COMPARATIVE STUDY OF INTRATHECAL NEOSTIGMINE AND CLONIDINE

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ABSTRACT

BACKGROUND

Providing good analgesia with adequate muscle relaxation during the intraoperative period and managing pain in the postoperative period is a good anaesthetic practice. Effective control of postoperative pain can reduce morbidity and mortality, early mobilization, patient comfort and satisfaction, less chances of deep vein thrombosis, cost and less bed occupancy. This study is designed to find the effect of adding clonidine or neostigmine to 0.5% hyperbaric bupivacaine for spinal anaesthesia to achieve quality regional block as well as good postoperative analgesia.

AIMS

This study is conducted to analyse the effect of adding adjuvant neostigmine 50 µg or clonidine 50 µg to intrathecal 0.5% hyperbaric bupivacaine and evaluating the intraoperative haemodynamic stability and total duration analgesia with each drug in patients undergoing lower abdominal and lower limb surgeries.

METHODS AND MATERIALS

The present study was carried out in the Department of Anaesthesiology, Govt. Chengalpattu Medical College, Chengalpattu, Tamilnadu in association with the Department of General Surgery, Orthopaedics and Department of Obstetrics and Gynaecology in which 90 patients of either sex of ASA grade I and II between the ages of 18 and 50 years. These patients were systematically randomized into 3 groups of 30 each, Group A – Receiving 0.5% bupivacaine alone, Group B - Receiving 0.5% bupivacaine with 50 µg neostigmine and Group C - Receiving 0.5% bupivacaine with 50 µg clonidine.

STATISTICAL ANALYSIS

The data was analysed by statistical software SPSS 17.0 for windows. Chi-square test was used to analyse categorical data.

RESULTS

Results show that intrathecal neostigmine additive has faster onset of sensory and motor blockade, but Intrathecal clonidine has longer duration of sensory and motor blockade. Intrathecal bupivacaine alone lags behind in onset as well as duration of sensory and motor blockade.

CONCLUSION

Intrathecal clonidine 50 µg or neostigmine 50 µg with bupivacaine is better in providing faster onset of blockade, out of which clonidine is a better adjuvant in providing good postoperative analgesia.

KEYWORDS

Intrathecal, Neostigmine, Clonidine, Spinal.

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INTRODUCTION

The most commonly administered anaesthesia is the spinal subarachnoid block, as it is easy to perform as a single shot technique. When compared to epidural and general anaesthesia, the main problem of spinal anaesthesia is that the postoperative analgesia which lasts only for a brief period.

As lower abdominal and lower limb surgeries are commonly performed under spinal anaesthesia, adding adjuvant which prolong the duration of anaesthesia and provide postoperative analgesia can be beneficial. So adjuvants like opioids and newer adjuvants like clonidine, neostigmine and ketamine to the local anaesthetic agents have been tried with varying success rates.

Additives decrease the requirement of local anaesthetic agents. They intensify and prolong the duration of analgesia. They have synergistic action, thus decreasing the dose of drug and side effects of individual agents.

Local anaesthetics bind in the "inner vestibule" of the closed Na+ channel and obstruct the external opening and maintains the channels in the closed inactivated state, which is not permeable to sodium, blocks the conduction of nerve impulses. Neostigmine acts on Lamina 2 substantia gelatinosa of Rolando and on lamina 3 and 4, and cause stimulation of muscarinic receptors M1 and M2.

Clonidine acts on the postsynaptic alpha 2 receptors (Stimulation) in substantia gelatinosa present in dorsal horn of the spinal cord. Clonidine also has the intrinsic property to block the conduction in C and A-δ fibres.

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AIMS AND OBJECTIVES

To compare the use of neostigmine 50 µg, clonidine 50 µg along with 0.5 % hyperbaric bupivacaine in spinal anaesthesia in patients undergoing lower abdominal and lower limb surgeries in providing postoperative analgesia with stability of the haemodynamic status.

The objectives of this study is comparative evaluation of clonidine and neostigmine with 0.5% bupivacaine in spinal anaesthesia with respect to:

1. Onset time of sensory and motor block.
2. Duration of motor block.
3. Duration of analgesia.
4. Intraoperative haemodynamics.
5. Side effects.

METHODS AND MATERIALS

After getting the approval by the Ethical Committee, study was conducted on 90 patients who underwent lower abdominal and lower limb surgeries under spinal anaesthesia. It is a comparative prospective randomized double blind controlled study. This study was done in the Department of Anaesthesiology, Govt. Chengalpattu Medical College, Chengalpattu with the supportive help of the Obstetrics and Gynaecology, General Surgery and Orthopaedics Departments for a period of one year. Patient counselling was done and informed consent obtained.

Inclusion Criteria

1. Age 18 – 50 years of both sex.
2. ASA I and II.
3. Elective lower abdominal and lower limb surgeries of <90 minutes' duration.

