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Research Article

Intrathecal clonidine for post-operative pain relief in lower abdominal surgeries

Smita S. Lele*, Kanchan R. Rupwate, Reepmala Minhas, Bharati Tendolkar

Department of Anaesthesiology, Lokmanya Tilak Muncipal Medical College & General Hospital, Sion, Mumbai, Maharashtra, India

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***Correspondence:**
Dr. Smita S. Lele,
E-mail: smitaslele@rediffmail.com

ABSTRACT

Background: Spinal anaesthesia is preferred method for surgeries of lower half of the body due to its efficacy, rapidity, minimal side effects. Generally bupivacaine is given as an spinal anaesthetic agent because of its analgesic effect in the initial postoperative period. For additional analgesic effect particularly for lower limb surgeries now-a-days it is recommended to add an adjuvant inj.clonidine. Hence the present study is aimed to compare the effects of combination of clonidine with bupivacaine and bupivacaine alone.
Methods: The study was prospective, randomized, double blinded and controlled study. 90 indoor patients between age group of 18-70 years of either sex of ASA physical status I/II who were to undergo lower abdominal surgeries including gynaecological, orthopaedic and surgical were selected for the study. Parameters like post operative analgesic effects, onset, peak level and two segment regression of sensory block and onset, peak and recovery of motor block, time of rescue analgesia and various side effects were assessed on administration of clonidine at a dose 60 mcg intrathecally and 75 mcg of bupivacaine and comparing the same with bupivacaine hydrochloride alone.
Results: Of 90 patients, the mean age group of the patients was 34, mean weight was 56 kgs and average height was 106 cm. The number of males was 63 and females were 27. Patients receiving bupivacaine 0.5% and different doses of clonidine 60 mcg and 75 mcg (group B and group C) respectively produced significant sensory and motor blockade, increases in time of rescue analgesic with lesser side effects compared to bupivacaine alone receiving group. When compared group B and group C, group receiving highest dose of clonidine produced good results compared to group B.
Conclusions: It is concluded that patients receiving bupavacaine with clonidine at different doses produced significant anaesthetic, analgesic effect and lesser side effects compared to bupavacaine alone receiving group.

Keywords: Spinal anaesthesia, Intrathecal clonidine, Bupavacaine

INTRODUCTION

Spinal anaesthesia as an anaesthetic technique for surgery was first used by August Bier in 1898, which is preferred method for surgeries on lower half of the body due to its efficacy, rapidity, minimal side effects on mental status, reduction of blood loss and protection against thrombo-embolic episodes.[1] It also reduces the risk of vomiting, pulmonary aspiration in patients with full stomach and with chronic airway diseases.

In routine practice, Spinal anaesthesia with bupivacaine is given for lower abdominal and limb surgeries. It also provides an analgesic effect in the initial post operative period and reduces the use of additional analgesia.[2] Patients receiving spinal anaesthesia, with local anaesthetic agent like bupivacaine, another intrathecal

drug as adjuvant had been administered that prolongs the analgesia.[3]

Various studies had shown that intrathecal clonidine produced prolonged spinal anaesthetic effect and reduced the need of post operative analgesic requirement. It is also evidenced that clonidine given intrathecally produced antinociceptive effects without any neurotoxicity and hence may be used in the treatment of somatic pain. Clonidine, an α2-adrenergic agonist has a variety of different actions, including the ability to potentiate the effects of local anesthetics.[4-7] It does not produce pruritus or respiratory depression and prolongs the sensory blockade and reduces the amount or concentration of local anesthetic required to produce postoperative analgesia.[4-6,8] The rationale behind intrathecal administration of clonidine is to achieve a high drug concentration in the vicinity of α-2 adrenoreceptors in the spinal cord and it works by blocking the conduction of C and Aδ fibres, increases potassium conductance in isolated neurons in vitro and intensifies conduction block of local anaesthetics.[9] Clonidine is now an acceptable adjuvant to local anaesthetics for epidural route; nevertheless clinical trials provide evidence that less clonidine is needed intrathecally than epidurally to produce nearly same analgesic effect with fewer side effects.

Therefore authors were interested to conduct a prospective, double blinded and randomized study on ninety patients and divided them in three groups namely A, B and C of thirty patients each with plain bupivacaine, bupivacaine with clonidine 60 mcg and bupivacaine with clonidine 75 mcg in lower abdominal surgeries. The effects on sensory parameters, motor parameters, postoperative analgesia along with various side effects shown by clonidine were assessed. The objectives of the study were aimed to determine time of onset, peak and two segment regression of sensory block, time of onset, peak and total duration of motor block, time of first rescue analgesia in all three groups along with side effects of clonidine in the concentrations of 60 and 75 mcg.

