Original Research Article

Efficacy of low dose intrathecal clonidine as an adjuvant to 0.5% hyperbaric bupivacaine for spinal anaesthesia

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Abstract

Background and Aims: Nowadays intrathecally various drugs adjvents are being used for the purpose of enhancing spinal action of local anaesthetic agents hence postoperative analgesia. The aim of this study was to observe the efficacy of low dose of Clonidine as an adjuvent to 0.5 % hyperbaric Bupivacaine for spinal anaesthesia. **Methods:** In this study total100 patients of age between 20 years and 50 years of either gender belonging to ASA Class I or Class II posted for elective lower abdominal and lower limb surgeries were selected for the study. The study population was randomly divided into 2 groups with 50 patients in each group (N=50). All cases were randomly allocated to two groups in double blind manner. Group B(Control group):received 2.5ml (12.5mg) of 0.5% hyperbaric Bupivacaine intrathecally. Group BC(Study group): received 2.5ml (12.5mg) of 0.5% hyperbaric Bupivacaine +1µg/kg of Inj. Clonidine intrathecally. Onset of sensory block noted and time to achieve highest level was recorded. Duration of sensory block was assessed by time to regression of analgesia to S2 segment. Degree of analgesia was assessed by scale as 1-4 (excellent to poor), degree of motor block assessed by Bromage scale Vitals parameters like Pulse, BP, RR, SpO2, sedation score and complications like PONV, sedation were noted. Postoperative pain was assessed using Visual Analog Scale (VAS) Score.Inj. Diclofenac 75 mg given intramuscularly at VAS 5 or as a rescue analgesic when demanded by patient. Total duration of analgesia was calculated from time of intrathecal injection to rescue analgesic given. **Results:** Results were analysed using Standard t test. Duration of effective analgesia was 130.4 ±13.24 Min. in Group B and 307.4 ± 41.93 Min. in Group BC (p value<o.oo1). Sedation and adverse effects were comparable in between two groups. **Conclusion:** To conclude use of clonidine with bupivacaine effectively increases the duration of anaesthesia hence postoperative analgesia and also provides sedation.

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INTRODUCTION

Pain is a complex human perception and always has its systemic implications. Pain is difficult to measure as it is subjective in nature. Inadequate treatment of postoperative pain may delay the therapeutic outcome and also may add fear and anxiety in indoor patients. Spinal anaesthesia is a safe, reliable and inexpensive technique with the advantage of providing surgical anaesthesia and also postoperative pain relief by adding various adjuvant drugs along with local anesthetic agents. Spinal anaesthesia is therefore commonly employed for lower abdominal & lower limb surgeries than general anaesthesia[1,2]. However hyperbaric bupivacaine alone

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may be insufficient to provide complete analgesia despite the high sensory block above T_4 level[3]. Therefore smaller doses of bupivacaine supplemented by intrathecal adjuvants have been recommended for spinal anaesthesia in lower abdominal and lower limb surgeries[1,3]. Different drugs like opioids and non-opioids are used as an adjuvant drugs along with local anaesthetic agents. Opioids can be associated with number of side effects. This prompted further research to develop non-opioid analgesics as adjuvents with fewer sideeffects[4]. Recently α-2 adrenoreceptor agonists are being evaluated as adjuvant to local anaesthetic agents because of their sedative, analgesic and hemodynamic stabilizing effects in neuraxial anaesthesia. Intrathecal administration of clonidine acts on α-2 adrenoceptors in spinal cord and blocks the conduction of C and Aδ fibers, increases potassium conductance and intensifies block of local anesthetics.[5,6] It thus exerts its antinociceptive effect and provides dose-dependent analgesia. The possibility that intrathecal administration of clonidine may produce better analgesic effect compared to epidural administration, with fewer side effects and at lower doses, provides the rationale of evaluating intrathecal clonidine[1]. However clonidine also has been tried epidurally for control of pain[7] For intrathecal use most of the available literatures have shown utilization of clonidine in low to high doses in the range of 30-150µg with 0.5% hyperbaric bupivacaine.But higher doses of clonidine results in reduction of mean arterial pressure and sedation[4]. Therefore it was proposed to conduct the study of efficacy of low dose intrathecal Clonidine along with 0.5% hyperbaric bupivacaine.[8,9] The Aim of this study was to evaluate the efficacy of clonidine 1µg/kg intrathecally with Bupivacaine over spinal anaesthesia, postoperative analgesia and side effects if any.

