/S-3) of Study Population

Group	No. of patients	Min.	Max.	Mean	S.D.
Group I	32	6.00	8.00	6.69	0.97
Group II	32	6.00	10.00	6.81	1.12
Group III	32	6.00	10.00	7.25	1.41
Total	96	6.00	10.00	6.92	1.19

F=2.001; p=0.141

Average time to achieve peak motor block (B/S-3) was minimum for patients of Group I (6.69±0.97 min) followed by Group II (6.81±1.12 min) and maximum in Group III (7.25±1.41 min). Time to achieve motor block was found to be comparable for above three groups.

Table 6: Comparison of Side Effects of Study Population

Side Effects	Total	Group I (n=32)		Group II (n=32)		Group III (n=32)	
		No.	%	No.	%	No.	%
Bradycardia	27	8	25.0	4	12.5	15	46.9
Nil	69	24	75.0	28	87.5	17	53.1

χ^2=9.585; p=0.008(Sig)

Incidence of bradycardia was significantly higher in Group III (46.9%) and Group I (25.0%) as compared to Group II (12.5%).

Table 7: Comparison of Number of Rescue Analgesia

Rescue Doses	Total	Group I (n=32)		Group II (n=32)		Group III (n=32)	
		No.	%	No.	%	No.	%
None	48	18	56.3	28	87.5	2	6.3
One	47	14	43.8	4	12.5	29	90.6
Two	1	0	0.0	0	0.0	1	3.1

χ^2=43.713; p<0.001(Sig)

Majority of the Group I and Group II cases did not require rescue dose during the procedure (56.3% & 87.5% respectively). Only 6.3% of Group III cases did not require rescue dose. Proportion of cases of Group III was higher as compared to Group I and Group II who required single rescue dose (90.6% vs. 43.8% & 12.5%) and two rescue doses (3.1% vs. 0.0% & 0.0%).

Table 8: Comparison of Time of first Rescue dose requirement

Group	No. of patients	Min.	Max.	Mean	S.D.
Group I	14	110.00	170.00	150.00	5.55
Group II	4	130.00	170.00	160.00	20.00
Group III	30s	90.00	170.00	147.33	23.92
Total	49	90.00	170.00	149.17	22.58

F=0.558; p=0.576

Time of requirement of first dose of rescue dose ranged from 90 to 170 minutes. Mean time was 149.17±22.58 minutes. Average time to first rescue dose of patients of above three groups was found to be comparable.

Discussion

Since the first use of spinal anesthesia in the late 19th century, it has emerged as a safer, more economical and highly convenient method of anesthesia as compared to the regional counterpart. Moreover, with an increase in number of surgical techniques used for various morbidities, spinal anesthesia has become widely accepted and highly popular amongst anesthesiologists.

Bupivacaine 0.5% has emerged with a monopoly in the field of drugs used for spinal anesthesia, since the discontinuation of lidocaine's intrathecal. Variations to the bupivacaine are available in form of hyperbaric bupivacaine; formulated by adding glucose to normal bupivacaine, adjuvants using neostigmine, opioids (morphine and fentanyl), clonidine, adrenaline etc.

The present study was conducted with an aim to compare effects of Neostigmine and Fentanyl as adjuvants to hyperbaric bupivacaine (0.5%) in spinal anaesthesia for lower abdominal and lower extremity surgery. Onset and duration of sensory and motor blockade, hemodynamic variables, time of use of first rescue analgesia, side effects and complications of Neostigmine and Fentanyl as adjuvants to hyperbaric Bupivacaine were evaluated. For this purpose 96 patients were randomly divided into three equal groups based on the different adjuvants Fentanyl or Neostigmine with hyperbaric Bupivacaine; forming Group I and Group II respectively and Group III consisting of patients administered with non-adjuvant hyperbaric Bupivacaine alone.

In present study, following induction, mean pulse rate was found to be significantly higher in neostigmine group as compared to the other two groups for most of the intraoperative period. However, no event of tachycardia was noticed in any of the groups. On the contrary, bradycardia rates were higher in fentanyl supplemented and bupivacaine alone groups as compared to neostigmine supplemented group. Thus in effect neostigmine was seen to have a better control over heart rate. As far as blood pressure values are concerned, systolic blood pressure was found to be higher in neostigmine supplemented group during the upto 10 minutes of intraoperative period, however, for diastolic blood pressure the three groups did not show a statistically significant difference throughout the intraoperative period. For MAP, though the mean values in neostigmine group were higher throughout the intraoperative period yet the difference was significant statistically at 10 minute intraoperative interval only. Thus, showing that the three drugs were in general hemodynamically stable and as such neostigmine supplemented group showed bradycardia sparing effect. Although neostigmine at higher dosages is reported to produce side effects including bradycardia**Error! Bookmark not defined.** **Error! Bookmark not defined.**, however, in present study we were using only 25 µg dose and this could be responsible for the bradycardia sparing effect of the drug. In the present study, neostigmine supplemented group had significantly lower bradycardia rate as compared to control group and bupivacaine + fentanyl group .Of the

two adjuvants used, neostigmine showed a higher efficacy in curbing the events of bradycardia.