Exclusion Criteria

1. Age <18 years and >50 years.
2. ASA III and IV.
3. Hypersensitivity to bupivacaine.
4. Haemodynamic instability.
5. Infection at the lumbar puncture site.
6. Patients on anticoagulants/bleeding disorders.
7. Patient refusal.
8. Patients with neuromuscular disorders.
9. Psychiatric illness.

PATIENTS WERE RANDOMLY DIVIDED INTO THREE GROUPS OF EACH

Group A – Control group – Receiving 0.5% bupivacaine alone.
Group B – Neostigmine group - Receiving 0.5% bupivacaine with 50 µg neostigmine.
Group C – Clonidine group - Receiving 0.5% bupivacaine with 50 µg clonidine.

Preoperative Evaluation

Age, weight, height, vital parameters, history of previous anaesthesia and surgery, significant medical illness and medications and allergies were recorded in all patients. Complete physical examination, airway assessment followed by laboratory investigations was done.

Haemoglobin, PCV, Total WBC count, Differential WBC count, ESR, Urine albumin and sugar, Blood urea, serum creatinine, liver function tests, ECG, X-ray chest, Blood grouping and typing and other relevant investigations.

METHODOLOGY

All the patients were premedicated with Tab. Ranitidine 150 mg and Tab. diazepam 5 mg, 2 hrs. before the spinal anaesthesia. On the day of surgery, Intravenous (IV) line with 18-G cannula was secured. Patients were connected to multiparameter monitor with Electrocardiogram (ECG), Oxygen Saturation (SPO2) and Non-Invasive Blood Pressure (NIBP) and basal readings recorded. All the patients were preloaded with 10 mL/kg of Ringer lactate. Under sterile aseptic precautions, subarachnoid block performed with 25-G Quincke's needle with the patient in the right lateral position.

Group A: Received 2.5 mL of 0.5% hyperbaric bupivacaine.

Group B: Neostigmine (0.5 mg/mL) 1 mL is diluted up to 5 mL with normal saline from which 0.5 mL (50 µg) is added to the 2.5 mL of 0.5% hyperbaric bupivacaine.

Group C: Clonidine (100 µg/mL) 0.5 mL (50 µg) is added to the 2.5 mL of 0.5% hyperbaric bupivacaine.

Vital signs were monitored at 2nd minute and every 5 minutes till completion of the surgery. Surgery was started after adequate surgical anaesthesia was obtained. Time of completion of the surgical procedures were noted. Patients were monitored in the recovery room until there was two segment regression of sensory block. Pain was assessed using Visual Analogue Scale (Figure 1) during recovery and postoperative period. Rescue analgesia (Inj. Pethidine 50 mg + Inj. Promethazine 12.5 mg IM) was given at the time of perception of pain, after noting the VAS score. Motor block was assessed using modified Bromage Scale (Table 1) for both lower limbs.

Score	Criteria
1	Complete block (unable to move feet or knee)
2	Almost complete block (able to move feet only)
3	Partial block (just able to move knee)
4	Detectable weakness of hip flexion, while supine (full flexion of knees)
5	No detectable weakness of hip flexion while supine
6	Able to perform partial knee bend

Table 1: Modified Bromage Score as used by Breen et al

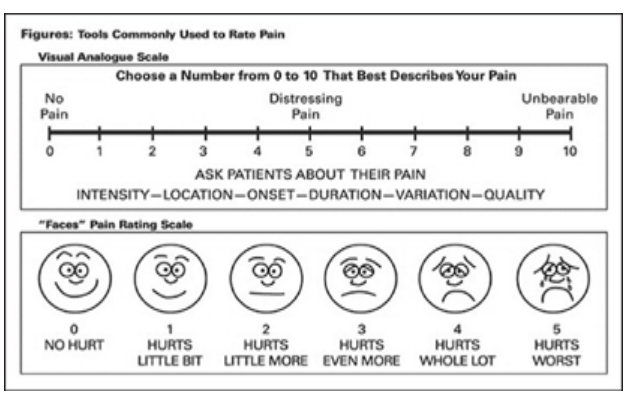


Fig. 1: Visual Analogue Scale

Parameters Noted

1. Heart rate.
2. Non-invasive blood pressure.
3. Oxygen saturation.
4. Respiratory rate.
5. Sensory block.
   a. Onset time.
   b. Maximum level of block.
   c. Duration.
6. Motor block.
   a. Onset time
   b. Duration.
7. Time of pain perception.

OBSERVATION

The following data were collected in this study.

1. Demographic profile such as age in years, sex, weight in kgs.
2. Onset time for sensory block.
3. Highest level of sensory block.
4. Onset and Duration of motor block.
5. Time for rescue analgesia (duration of analgesia) – Time of pain perception.
6. Heart rate, systolic blood pressure, diastolic blood pressure and at baseline, 2 minutes after spinal and every 5 minutes thereafter.

The duration of surgeries were noted. Postoperative analgesia was calculated from the time of end of the surgical procedure to the time of pain perception, which was assessed by Visual Analogue Scale and the VAS score was noted.

STATISTICAL METHODS

The data was analysed by statistical software SPSS (Statistical Package for Social Sciences) 17.0 for windows. Chi-square test was used to analyse categorical data.