METHODS

This was a prospective, randomized, double blinded and controlled study, conducted in Lokmanya Tilak Muncipal Medical College & General Hospital, Mumbai, India in 90 indoor patients between age group of 18-70 years of either sex of ASA physical status I/II who were to undergo lower abdominal surgeries including gynaecological, orthopaedic and surgical. After obtaining approval from Departmental Review Board and ascertaining selection criterias, informed, valid written consent was obtained from each of the 90 patients for participation in the trial to study the post operative analgesic effects, onset, peak level and two segment regression of sensory block and onset, peak and recovery of motor block, time of rescue analgesia and assessment of various side effects of clonidine given intrathecally 60 mcg and 75 mcg along with bupivacaine in comparison with bupivacaine hydrochloride alone. Patients having ASA III/IV status, age below 18 years and/or above 70 years of age, hypersensitive to the drug, with brady arrhythmias or AV block, haemodynamic instability, bleeding diathesis, gross spinal deformity, peripheral neuropathy, patients on chronic analgesic therapy, local infection at the site of injection were excluded from the study.

Preoperative evaluation was carried out in all patients with detailed clinical history, physical examination including height, weight, evidence of spinal deformities or any neurological disease and mental status of the patient. Vital parameters were noted and systemic examination was performed along with general and spine examination.

Complete haemogram, urine analysis-routine and microscopic examinations were carried out. Fasting and postprandial blood sugar levels, electocardiogram and X-ray chest, blood urea nitrogen and serum creatinine and other investigations according to the requirements were carried out in patients more than 40 years.

The patients were randomly divided into three groups. Group A: 3 ml Bupivacaine 0.5% (Hyperbaric)+0.4 ml normal saline; Group B: 3 ml Bupivacaine 0.5% (Hyperbaric))+60 mcg clonidine and Group C: 3 ml Bupivacaine 0.5% (Hyperbaric)+75 mcg clonidine were treated. Preoperatively adequate starvation was confirmed and baseline heart rate, blood pressure were noted. Noninvasive monitoring was started using cardioscope, pulse oximeter and sphygmomanometer. Patients were premedicated with Ranitidine 1 mg/kg and Ondanesetron 0.08 mg/kg.

Anaesthetic procedure

After explaining the patient about the procedure, subarachnoid block was given in sitting position with midline approach with aseptic precautions using 25G spinal needle. After confirming the clear and free flow of cerebrospinal fluid, the study drug was injected intrathecally as per the grouping. Patients were immediately placed in supine position with a pillow supporting the head and shoulders. Oxygen face mask was applied with flow rate of 5 l/min. The highest level of sensory block was checked by pinprick method caudal to cephalad direction every 2 minutes after the procedure of subarachnoid block was complete and time taken to achieve this was noted.

Motor block was checked by Modified Bromage scale.[10]

0 - Full flexion of knees and feet (0% block)
1 - Just able to flex knees, full flexion of feet possible (partial)(33%)

2 - Unable to flex knees, but some flexion of feet possible (acceptable)(66%)
3 - Unable to move legs or feet (100%)

Vital parameters like heart rate, arterial blood pressure, respiratory rate, peripheral oxygen saturation and sedation score noted every 1 minute for 5 minutes thereafter every 5 minutes till 30 minutes then every 30 minutes till 2 hours then at 3rd hour then every 2 hourly till 12 hours. Surgery was allowed after satisfactory subarachnoid block was established.

Intra-operatively sedation was graded as follows:[11]

0 - Wide awake
1- Sleeping comfortably, responding to verbal commands
2 - Deep sleep but arrousable
3 - Not arousable

At the end of surgery, no prophylactic pain relief was given and patients were transferred to post anaesthesia care unit and monitoring was continued for vital parameters. Sedation score, level of sensory block, motor level and visual analogue score (VAS) were noted every 15 minutes for first 2 hours, every 30 minutes for next 4 hours and thereafter at 2 hours interval for 12 hours.

Duration of sensory blockade was defined as - from the time of injection of subarachnoid drug till the level of regression upto L5-S1. Level assessed by re-appearance of sensation on heel and sole of foot. Duration of motor blockade from the time of injection of subarachnoid drug till the time when patient was able to flex hip, knee and ankle (Bromage scale 0) of non-operated limb in case of limb surgery.