METHODS

After the approval of Hospital Ethical Committee and obtaining proper consent from participants, this study was conducted on 100 patients of age between 20 to 50 years of either gender belonging to ASA Class I or II posted for elective lower abdominal and lower limb surgeries. The study population were randomly divided into 2 groups with 50 patients in each group (n=50) in double blind manner. Group **B**(Control group): received 2.5ml (12.5mg) of 0.5% hyperbaric Bupivacaine intrathecally. Group **BC**(Study group): received 2.5ml (12.5mg) of 0.5% hyperbaric Bupivacaine +1µg/kg of Clonidine intrathecally. All the patients were thoroughly evaluated and investigated before surgery and valid written consent obtained after explaining the procedure and VAS to each one of them.

Exclusion criteria:

Patients belonging to ASA class III or IV, height less than 150 cm and patients having any absolute contraindications for spinal anaesthesia were excluded from study. Data was collected in prescribed proforma meeting the objectives of the study of both group B and BC**.** In operating room intravenous line was obtained and preloading done with Ringer lactate 7ml/kg. Premedication with antacid and antiemetics given and monitors were attached (Defigaurd 5000 multipara monitor by Schiller India pvt Ltd.) Lumbar puncture was performed at the level of L_2–$L_3$with 25G needle in sitting position and study drug injected and following parameters were noted.

- Onset of sensory and motor blockade, time taken to attain maximal blockade
- Hemodynamic changes and side effects if any, time for two segments sensory regression.
- Total duration of sensory blockade and motor blockade, total duration of analgesia was noted.

Sensory level was determined by pinprick using 24 gauge hypodermic needle, tested every 5 minutes till maximum level was attended. Quality of motor blockade was assessed according to modified Bromage scale from grade 0- grade lll Sedation was judged by Ramsay Sedation Score 1-6 All patients were monitored during the surgery and perioperative period till complete sensory and motor recovery. Postoperatively duration of spinal action, pain by VAS at the time of rescue analgesic and haemodyanamic parameters were also recorded.

Adverse effects: All patients were monitored for any signs of cardiovascular toxicity, haemodynamic changes and other complications. The adequacy of surgical anaesthesia was determined on the basis of the patient's subjective response to surgery and comfort. If there was pain or discomfort during surgery, Inj. Fentanyl 1µg/kg with Inj. Midazolam 0.02mg/kg was given intravenously. Patients were evaluated for possible adverse events related to drugs every day until discharge from the hospital and at a follow up of 2-3 weeks after surgery.

Statistical analysis:-Parametric Data was expressed as Mean ± Standard deviation. Analysis of data was done by using student's unpaired t-test for parametric data and Fischer exact test for non- parametric data. P value less than 0.05 was considered to be significant.

RESULTS AND OBSERVATIONS

Demographic characteristics involved were age, height, weight and ASA grade. Pre-operative heartrate, blood pressure and respiratory rate were recorded prior to administering the block and at intervals of[1,3,5,10] minutes and every 10 minutes till end of the surgery. Bromage scale and level of sensory block at[2,4,6,8] and 10 minutes were recorded.

Table 1: The patient characteristicsare shown

CHARACTERISTICS		GROUP B (Bupivacaine)	GROUP BC (Clonidine)	P value
Age (years)		38.94±7.4	37.48± 6.9	0.3895
Weight (kgs)		53.74±5.45	46.68±4.5	0.391
Height (cms)		161.06±5.9	159.76±5.7	0.267
GENDER	Males	27 (54%)	23(46%)	0.469
	Females	23 (46%)	27 (54%)	
ASA	Grade 1	38 (76%)	40 (80%)	0.8097
	Grade 2	12 (24%)	10 (20%)	

Parametric Data expressed as Mean ± S.D. There was no statistical difference among groups as far as age, height, weight, Gender and ASA grade of the patient (P > 0.05).