RESULTS

The three groups were comparable with respect to the age, weight and sex. There was no statistical difference between the two groups in demographic profile (Tables 2, 3, 4; Figures 2, 3, 4).

	Group A	Group B	Group C	P value
Age (Mean ± SD)	41.45 ± 12.458	43.4 ± 8.923	39.15 ± 11.811	0.489

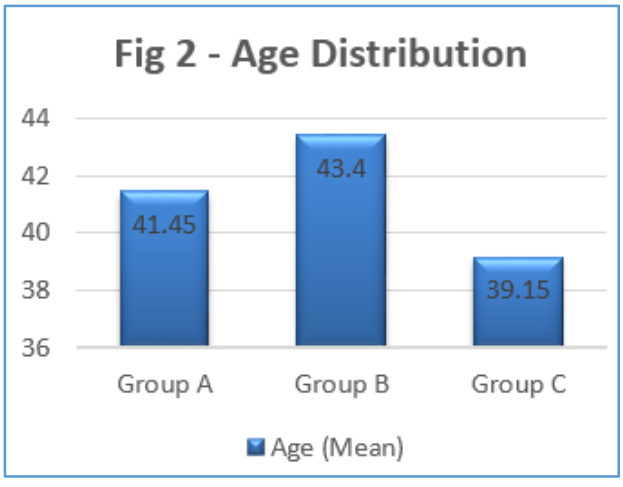
Table 2: Age Distribution

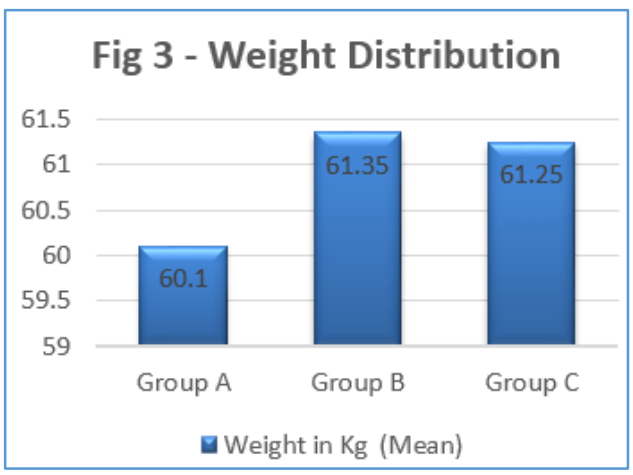
	Group A	Group B	Group C	P value
Weight in kg (Mean ± SD)	60.1 ± 6.593	61.35 ± 9.213	61.25 ± 7.247	0.852