Postoperative pain was assessed by visual analogue score (VAS) using a pain scale measuring 10 mm with 1 mm marking.[12]

Duration of analgesia was considered as interval from time of intrathecal injection to the time of rescue analgesic demanded postoperatively or when VAS score was more than 40 mm, Inj. Tramadol 1 mg/kg intravenously was used as rescue analgesic. The total number of analgesic doses in the first 12 hours was noted. All the patient were observed for any side effect or complications in the postoperative period for 12 hours and complications if occurred were noted and treated with conventional methods.

Statistical analysis

The results were statistically analysed using Analysis of Variance (ANOVA). Multiple Bonferroni test was carried out for intergroup comparison. The 'p' value of <0.05 was considered as statistically significant.

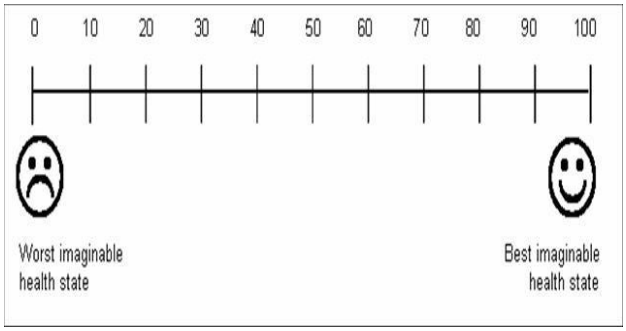

Figure 1: Visual analogue score scale.

RESULTS

This prospective randomized double blinded study was carried out in 90 adult patients of either sex undergoing lower abdominal surgeries under subarachnoid block. The patients were divided into three groups of thirty patients each using chit method and received drug as follows: Group A: receiving 3 cc plain bupivacaine 0.5% (H)+placebo (normal saline); Group B: Receiving 3 cc plain bupivacaine 0.5% (H)+Clonidine 60 mcg; Group C: Receiving 3 cc plain bupivacaine 0.5% (H)+Clonidine 75 mcg.

Table 1, presents the demographic data, shows the comparison of mean age, weight, height, duration of surgery, male female ratio (M:F) and ASA grade I, II among the three groups (A, B, C) of patients. Test applied for age, weight, height was ANOVA (analysis of variance) and for M: F and ASA grading Chi square test. P-value for each of these variables is >0.05 indicating that there is no significant difference among the three groups with respect to these variables.

Table 2 shows that majority of the surgeries done in all three groups were of equal distribution.

Table 3 shows, the comparison of sensory parameters including onset of action, time to achieve peak sensory block and time for 2 segment regression. It was found that all three groups had significant difference for all these parameters.

Mean time for 2 segment regression was calculated and the difference was significant when group A with B and group A with C was compared and was not significant when group B with C was compared as shown in Table 4.

Table 5 presents, comparison of motor parameters including time of onset, time to achieve peak level and total duration of block. It was found that all three groups had significant difference among all these parameters.

Table 1: Demographic data.

	Group A		Group B		Group C		ANOVA
	Mean	S.D.	Mean	S.D.	Mean	S.D.	p-value
Age	34.83	13.496	34.07	13.049	34.7	13.334	0.972
Weight	56.47	7.66	56.93	7.917	57.53	7.243	0.863
Height	160.97	6.936	161	7.061	161.87	6.827	0.851
DOS	76.5	42.164	82	44.365	82	44.365	0.853
Sex (%)	**Chi square= 0.317 p value= 0.853**						
Male	21(33.30%)		20(31.70%)		22(34.90%)		Total 63
Female	9(33.30%)		10(37%)		8(29.60%)		Total 27
ASA grade (%)	**Chi square=0.443 p-value=0.801**						
I	21(33.30%)		23(37.40%)		21(33.30%)		Total 65
II	9(36%)		7(28%)		9(36%)		Total 25

Table 2: Comparison of types of surgeries.

Name of surgery	Group A		Group B		Group C	
	n	%	n	%	n	%
IHR	6	20.00	6	20.00	6	20.00
HDCR	2	6.66	0	0.00	0	0.00
SSG	5	16.66	6	20.00	4	13.32
ORIF Patella	3	10.00	2	6.66	4	13.32
APP	8	26.66	9	30.00	7	23.33
Colostomy	1	3.33	0	0.00	0	0.00
TF ORIF	1	3.33	2	6.66	3	10.00
F ORIF	1	3.33	1	3.33	1	3.33
T EF	1	3.33	3	10.00	1	3.33
WW	1	3.33	0	0.00	0	0.00
BKA	1	3.33	0	0.00	0	0.00
Total	30	100	30	100	30	100

Table 3: Comparison of sensory parameters.