Table 2: Mean Time for onset of sensory blockade

Parameter	Group B (Bupivacaine)	Group BC (Bupivacaine + Clonidine)	P value
Onset of sensory blockade (in mins) Mean ± S.D.	4.336± 1.555	2.200±0.528	0.001

Onset of sensory analgesia was defined as loss of pinprick sensation at the perineum. Time required for loss of pinprick sensation at perineum was quick in study groups and found to be statistically significant (P < 0.05).

Mean Time For Maximum Sensory Blockade In Minutes Time required to reach maximum sensory level was between 4 to 26 minutes but was shorter for Group BC (study group(Clonidine) ie. 2.20 ± 0.562 min while Mean time required to reach maximum sensory level in Group B (0.5% hyperbaric Bupivacaine) was longer i.e. 4.336 ± 0.52min. This differencewas statisticallyhighly significant(p<0.05)

Table 3: Mean Time For Onset For Motor Blockade

PARAMETER	GROUP B (Bupivacaine)	GROUP BC (Bupivacaine+Clonidine)	P VALUE
Mean Time for Onset of Motor Blocked	7.80 ± 2.914	2.45 ± 0.582	0.001

The onset of motor blockade was recorded when patient had inability to raise the extended leg (Grade I Bromage scale).

The mean time for onset of motor blockade in Group B (0.5% hyperbaric Bupivacaine) was 7.80 ± 2.91 minutes and in Group BC (0.5% hyperbaric Bupivacaine+1µg/kg Inj. Clonidine) was 2.45 ± 0.58 minutes i.e. earlier than control group and statistically was highly significant. (P <0.05)

Time required for motor blockade:

Table 4: Mean Time Required For Maximum Motor Blockade

Parameter	Group b (bupivacaine)	Group bc (bupivacaine+ clonidine)	P value
MEAN TIME TO MAXIMUM MOTOR BLOCKADE (MINUTES) Mean ± S.D.	8.04 ± 1.087	6.81± 0.925	0.001

The mean time required to achieve maximum motor blockade in Group B was 8.04 ± 1.087 mins and in Group BC was 6.81± 0.925 The difference seen between them was statistically significant(Figure – 3).

Table 5: Comparison of duration of analgesia.

Group	No. of pts.	Mean duration of analgesia in minutes	SD	ANOVA F-value	P value
Group B (Bupivacaine**)**	50	156.17	41.032	64.8	
Group BC (Clonidine)	50	346.83	79.871		<0.001

Duration of Analgesia in Group BC (Study group) was significantly longer ie. 346.83 min. than Group B(Control Group) 156.17. The duration of analgesia was compared between two groups by using ANOVA Test. The difference between two groups was found to be statistically significant. P value < 0.001(Fig. 4)

Vital Parameters: Basal pulse rate, blood pressures and SpO2 were comparable and statistically not significant in both group.

Table 6: Incidence Of Hypotension

PARAMETER	GROUP B (Bupivacaine)	GROUP BC (Clonidine)	P VALUE
No. of patients with Hypotension	3 out of 50 (6%)	6out of 50 (12%)	>0.05

Two patients in Group B (Bupivacaine) and 5 patients in Group BC (Clonidine) had hypotension and required vasopressors and additional fluids. Thus more patients required additional fluid and vasopressors in Group BC as compared to patients in Group B but this difference was found to be statistically not significant. (P > 0.05) (Table No 6)

Table 7: mean time for two segment regression

Parameter	Group b (bupivacaine)	Group bc (clonidine)	P value
Mean time for two segment regression (minutes) Mean ± SD	74.88± 11.155	130.72± 11.794	**< 0.001**