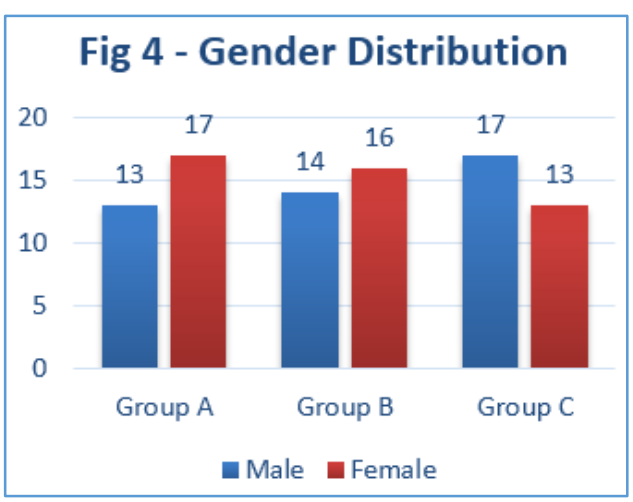
Table 3: Weight Distribution

Gender	Group A	Group B	Group C
Male	13	14	17
Female	17	16	13

Table 4: Gender Distribution





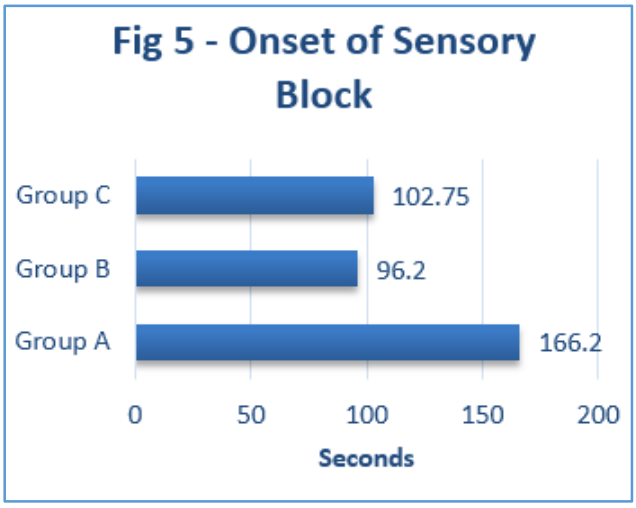


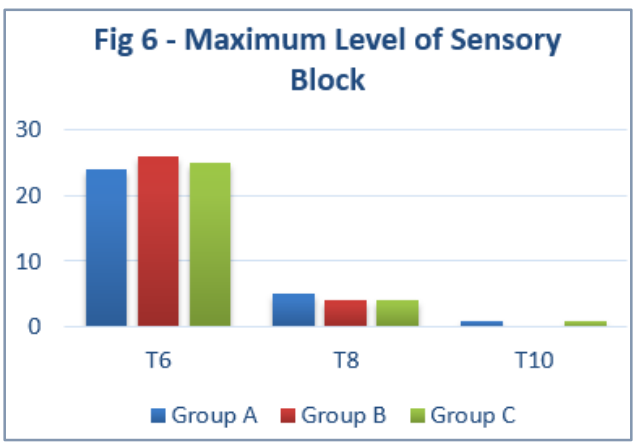
The mean onset time of sensory block (Table 5, Figure 5) in each groups were as follows. Group A is 166.2±7.824, Group B is 96.2±29.24 and Group C is 102.75±29.99 seconds. Onset of sensory block is faster in the neostigmine group than the other two groups. There was statistically significant difference between the three groups (p<0.0001).

Onset	Group A	Group B	Group C	P value
Sensory Block (Seconds)	166.2± 7.824	96.2 ± 29.24	102.75 ± 29.99	<0.0001

Table 5: Mean Onset of Sensory Block

The maximum level of sensory block achieved was noted to be between T6 and T10. Most of the patients in the three groups were found to have block up to the T6 level (Table 6, Figure 6). There was no significant difference between the three groups (p >0.5).





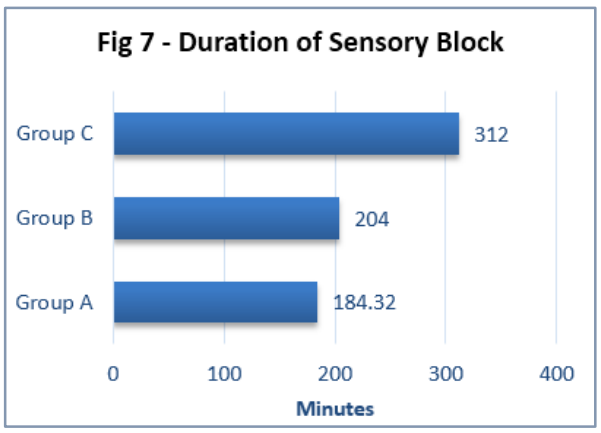
Maximum Level	Group A	Group B	Group C
T6	24	26	25
T8	5	4	4
T10	1	0	1

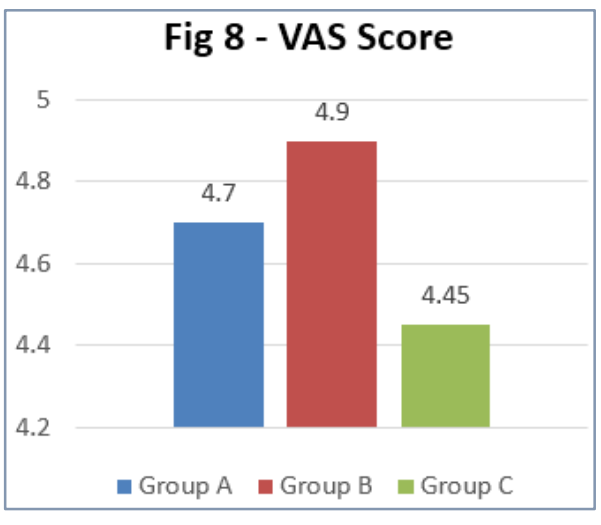
Table 6: Maximum Level of Sensory Block Achieved

The mean duration of sensory block (Table 7, Figure 7) (Time from the onset to the time of pain perception) was statistically significant in all three groups. Group A 184.32±17.16, Group B 204±20.1 and in Group C it is 312±37.38 minutes. The duration was significantly longer in the clonidine group (p<0.0001).

	Group A	Group B	Group C	P value
Sensory Block (min)	184.32 ± 17.16	204 ± 20.1	312 ± 37.38	<0.0001

Table 7: Mean Duration of Sensory Block





VAS Score

(Table 8, Figure 8) at the time of pain perception was 4.7±0.47 in Group A, 4.9±1.071 in Group B and 4.45±0.51 in Group C. There was no statistically significant difference between the three groups (p=0.163).

	Group A	Group B	Group C	P value
VAS Score	4.7 ± 0.47	4.9 ± 1.071	4.45 ± 0.51	0.163

Table 8: VAS Score

The mean onset time of motor block (Table 9, Figure 9) in Group A is 176.2±6.95 seconds, in Group B is 96.9±19.47 seconds and in Group C is 113.95±14.66 seconds. Onset of motor block was significantly faster with the neostigmine group. There was statistically significant difference between the three groups (p<0.0001).