Time	Sensory Parameters						
	Group A		Group B		Group C		ANOVA
	Mean	S.D.	Mean	S.D.	Mean	S.D.	p-value
Onset	4.87	1.502	3.37	1.351	3.17	1.416	<0.001
Time for peak level	11.83	3.677	11.63	3.662	6.1	1.9	<0.001
2 Segment regression	81.33	7.107	120.77	7.128	121.4	9.22	<0.001
Multiple Comparisons Bonferroni							
Dependent Variable	Group category					p-value	
Onset	Group A		Group B			<0.001	
	Group A		Group C			<0.001	
	Group B		Group C			1	
Time peak Level	Group A		Group B			1	
	Group A		Group C			<0.001	
	Group B		Group C			<0.001	
2 segment regression	Group A		Group B			<0.001	
	Group A		Group C			<0.001	
	Group B		Group C			1	

Table 4: Comparison of sensory peak level.

Sensory peak	Group A		Group B		Group C		Total	
	n	%	n	%	n	%	n	%
T6	15	34.90%	14	32.60%	14	32.60%	43	100.00%
T8	15	31.90%	16	34.00%	16	34.00%	47	100.00%
Total	30	33.30%	30	33.30%	30	33.30%	90	100.00%
Chi square= 0.089; p-value =0.956								

Table 6 shows the mean time of rescue analgesia (Tramadol 1 mg/kg). ANOVA test was applied on three groups and showed significant difference. Mean total number of analgesics required in all three groups were 2.67± 0.661 in group A, 2± 0 in group B and 1.83± 0.379 in group C which was statistically significant.

Table 5: Comparison of motor parameters.

	Group A		Group B		Group C		ANOVA
	Mean	S.D.	Mean	S.D.	Mean	S.D.	p-value
Onset	5.63	2.008	4	1.41	3.3	1.343	< 0.001
Time for max	11.97	4.14	11.6	3.233	7.3	2.83	<0.001
Duration motor	158.47	12.665	168.63	7.078	180.57	8.435	<0.001
Multiple Comparisons Bonferroni							
Dependent variable			**Group category**				**p-value**
Onset			Group A	Group B			0.001
			Group A	Group C			<0.001
			Group B	Group C			0.291
Max Block			Group A	Group B			1
			Group A	Group C			<0.001
			Group B	Group C			<0.001
Duration			Group A	Group B			<0.001
			Group A	Group C			<0.001
			Group B	Group C			<0.001

Table 6: Comparison of time of rescue analgesia.

	Group A		Group B		Group C		ANOVA
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**p-value**
Time of RA	172.53	18.54	197.33	11.87	216.60	13.77	<0.001
Analgesics	2.67	0.661	2	0	1.83	0.379	0.001
Multiple Comparisons Bonferroni							
Dependent variable	**Group category**						**p-value**
Time of rescue analgesia	Group A			Group B			<0.001
	Group A			Group C			<0.001
	Group B			Group C			<0.001
No. of analgesics in 12 hrs	Group A			Group B			<0.001
	Group A			Group C			<0.001
	Group B			Group C			0.438

Table 7 presents changes in heart rate during observation period and it was found that fall in pulse rate was more in patients receiving bupivacaine along with clonidine intrathecally (Group B and C) as compared to patients receiving only bupivacaine (Group A).

Baseline pulse rate in all three groups was comparable. After 5 min of post spinal comparative fall in pulse rate was higher in group B and group C as compared to group A and when group B and C were compared the fall in pulse rate was slightly more in group C. There was

gradual fall in the pulse rate in group B and C which was lowest at around 90 minute and it remained for further 4 hours.

Changes in systolic blood pressure in observation period were tabulated in Table 8. Fall in Systolic blood pressure was more in group B and C as compared to group A. Although baseline B.P in all three groups was comparable, after 5 minute of spinal anaesthesia fall in systolic blood pressure was more in group B and group C than group A. Between group B and group C, group C showed slight fall in systolic blood pressure and 3 patients from group B and 3 from group C required injection.

Changes in diastolic blood pressure in observation period were shown in Table 9. It was found that baseline blood pressure in all three groups was comparable. 5 minutes after spinal anaesthesia, fall in diastolic blood pressure in group B and group C was higher as compared to group A and in between group B and group C, it was slightly more in group C. In all three groups diastolic blood pressure showed gradual decrease which was maximum at around 60 min and then it showed increasing in all the groups.

Level of sedation (compared by Ramsay Sedation Score) among the three groups in observation period are presented in Table 10. No patient was sedated preoperatively. It was observed that patients in group B and group C were more sedated as compared to those in group A and in between group B and group C, group C patients were more sedated. The maximum level of sedation was present till 90 min in group B and group C, later on it showed gradual fall in level of sedation.