In present study, the achievement of sensory block at T10 or above levels was achieved by 6 minutes in all the three groups, however, the proportion of those achieving it within 2 minutes of intrathecal injection was lower in fentanyl supplemented group as compared to neostigmine supplemented groups and bupivacaine alone groups. It was seen that as many as 78.1% of neostigmine supplemented group and 75% of bupivacaine alone group patients achieved sensory block level T10 or above by 2 minutes as compared to only 56.2% of bupivacaine + fentanyl group patients. The findings in effect suggest that the achievement of sensory block was faster in both the supplemented groups as compared to control group. However, we found no significant difference among groups to achieve the sensory block T6 or above. In present study too, we found that in both the adjuvant groups, at 2 mins time interval the achievement of block level T10 or above was significantly higher in supplemented groups as compared to bupivacaine alone group. However, we did not find a significant difference among groups with respect to achievement of peak sensory block.

In present study, number of patients requiring rescue analgesia was significantly lower in bupivacaine + neostigmine (12.5%) as compared to bupivacaine + fentanyl (43.8%) and bupivacaine alone (93.1%) groups, thus showing that addition of both the drugs reduced the rescue analgesic need, however, addition of neostigmine was more effective as compared to fentanyl. In present study, among patients requiring rescue analgesia, we did not find a significant difference among groups with respect to time for rescue analgesia, however, we found a significant difference among groups with respect to effective analgesia time which was also found to be longest in neostigmine group (319.25 min) followed by fentanyl group (166.56 min) and minimum in control group (118.97 min). The VAS scores (>3) at the time of rescue analgesia were also higher in control group (93.7%) as compared to fentanyl supplemented group (43.8%) and neostigmine-supplemented groups (12.5%). As far as analgesic effect is concerned, the findings in present study are unique and do not correspond with the observations of all the three previous studies comparing the three drug combinations**Error! Bookmark not defined.**-**Error! Bookmark not defined.**. In all the previous studies comparing the three drug combinations fentanyl + bupivacaine combination has the maximum efficacy followed by bupivacaine + neostigmine combination and bupivacaine only group.. Different drug-dose combinations might affect the outcome. Despite this explanation, the findings of present study show an extraordinarily high performance of neostigmine as compared to fentanyl which is different from the contemporary literature available so far. As such there is limited literature comparing fentanyl and neostigmine for intrathecal use as adjuvant to bupivacaine for lower extremity surgeries, we would recommend further studies to validate the findings of present study.

In present study no other serious side effect was noted. Nausea and vomiting were seen as the only mentionable side effects which were more common in fentanyl supplemented or bupivacaine alone group and were absent altogether in neostigmine supplemented group. As such none of the previous studies also report of any serious side effect. However, no such protective effect of neostigmine against nausea/vomiting has been reported in any of the previous studies. On the contrary, Ahmed *et al.*[18] in their study reported incidence of nausea/vomiting to be maximum in neostigmine supplemented group (14.6%) as compared to 4.8% and 7.3% in bupivacaine alone and fentanyl supplemented group.

The better efficacy of neostigmine in present study could be owing to a possible sedative effect of neostigmine that reduces the perception of pain. In a previous study, Kaya *et al*. found that in patients posted for elective cesarean study under combined spinal-epidural using epidural neostigmine showed that total duration of post-operative analgesia and global pain satisfaction scores were reduced in the neostigmine group. The possible sedative property of neostigmine could thus offer a possible valid explanation for the findings in present study. However, one of the limitations of the study was that we did not include sedation as an outcome and hence are not in a position to comment with authority on this aspect. Further studies on a larger sample size with inclusion of more variables are recommended.

Conclusion

The present study was conducted in the Department of Anaesthesiology, Era's Lucknow to compare the effect of Neostigmine and Fentanyl as adjuvant to hyperbaric bupivacaine in spinal anaesthesia for lower abdominal and lower extremity surgery. Out of cases scheduled for lower abdominal or lower extremity surgery 96 ASA Grade I & II cases fulfilling the inclusion criteria were enrolled and randomly divided in three groups, all the cases were given hyperbaric bupivacaine (0.5%), of these 32 cases were given fentanyl (25 mcg) and another 32 cases were given neostigmine (25 mcg) as adjuvant, rest 32 cases were not given any adjuvant. Age of patients ranged from 18 to 70 years, 51% were females, had mean body weight of 57.14±9.34 kg and duration of surgery was 114.09±8.87 min. Patients of above three groups were comparable for age, gender, body weight,

ASA Grade and duration of surgery. Baseline hemodynamic parameters (Pulse, Systolic & diastolic BP, MAP and oxygen saturation level of the patients of above three groups were comparable. Hemodynamic parameters were recorded at baseline (just before start of anaesthesia) and thereafter at an interval of 2 min upto 10 min thereafter at an interval of 20 min upto 170 min. Findings of the study led to following conclusions:

Pulse rate of cases of neostigmine adjuvant group was found to be significantly higher than that of fentanyl adjuvant and no-adjuvant group at all the periods of observation while that of fentanyl adjuvant and non-adjuvant groups was comparable.