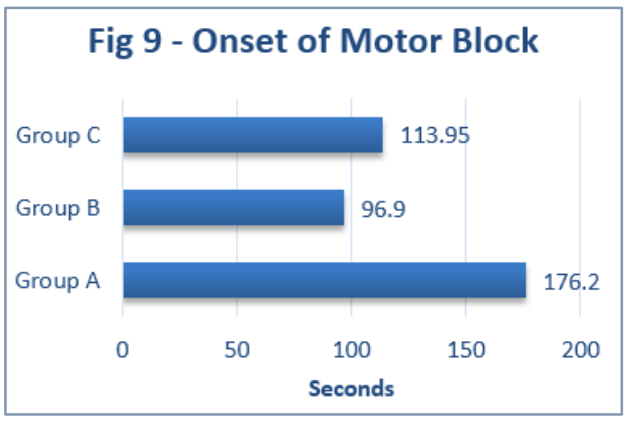
The mean duration of motor block (Table 10, Figure 10) was statistically significant in all three groups. Group A 146.16±20.76, Group B 176.22±13.02 and in Group C it is 252±13.92 minutes.

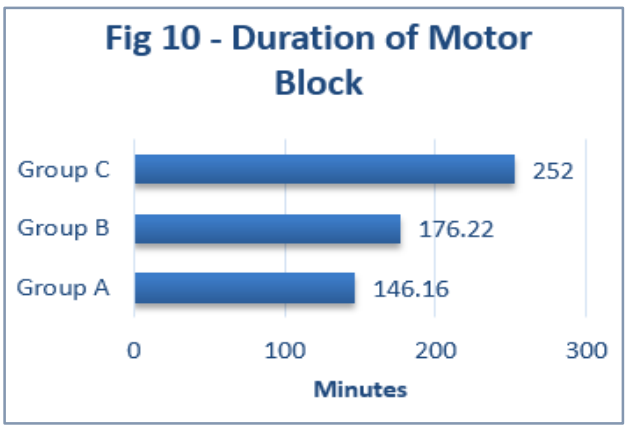
	Group A	Group B	Group C	P value
Motor (Seconds)	176.2 ± 6.95	96.9 ± 19.47	113.95 ± 14.66	<0.0001

Table 9: Mean Onset of Motor Block

	Group A	Group B	Group C	P value
Motor Block (Min)	146.16±20.76	176.22± 13.02	252± 13.92	<0.0001

Table 10: Mean Duration of Motor Block

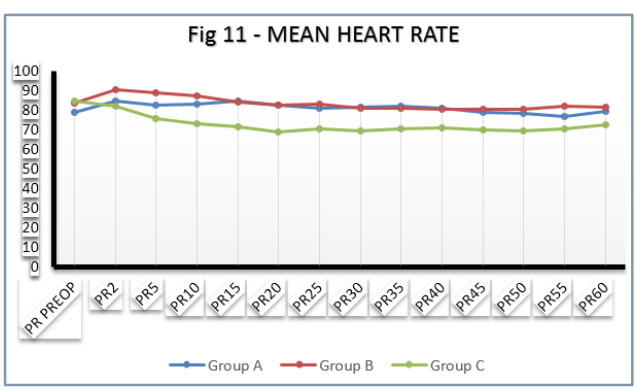




The preoperative heart rate was not statistically significant in the three groups, but heart rates after the tenth minute of spinal anaesthesia were significant statistically. There is a significant drop in the heart rate with the clonidine Group C (Table 11, Figure 11).

Time	Group A		Group B		Group C		P value
	Mean	SD	Mean	SD	Mean	SD	
PR PREOP	78.9	9.968	83.5	14.468	84.55	8.947	0.256
PR2	84.45	7.185	90.38	11.815	81.9	9.586	0.025
PR5	82.45	8.338	88.8	11.848	75.75	9.591	0.001
PR10	83.05	7.366	87.3	10.006	73.15	9.366	0.0001
PR15	84.55	9.768	83.9	12.143	71.55	8.338	0.0001
PR20	82.7	10.408	82.45	10.47	68.8	8.912	0.0001
PR25	81.1	10.809	83.15	9.778	70.3	7.02	0.0001
PR30	81.65	10.52	81.25	8.46	69.45	6.468	0.0001
PR35	82.15	8.928	80.9	7.907	70.7	6.937	0.0001
PR40	81.15	8.061	80.55	7.38	71	6.432	0.0001
PR45	79	7.064	80.5	6.573	69.75	6.077	0.0001
PR50	78.45	7.395	80.7	5.639	69.2	6.144	0.0001
PR55	77	8.105	82.05	6.1	70.25	6.64	0.0001
PR60	79.33	9.018	81.35	4.676	72.5	5.967	0.001