Table 7: Comparison of pulse rates.

Time	Pulse rate						
	Group A		Group B		Group C		ANOVA
	Mean	S.D.	Mean	S.D.	Mean	S.D.	p-value
0 min	80.33	5.803	78.93	7.315	79.3	6.919	0.056
1 min	81.07	5.771	75.87	6.981	76.03	6.36	0.003
2 min	81.67	6.514	75.23	6.811	75.37	6.25	<0.001
3 min	81.47	6.725	73.43	6.831	73.87	7.055	<0.001
4 min	80.47	6.356	72.07	6.416	71.33	6.915	<0.001
5 min	77.8	6.403	70.3	6.513	68.6	5.84	<0.001
10 min	75.57	6.089	67.73	6.225	64.73	5.477	<0.001
15 min	74.13	5.806	65.4	5.858	63.5	5.557	<0.001
20 min	72.7	6.018	62.57	6.067	59.5	5.482	<0.001
25 min	70.6	6.055	59.7	5.26	56.7	3.725	<0.001
30 min	69.3	6.67	57.53	5.05	54.9	3.325	<0.001
60 min	68.1	6.397	56.4	4.477	53.8	3.089	<0.001
90 min	68.57	6.632	56.63	5.732	53.5	3.267	<0.001
2 hr	72.9	6.37	57.2	6.815	55.97	5.543	<0.001
3 hr	76.47	5.698	60.1	8.302	60.6	6.826	<0.001
4 hr	78.97	4.507	66.4	7.171	68.97	6.338	<0.001
6 hr	78.83	4.8	69.87	7.157	72.67	5.441	<0.001
8 hr	78.97	4.895	73	7.268	75.97	4.279	<0.001
10 hr	78.7	4.617	74.4	7.271	77.33	2.82	0.007
12 hr	77.9	4.122	76.23	5.71	77.03	4.263	0.401

Table 11 shows at 3rd hour when level of sensory block started wearing off group A had VAS 3.57± 0.93, Group B had 3.63±0.556, and Group C had 3.23± 0.679, which was not statistically significant, but comparison of gradual increase among them starting from 60 min was statistically significant. Likewise at 8th hour also the p value was notsignificant but before and after that it was significant varying according to the doses of rescue analgesia given in the three groups.

Table 12 displays incidence of side effects in all groups. Bradycardia was found in 5 cases of group B and 4 cases of Group C, Hypotension was observed in 3 cases of group B and C, nausea/ vomiting as 1 case each, in group A and B. Sedation score as RSS 2 was 2 cases in group B and 18 cases in group C was found considering RSS 2. No patient in any group had fall in respiratory rate below 12/min, fall in Spo2 < 95%, urinary retention or high spinal level.

Table 8: Comparison of systolic blood pressure.

Time	Systolic blood pressure						
	Group A		Group B		Group C		ANOVA
	Mean	S.D.	Mean	S.D.	Mean	S.D.	p-value
0 min	126.33	11.29	125.67	9.038	123.87	7.219	0.573
1 min	126.67	11.888	124.73	9.519	123.53	7.04	0.453
2 min	126.53	11.849	122.93	9.962	118.57	21.757	0.14
3 min	125.67	11.639	120.67	9.371	118.93	7.1	0.021
4 min	124.13	11.673	118.2	8.826	115.4	7.127	0.002
5 min	122.07	11.925	115.6	8.7	112.2	6.975	<0.001
10 min	120.27	12.83	113.33	8.21	109.47	6.495	<0.001
15 min	118.07	13.125	109.53	7.551	106.07	5.595	<0.001
20 min	116.4	13.291	107.93	6.378	103.27	5.159	<0.001
25 min	114.87	13.643	106.07	5.717	100.87	3.665	<0.001
30 min	113.4	11.805	104.53	5.532	101.67	4.003	<0.001
60 min	111.93	10.77	104	4.068	101.47	4.1	<0.001
90 min	113.73	9.392	105.47	4.812	102.53	4.577	<0.001
2 hr	116.2	8.652	107.6	4.966	105.33	6.288	<0.001
3 hr	119.33	8.425	113.27	6.716	109.2	5.372	<0.001
4 hr	121.53	8.382	119.07	7.441	114.93	5.324	0.002
6 hr	123.2	7.402	120.73	6.654	116.67	6.065	0.001
8 hr	123.67	7.595	123.53	7.551	120	4.549	0.062
10 hr	123.53	8.283	127.27	8.196	121.33	4.342	0.007
12 hr	123.13	8.046	127.47	8.186	122.33	6.261	0.021

Table 9: Comparison of diastolic blood pressure.