During first 10 minutes, systolic BP of neostigmine adjuvant group was found to be significantly higher than that of fentanyl adjuvant and non-adjuvant groups.

Diastolic BP and MAP of patients of above three groups were comparable at all time points of observation. Oxygen saturation level was maintained >95% for all the patients throughout the period of observation.

Mean time to achieve peak sensory block (T6) was 6.10±1.21 minutes. Difference was found to be clinically insignificant, almost similar in all three group.

Mean time to achieve motor block (B/S-3) was 6.92±1.19 min. Though fentanyl adjuvant group achieved the same at earliest followed by neostigmine adjuvant and last in non-adjuvant group but difference was not found to be significant.

Bradycardia was observed in higher proportion of non-adjuvant group, followed by fentanyl adjuvant and least in neostigmine adjuvant group (46.9%, 25.0% & 12.5%).

Majority of the neostigmine adjuvant cases (87.5%) and fentanyl adjuvant cases (56.3%) did not require rescue analgesia, rest of them required only single dose. Requirement of rescue doses was minimum in neostigmine adjuvant followed by fentanyl adjuvant and maximum in non-adjuvant group.

Duration of effective analgesia was maximum in neostigmine adjuvant followed by fentanyl adjuvant and minimum in non-adjuvant group while VAS scores as measure of pain was minimum in neostigmine adjuvant followed by fentanyl adjuvant and maximum in non-adjuvant group.

Incidence of nausea and vomiting was maximum in non-adjuvant cases followed by fentanyl adjuvant. Nausea and vomiting was not observed in any of the neostigmine adjuvant cases.

References

1. Bier A. Experiments regarding the cocainization of the spinal cord. Zietschrift fur chirurgie 1889; 51:361-368.
2. Farman JV. Regional anaesthesia. In: Anaesthesia and the E.M.O. system, 1st edition. Great Britain Pitman Press, Bath, 1980; 11:159- 171.
3. Bernards CM. Epidural and spinal anesthesia. In: Barash PG, Cullen BF, Stoelting RK, Cahalan MK, Stock MC, eds. Clinical Anesthesia. 6th ed. China: Lippincott Williams & Wilkins; 2009: 929-951.
4. Niemi, G. Advantages and disadvantages of adrenaline in regional anaesthesia. Best Practice & Research Clinical Anaesthesiology, 2005; 19(2), 229–245.
5. Moore JM, Liu SS, Pollock JE, Neal JM, Knab JH. Epinephrine prolongs bupivacaine spinal anesthesia. Anaesthesia& Analgesia 1998; 86(2S): 295S.
6. Kathirvel S, Sadhasivam S, Saxena A, Kannan TR, Ganjoo P. Effects of intrathecal ketamine added to bupivacaine for spinal anaesthesia. Anaesthesia 2000; 55(9): 899-904.
7. Liu SS, Hodgson PS, Moore JM, Trautman WJ, Burkhead DL. Dose-response effects of spinal neostigmine added to bupivacaine spinal anesthesia in volunteers. Anaesthesiology 1999; 90: 710-7.
8. Kumar P, Rudra A, Pan AK, Acharya A. Caudal additives in pediatrics: a comparison among midazolam, ketamine, and neostigmine coadministered with bupivacaine AnesthAnalg, 2005; 101: 69-73
9. Karaaslan K, Gulcu N, Ozturk H, Sarpkaya A, Colak C, Kocoglu H. Two different doses of caudal neostigmine co-administered with levobupivacaine produces analgesia in children. PediatrAnesth, 2009; 19(5): 487-493
10. Klamt JG, Slullitel A, Garcia IV, Prado WA. Postoperative analgesic effect of intrathecal neostigmine and its influence on spinal anesthesia. Anesthesia 1997; 52:547-51
11. Singh H, Yang J, Thornton K, Giesecke AH. Intrathecal fentanyl prolongs sensory bupivacaine spinal block. Can J Anaesth. 1995; 42: 987–91.
12. Unal D, Ozdogan L, Ornek HD, Sonmez HK, Ayderen T, Arslan M, et al. Selective spinal anaesthesia with low-dose bupivacaine and bupivacaine fentanyl in ambulatory arthroscopic knee surgery. J Pak Med Assoc. 2012; 62: 313–8.