Table 11: Mean Heart Rate

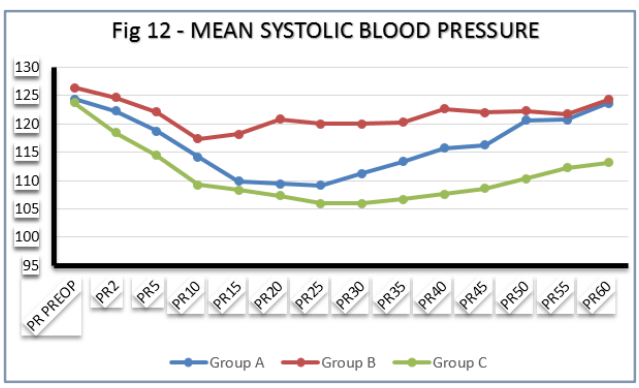


The preoperative systolic BP was not statistically significant in the three groups, but after the tenth minute of spinal anaesthesia the differences were significant statistically. There is a significant drop in the systolic BP with the neostigmine Group B and in the clonidine Group C when compared to the control Group A (Table 12, Figure 12).

Time	Group A		Group B		Group C		P value
	Mean	SD	Mean	SD	Mean	SD	
PR PREOP	124.35	10.07	126.35	13.124	123.7	10.322	0.741
PR2	122.3	8.467	124.6	11098	118.45	12.857	0.227
PR5	118.7	8.578	122.05	10.185	114.4	12.15	0.075
PR10	114.15	8.887	117.35	11.061	109.2	9.099	0.035
PR15	109.9	8.867	118.2	12.344	108.3	9.581	0.008

PR20	109.45	10.4	120.85	12.214	107.3	10.204	0.0001
PR25	109.1	12.49	120	11.734	105.95	9.73	0.0001
PR30	111.25	13.932	120	12.439	105.95	8.029	0.0001
PR35	113.3	12.704	120.25	12.212	106.7	8.542	0.002
PR40	115.75	9.797	122.65	14.694	107.55	7.373	0.001
PR45	116.3	9.274	122	12.057	108.6	7.883	0.0001
PR50	120.6	9.213	122.3	9.437	110.3	8.615	0.0001
PR55	120.7	8.682	121.75	9.657	112.2	8.667	0.002
PR60	123.67	7.608	124.24	9.384	113.19	7.323	0.001

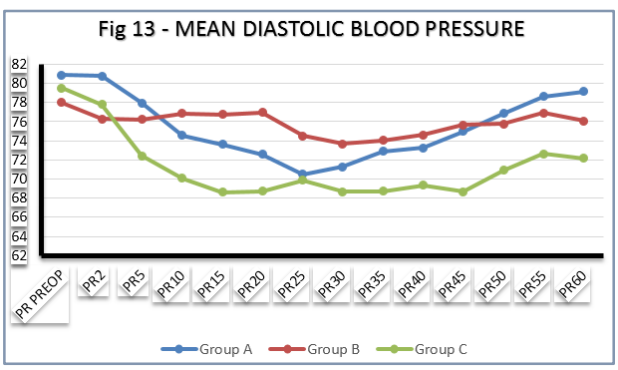
Table 12: Mean Systolic Blood Pressure



The preoperative diastolic BP was not statistically significant in the three groups, but after the tenth minute of spinal anaesthesia the differences were significant statistically. There is a significant drop in the diastolic BP with the neostigmine Group B and in the clonidine Group C when compared to the control Group A (Table 13, Figure 13).

Time	Group A		Group B		Group C		P value
	Mean	SD	Mean	SD	Mean	SD	
PR PREOP	80.85	6.753	78	7.567	79.5	10.185	0.558
PR2	80.75	7.999	76.3	7.651	77.8	10.139	0.264
PR5	77.95	6.245	76.25	6.512	72.45	12.437	0.143
PR10	74.55	8.062	76.85	6.201	70.1	7.704	0.018
PR15	73.65	6.419	76.75	4.179	68.6	7.83	0.001
PR20	72.6	5.725	76.95	2.665	68.7	8.367	0.0001
PR25	70.5	6.091	74.5	5.463	69.85	6.8	0.042
PR30	71.3	5.048	73.7	5.017	68.65	5.102	0.01
PR35	72.9	5.647	74.05	5.605	68.75	5.28	0.009
PR40	73.25	6.086	74.6	6.286	69.35	4.38	0.013
PR45	75	3.92	75.65	5.412	68.65	7.088	0.0001
PR50	76.85	4.837	75.75	5.26	70.9	7.29	0.005
PR55	78.65	4.095	76.9	6.078	72.65	5.234	0.002
PR60	79.17	2.368	76.06	5.662	72.19	4.996	0.002