Time	Diastolic Blood Pressure						
	Group A		Group B		Group C		ANOVA
	Mean	S.D.	Mean	S.D.	Mean	S.D.	p-value
0 min	76.93	8.283	74.87	7.696	76.87	6.027	0.473
1 min	77.07	8.25	74.27	7.158	76.8	6.025	0.257
2 min	77.2	8.248	73.73	7.909	74.87	6.781	0.209
3 min	77.07	8.217	73.07	7.714	72.73	7.076	0.057
4 min	76.6	8.19	71.73	8.03	71.47	7.537	0.022
5 min	75.93	8.111	69.53	7.496	68.47	6.862	<0.001
10 min	73.67	8.222	68.33	7.429	66.13	6.301	<0.001
15 min	72.27	7.978	65.8	7.49	64.87	6.72	<0.001
20 min	71.07	7.856	64.87	7.176	63.13	6.574	<0.001
25 min	70.6	8.054	64	7.047	62.2	6.266	<0.001
30 min	69.47	8.102	62.73	6.378	61.67	5.175	<0.001
60 min	69.2	6.9	63.13	6.05	61.13	5.27	<0.001
90 min	69	6.449	64.93	7.08	63.2	5.598	0.002
2 hr	70.67	7.303	65.53	7.118	65.47	5.964	0.005
3 hr	71.2	7.819	68.07	7.817	68.2	6.895	0.195
4 hr	72.6	8.037	72.53	6.684	71.27	7.325	0.733
6 hr	74.37	7.641	76.47	5.501	73.33	7.581	0.214
8 hr	74.87	7.624	77.67	5.04	75.33	7.303	0.233
10 hr	74.8	7.712	77.67	5.04	76	6.747	0.245
12 hr	76.23	8.468	78.2	5.156	76.67	6.065	0.494

Table 10: Comparison of sedation score.

Time	Sedation Score						
	Group A		Group B		Group C		ANOVA
	Mean	S.D.	Mean	S.D.	Mean	S.D.	p-value
0 min	0	0	0	0	0	0	.
1 min	0	0	0	0	0	0	.
2 min	0	0	0	0	0	0	.
3 min	0	0	0	0	0.03	0.183	0.372
4 min	0.07	0.254	0.03	0.183	0.13	0.346	0.346
5 min	0.1	0.305	0.67	0.479	0.5	0.509	<0.001
10 min	0.2	0.407	0.73	0.45	0.77	0.568	<0.001
15 min	0.27	0.45	0.87	0.346	1.1	0.662	<0.001
20 min	0.3	0.466	1.03	0.183	1.23	0.728	<0.001
25 min	0.3	0.466	1.07	0.254	1.43	0.774	<0.001
30 min	0.3	0.466	1.07	0.254	1.43	0.774	<0.001
60 min	0.3	0.466	1.07	0.254	1.4	0.77	<0.001
90 min	0.03	0.183	1.07	0.254	1.37	0.809	<0.001
2 hr	0	0	0.83	0.379	0.87	0.776	<0.001
3 hr	0	0	0	0	0.43	0.504	<0.001
4 hr	0	0	0	0	0	0	.
6 hr	0	0	0	0	0	0	.
8 hr	0	0	0	0	0	0	.
10 hr	0	0	0	0	0	0	.
12 hr	0	0	0	0	0	0	.

Table 11: Comparison of visual analouge scale.

Time	Visual Analouge Score							
	Group A		Group B		Group C		ANOVA	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	F	p-value
0 min	0	0	0	0	0	0	.	.
1 min	0	0	0	0	0	0	.	.
2 min	0	0	0	0	0	0	.	.
3 min	0	0	0	0	0	0	.	.
4 min	0	0	0	0	0	0	.	.
5 min	0	0	0	0	0	0	.	.
10 min	0	0	0	0	0	0	.	.
15 min	0	0	0	0	0	0	.	.
20 min	0	0	0	0	0	0	.	.
25 min	0	0	0	0	0	0	.	.
30 min	0.03	0.183	0	0	0	0	1	0.372
60 min	0.9	0.662	0.1	0.305	0.1	0.305	30.762	<0.001
90 min	2.2	0.887	1.23	0.43	1.23	0.43	24.244	<0.001
2 hr	3.1	0.662	2.57	0.568	2.57	0.568	7.873	0.001
3 hr	3.57	0.935	3.63	0.556	3.63	0.556	0.089	0.915
4 hr	1.83	1.177	1.33	1.918	1.33	1.918	0.858	0.428
6 hr	3	0.871	1.33	0.994	1.33	0.994	30.462	<0.001
8 hr	3.07	0.907	3.33	1.124	3.33	1.124	0.636	0.532
10 hr	3.07	1.23	1.2	1.864	1.2	1.864	12.35	<0.001
12 hr	2.87	1.042	1.57	1.104	1.57	1.104	14.386	<0.001

Table 12: Comparison of side effects.