Mean time of two segment regression of sensory analgesia in Group B (0.5% bupivacaine) was130.72± 11.794mins was statistically significant. (P < 0.05)

Total Duration of Sensory Blockade

Table 8: Mean Total Duration Of Sensory Blockade

Parameter	Groupb (bupivacaine)	Group bc (clonidine)	P value
MEAN TOTAL DURATION OF SENSORY BLOCKADE (MINUTES) Mean ± S.D.	130.4± 13.24	**307.4 ± 41.933**	**< 0.001**

Return of pinprick sensation at great toe indicates full recovery from sensory blockade and mean time required for it (Total Duration of Sensory Block) was130.4 ± 13.24mins in Group B (Bupivacaine) and307.4 ± 41.933 Mins. In Group BC(Clonidine) and the difference was statistically highly significant**.** (P<0.0001)

Total Duration Of Motor Blockade

Table 9: Mean Total Duration Of Motor Blockade

Parameter	Group b (bupivacaine)	Group bc (clonidine)	P value
DURATION OF MOTOR BLOCKADE (MINUTES) Mean ± S.D.	147.80± 13.893	**307.34 ±46.029**	**<0.05**

The mean total duration of motor blockade in Group B (Bupivacaine) was147.80± 13.893 mins and in Group BC (Clonidine) was307.34 ±46.029mins and difference wasstatistically significant. (P < 0.05) (Figure 6)

Requirement of additional analgesia(intraoperative):

Table 10: Number Of Patients Requiring Additional Analgesia

Supplementation Analgesia	Group b (bupivacaine)	Group bc (clonidine)	P value
Required	6 (12%)	2 (4%)	0.3178
Not Required	44 (88%)	48 (96%)	

Patients who complained of pain or discomfort intraoperatively were supplemented with analgesia in Group B 6 patients required while only 2 patients in Group BC the difference was not statistically significant. (P > 0.05).

Complications: Complications Seen During The Study Is Tabulated In Table 10

Table 10: Complications

Complications	No. Of patients (%) Group b (bupivacaine)	Group bc (clonidine)
Nausea	3 (6%)	3 (6%)
Vomitting	1 (2%)	1 (2%)
Hypotension	3 (6%)	6 (12%)
Bradycardia	1 (2%)	3 (6%)
Shivering	4 (8%)	1 (2%)
Headache	0	0

Number of patients requiring vasopressors for **hypotension** was 3 in Group B (Bupivacaine) compared to 6 in Group BC (Clonidine). The difference was statistically insignificant. (P > 0.05) 1 patient in Group B (Bupivacaine) required Inj. Atropine for **bradycardia** while 3 patients in Group BC (Clonidine) required treatment for bradycardia. The difference was statistically in significant (P > 0.05) **Shivering** occurred in 4 patients in Group B (Bupivacaine) compared to 1 patients in Group BC (Clonidine).No patients in both the groups experienced post dural puncture headache.

Complications are comparable in both groups but hypotension is more common in study group however not severe enough or life threatning and easily reversible with ephedrine doses. Sedation score was compared between two groups. The difference among two groups was found to be statistically significant. (Table11)

Table 11: Comparison of mean sedation score

Group	No of patients	Mean sedation score	P
B Bupivacaine	50	1.93	<0.001 HS
BC Bupivacaine + Clonidine	50	2.63	

Sedation was more in clonidine group than bupivacaine received patients.