Table 13: Mean Diastolic Blood Pressure



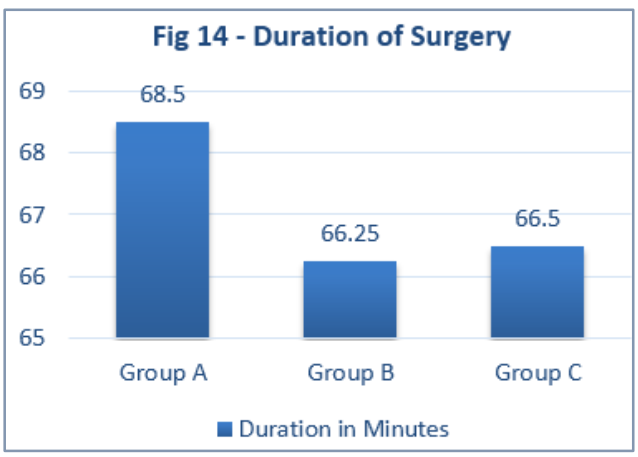
The mean duration of surgery (Table 14, Figure 14) was comparable in all the three groups. The time of completion of surgery was noted following which time for postoperative analgesia was calculated until the time when the patients perceived pain. The postoperative analgesia (Table 15, Figure 15) was 115.7±20.84 minutes in Group A, 137.75±25.46 minutes in Group B and 245.5±36.96 minutes in Group C. The duration is prolonged in Groups B and C, but is significantly prolonged in group C (Clonidine group).

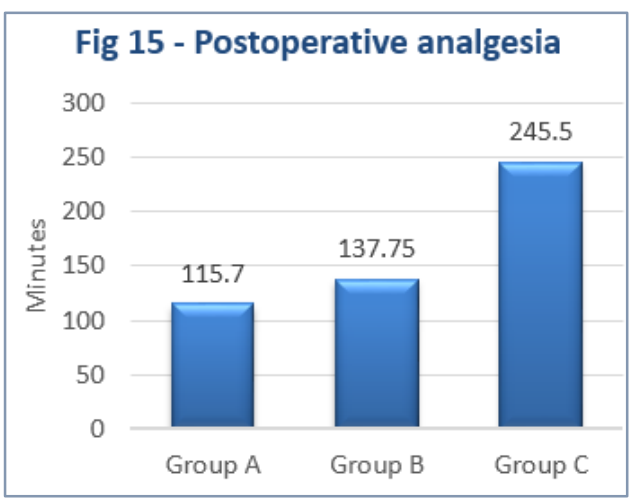
Group	A	B	C
Duration in Minutes (Mean ± SD)	68.5±8.217	66.25±8.416	66.5±10.336

Table 14: Mean Duration of Surgery

	Group A	Group B	Group C	P value
Postop Analgesia	115.7±20.84	137.75±25.46	245.5±36.96	0.0001

Table 15: Duration of Postoperative Analgesia

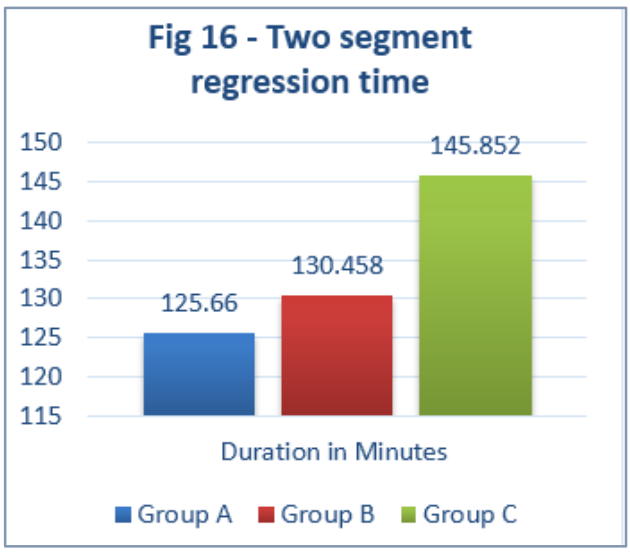


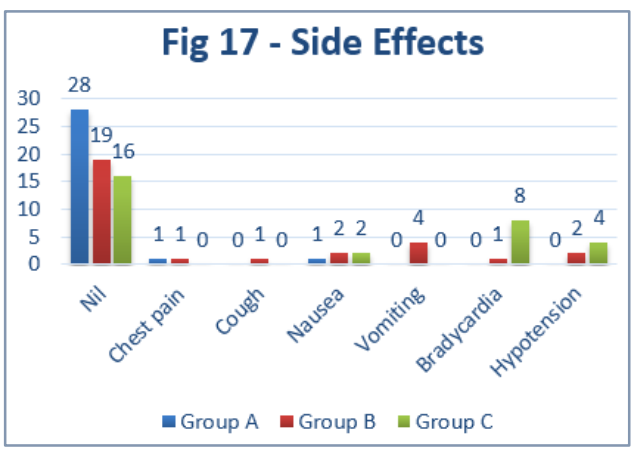


The two segment regression time (Table 16, Figure 16) for the three groups is as follows. In Group A 125.66±20.56 minutes, Group B 130.458±32.46 and in Group C 145.852±36.58. There was statistically significant difference between the three groups (p<0.0001).

	Group A	Group B	Group C	P value
Duration in Minutes	125.66 ± 20.56	130.458 ± 32.46	145.852 ± 36.58	<0.0001

Table 16: Two Segment Regression Time





Side Effects

Chest pain, cough, nausea, vomiting, bradycardia and hypotension were the noted side effects in this study (Table 17, Figure 17). Group A with minimal side effects, Group B with nausea 2 and vomiting 4 and Group C with more incidences of bradycardia 8 and hypotension 4.