Side effects	Group A	Group B	Group C
B	1	3	3
H	0	3	3
N/V	0	1	1
S (RSS-2)	0	2	18
UR	0	0	0
HS	0	0	0

DISCUSSION

Spinal anaesthesia is a popular, simple and reliable anaesthetic technique for lower abdominal and lower limb surgeries. It has been used widely in clinical practice of anaesthesia because of rapid onset, high reliability and low cost. It produces excellent operating conditions and has high success rate. Though it provides effective analgesia in the initial postoperative period, the effect needs supplementation of potent opioid analgesics systemically to extend the period. Systemic opioids have been associated with respiratory depression, nausea, vomiting, itching, and urinary retention.

Hence, attempts were made to increase duration of analgesia produced by subarachnoid block by adding various agents intrathecally, like opioids e.g morphine, buprenorphine, hydromorphone, fentanyl, and non-opioids e.g ketamine, neostigmine, midazolam but none of them have been accepted in clinical practice due to their side effect or non-availability.

Clonidine, is an α-2 adrenergic agonist that produces analgesia in humans mediated by α-2 adrenoreceptors, located postsynaptically in the dorsal horn of spinal cord. Administered intrathecally it has shown good results, as it prolongs the duration of intrathecally administered local anaesthetics and has potent antinociceptive properties.[7,8] Although such prolongation of the effects of local anaesthetics has also been reported for oral and IV9 administration, the intrathecal route is more effective in prolonging bupivacaine spinal anaesthesia.[8,12] Clonidine achieves a high drug concentration in the vicinity of α-2 adrenoreceptors in the spinal cord. It blocks the conduction of C and Aδ fibres, increases potassium conductance in isolated neurons in vitro and intensifies conduction block of local anaesthetics.[9]

A number of studies have been carried out using intrathecal clonidine in dose range of 5 mcg to 150 mcg along with different doses and baricity of bupivacaine to determine the most advantageous combination in terms of effects versus side effects, but best in our knowledge not a single study is there for 3 ml bupivacaine 0.5% hyperbaric along with 60 mcg and 75 mcg clonidine.7,9 Therefore authors were interested to evaluate and compare the effects of, intrathecal clonidine 60 mcg and 75 mcg added to 3 ml bupivacaine 0.5% hyperbaric and 3 ml bupivacaine with placebo (0.4 ml Normal saline), on the quality of subarachnoid block, postoperative analgesia and side effects in patients undergoing lower abdominal surgeries.

In the present study, 90 patients (as most of the studies were carried out with this sample size) belonging to ASA I/II, between 18-60 years of age (as wide variety of studies show safety of clonidine in elderly age group also) undergoing lower abdominal surgeries were studied. Patients were randomly divided into three groups of 30 each using chit method, where group A received 3 ml bupivacaine 0.5% hyperbaric with 0.4 ml Sodium chloride (0.9%), group B received 3 ml bupivacaine. (0.5% hyperbaric) with clonidine 60mcg and Group C received 3 ml bupivacaine (0.5% hyperbaric) with clonidine 75 mcg. We used 3 ml bupivacaine 0.5% hyperbaric in all three groups as the study included all lower abdominal surgeries which needed level upto T6 level. To avoid bias, patients on any analgesic or sedative medication were excluded. They were premedicated with Inj. ranitidine 1 mg/kg and Inj. Ondanesetron 0.08 mg/kg. In the present study all three groups were comparable in terms of demographic parameters, duration of surgery and the nature of surgery.

In the present study, it was found that, time of onset of action of sensory block was 4.87±1.502 min, 3.37±1.351 min, and 3.17±1.416 min in groups A, B and C, respectively. It showed that adding clonidine to bupivacaine decreased the time of onset of action of block when compared with placebo group. The difference was not significant in between clonidine 60 mcg and 75 mcg groups, probably because difference of doses was small and sample size chosen to comment on this was also not sufficient. Regarding onset-time, Saxena et al found a dose dependant hastening of onset with addition of clonidine.[13] They used clonidine in the doses of 15 mcg, 30 mcg and 37.5 mcg added to 12.5 ml bupivacaine 0.5% hyperbaric and found the lowest onset-time with the 37.5 mcg which was significantly lower than the 13.5 mcg group.

Peak level of sensory block achieved by all three group patients was either T6 or T8 which was significantly different. This can be explained as in all three groups 3 ml of hyperbaric bupivacaine was used, equal volume of drug was injected with equal speed, and ultimately according to the positioning of the operation table, the level of the block was achieved. This was similar to the results found by Sethi et al and Saxena et al who found no difference between the extension of sensory block.[9,13]

In the present study, time to achieve peak level was 11.83±3.67 min, 11.63±3.62 min and 6.1±1.9 min in group A, B and C respectively, which was significant except in comparison of bupivacaine +placebo group with bupivacaine+clonidine 60 mcg group. Similar results were reported by Saxena et al.[13] This finding was different from that reported by Grandhe et al who found no difference in the time to achieve peak level.[14] In this study, time for two segment regression was 81.3±7.1 min, 120.7±7.1 min and 121.4±9.22 min, showing increased

time for regression when clonidine was added to bupivacaine groups as against bupivacaine+placebo group, but no significant difference was found when bupivacaine+clonidine 60mcg group and bupivacaine+clonidine 75 mcg group were compared. This was similar to the findings of Dobrydnjov et al who found that time for two segment regression of sensory block on dependent side (in unilateral block) was significantly lesser in bupivacaine+placebo group compared to bupivacaine+clonidine 30 mcg group.[8] Grandhe et al also found significant prolongation of sensory block (regression to L4 segment required 3.8hour in plain bupivacaine group as against 4.9 hour and 6.2 hour in the clonidine 1 mcg/kg and 1.5 mcg/kg groups respectively).[8]

Time to achieve peak level (modified Bromage III) was 11.97±4.14 min, 11.6±3.23 min and 7.3±2.83 min in group A, B and C respectively showing decrease in the time to achieve the level with addition of clonidine. However no significant difference was found on comparing bupivacaine+clonidine 60 mcg group and bupivacaine+ clonidine 75 mcg group. Total duration of motor block was 158.47±12.6 min, 168.63±7 min and 180.57±8.43 in group A, B and C respectively, showing dose dependent increase.

The prolongation of motor block in the present study was comparable to studies of Sethi et al, Saxena et al and Grandhe et al.[9,13,14]

When maximum level of motor block achieved was measured (modified Bromage III score) it was found that all three groups showed Bromage III level. This result was supported by study conducted by Dobrydnjov et al who found no significant differences in motor block (between Groups B and BC15) with addition of clonidine although the dose of clonidine was lesser compared to the present study.[8]

In the present study it was found that clonidine significantly increased the interval from spinal anaesthesia to the first request for supplemental analgesia (Tramadol 1 mg/kg) in dose dependent manner. A reduction in the analgesics demanded by patient in observation period (12 hours) was 2.67±0.661 in group A, 2± 0 in group B and 1.83± 0.379 in group C. Similar results were reported by Neimi et al and others.[1-9,13,14]

The mean sedation score in bupivacaine+clonidine 75 mcg group was highest among the three with lowest in bupivacaine+placebo group. In bupivacaine+clonidine 75 mcg group 18 patients had Ramsay Sedation Score 3 (sleepy but arousable after glabellar tap) which is the highest level of sedation achieved in the our study, as against only 2 in bupivacaine +clonidine 60 mcg group and none in bupivacaine +placebo group. Sedation is a well-known effect of clonidine. Kanazi et al have reported that intrathecally administered α2-agonists have a dose-dependent sedative effect.[15] The results were similar to those of Sethi et al.[9]

In the present study it was found that, the pulse rate was comparatively lower intraoperatively in the patients who received clonidine, 3 patients in group B and 3 patients in group C required treatment for bradycardia, as against 1 in group A who required the treatment (Inj. Atropine). This difference is statistically insignificant. Grandhe et al reported in their study that hypotension following intrathecal administration of a bupivacaine-clonidine combination is more commonly associated with the use of hyperbaric solutions, a low dose of bupivacaine and a high dose of clonidine.[14]

CONCLUSION

Addition of clonidine 60 mcg and 75 mcg to 3 ml 0.5% hyperbaric bupivacaine for lower abdominal surgeries decreases the time taken for onset and achievement of peak levels of sensory and motor blockade without significant haemodynamic instability. Addition of 75 mcg clonidine significantly prolongs the total duration of analgesia, sensory and motor blockade without additional side effects as compared to clonidine 60 mcg.

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