Side Effects	Group A	Group B	Group C
Nil	28	19	16
Chest pain	1	1	0
Cough	0	1	0
Nausea	1	2	2
Vomiting	0	4	0
Bradycardia	0	1	8
Hypotension	0	2	4

Table 17: Side Effects

Intrathecal Neostigmine group produces faster onset of motor and sensory blockade, longer duration of motor as well as sensory block compared to the control group. Intrathecal Clonidine group produces considerable longer duration of motor block and sensory block when compared to the control and the neostigmine groups. At the same time intrathecal clonidine produces more incidences of hypotension and bradycardia.

DISCUSSION

Lower limb surgeries and lower abdominal surgeries like hernioplasty, appendicectomy and abdominal hysterectomies are performed under spinal anaesthesia, as it is easy to perform, single shot technique when compared to epidural and general anaesthesia. But its main drawback is that the analgesia is of limited duration. Hence, additives which cause the prolongation of the duration of motor as well as sensory block will be beneficial in reducing the morbidity of the patients in the postoperative period.

This study was performed to compare the effects of adjuvants neostigmine and clonidine along with 0.5% hyperbaric bupivacaine for spinal anaesthesia.

Akinwale MO.[1] et al showed that spinal neostigmine 25 µg added to hyperbaric bupivacaine and fentanyl provided a significantly longer surgical analgesia and insignificant adverse effects in male adults who had lower abdominal surgery under spinal anaesthesia. Pan PM.[2], Huang CT, Wei TT, Mok MS in 1998 found that the onset of sensory block was rapid in neostigmine group than the clonidine group in caesarean patients.

Yoganarasimha.[3] and co-worker in 2014 also found that the onset of sensory and motor block was faster in neostigmine when compared to clonidine.

Elia.[4] et al found that the two segment regression time, delay in regression time to L2, time needed for the first rescue analgesia and motor block was extended with Intrathecal clonidine. They also found that there is an increased incidence of arterial hypotension.

Andrieu.[5] et al in 2004 found significant reduction in morphine requirement during the first 48 postoperative hours after a radical prostatectomy. The addition of clonidine to intrathecal morphine reduced intraoperative sufentanil use, prolonged time until first request for PCA rescue and further prolonged analgesia at rest and with coughing.

Strebel.[6] et al in 2004 studied the effect of different doses (37.5, 75 and 150 µg) of clonidine and conclude that small doses of intrathecal clonidine (≤ 150 µg) significantly prolong the anaesthetic and analgesic effects of bupivacaine in a dose-dependent manner.

Kanazi.[7] et al in 2006 showed that the patients added α-2 agonists with spinal bupivacaine had rapid onset time of motor block and took longer time for sensory and motor regression.

Marrivirta.[8] et al 2010 found prolongation of motor block in patients who received intrathecal clonidine. They also showed that there is more vasopressor requirement and less postoperative pain.

Rochette.[9] et al demonstrates that clonidine 1 µg/kg doubles neonatal spinal anaesthesia duration without providing undesirable haemodynamic effects in the immediate postoperative period.

De Kock M.[10] et al showed that a small-dose of intrathecal clonidine (15 µg) plus 8 mg intrathecal ropivacaine produces adequate and short-lasting anaesthesia for knee arthroscopy.

Dobrydnjov I et al[11] found that the addition of clonidine 15 micro g to 6 mg of hyperbaric bupivacaine increases the spread of analgesia, prolongs the time to first analgesic request and decreases postoperative pain compared with bupivacaine alone during inguinal herniorrhaphy under spinal anaesthesia. They also compared intrathecal clonidine and oral clonidine and found that addition of intrathecal clonidine prolonged analgesia and decreased morphine consumption postoperatively more than oral clonidine.[12] Hypotension was more pronounced after oral than after intrathecal clonidine. Intrathecal clonidine is therefore recommended.

Sethi BS et al[13] study has demonstrated that addition of clonidine to bupivacaine in the dose of 1 µg/kg significantly increases the duration of analgesia following its placement in subarachnoid space as compared to bupivacaine alone.

Gupta S.[14] observed enhanced analgesia by intrathecal neostigmine in 75 µg dose as is shown by less consumption of intramuscular diclofenac sodium.

Liu SS et al[15] showed that the addition of 50 µg neostigmine prolonged the duration of sensory and motor block.

CONCLUSION

This study concludes that the addition of neostigmine to 0.5% hyperbaric bupivacaine intrathecal hastens the onset of sensory block. It also prolongs the duration of sensory and motor block when compared to 0.5% hyperbaric bupivacaine alone.

Adding clonidine to 0.5% hyperbaric bupivacaine intrathecal significantly prolongs the duration of motor as well as sensory block when compared to bupivacaine alone and the neostigmine groups. Intrathecal clonidine is a better choice for prolonging the duration of postoperative analgesia of 0.5% hyperbaric bupivacaine.

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