DISCUSSION

The subarachnoid block, even though mostly practiced, to make it ideal regarding enhanced duration of action in postoperative period many drug adjuvents were studied with local anaesthetic agents[10,11]. Intrathecal opioids were used many times even for labour analgesia and orthopedic surgery[12].However the combination with opioids would seem less attractive for obvious reasons. Clonidine is a selective partial alpha-2 adrenergic agonist is believed to be involved in the analgesic effect when injected intrathecally[5]. Different doses of Clonidine were studied intrathecally and reported some complications with higher doses. However intrathecal clonide in low dose appears to be effective with less complications [4,13]. Hence in this study we used 1ug/kg dose. As illustrated in tables below many authors conducted studies using clonidine as adjuvant in various doses intrathecally in different surgeries with complications. In this study we found a significant reduction in onset time of sensory and motor blockade also maximum block was attended within short interval. This finding was in concurrent with similar study conducted by Saxena H *et al*[18].This can be due to liphophilicity of clonidine, its spinal effects are more pronounced and selective after intrathecal than epidural administration. Clonidine has been demonstrated to prolong sensory and motor blockade from intrathecal local anaesthetics.[19,20] Similar l motor blockade of lower extremity in all patients was observed to be bromage grade III in clonidine group indicating the quality of blockade was satisfactory.[4,18] In this study we observed that the duration of action of spinal anaesthesia hence duration of postoperative analgesia was prolonged .[16,10,11] but duration was not extensive like that of some studies reported [10,23]. Higher doses 3µg/kg of clonidine [13] was effective but without additional benefit on contarary low doses 25-50µg were reported effective.[18,11] Dobrydnjoy *et al*[16] in their study found that addition of intrathecal clonidine prolonged analgesia and decreased morphine consumption post operatively more than oral clonidine. Intrathecal clonidine was also reported safe and effective even elderly with higher doses without affecting haemodynamic stability[24,25]. Inour study vital parameters were less affected as the lower dose of clonidine used however hypotesion was common observation but less threatening to life like other studies(intrathecal clonidine (150µg) reported as heart rate was unaffected[24,25]. However in our study six patients in clonidine group developed hypotension which was easily managed by IV fluids and vasopressers .None of the patients required any therapeutic intervention. In a study conducted by Sethi B S *et al*[4] authors observed lowest mean MAP (70 mm of Hg) in a clonidine group despite low dose (1µg /kg) Bradycardia was observed in these patients which was easily reversed with 0.6 mg inj atropine[10]

Table 12: depicting the various studies, doses and the effects of intrathecal clonidine

Author	Year	Dose of clonidine used	Onset of sensory block in clonidine group	Max sensory level attained	Duration of analgesia in clonidine group	Quality of motor block attained	Duration of motor block in clonidine group	Side effects
Benhamou D *et al*[14]	1998	75µg	–	–	183±80min	Bromage grade3	137±35 Min	Moderate sedation in 40% of patients
De kock M *et al*[15]	2001	15µg 45 µg 75 µg	–	T8 T8 T6	160±37min 183±80min 194±40min	Bromage grade3	137±32min 138±34min 164±38min	Fall in MAP in clonidine groupof 45 µg ,75 µg
Dobrydnjoy I *et al*[16]	2003	15µg 30 µg	–	T6 T8	274± 94 min 253 ±71 min	Bromage grade3	155± 37 min 182± 55 min	
Strebel S *et al*[9]	2004	37.5µg 75 µg 150 µg	–	T1 _T10	3a± 75 min 381± 117 min 445± 136 min	Bromage grade3	–	1/17 0/18 1/20 (mean arterial BP decrease >30%
Van Tugil *et al*[8]	2006	75µg	–	–	129± 13.8 min	–	–	No deleterious side effects
Kanazi GE *et al*[10]	2006	30µg	7.6±4.4min	T6 T5	272± 38 min	Bromage grade3	216± 35 min	Hypotention 3/16 patients
Kaabachi O *et al*[17]	2007	1µg/kg	–	–	461± 147 min	Bromage grade3	252± 79 min	Hypotention (12/42 patients) and Bradycardia(9/42 patients) in clonidine group
Sethi BS *et al*[4]	2007	1µg/kg	–	–	614 min	Bromage grade3	205 min	16 out of 30 patients had sedation in clonidine group
Grandhe RP *et al*[23]	2008	1µg/kg 1.5 µg/kg	7.1± 4.2 min 8.2± 3.4min	T6 T5	6.3± 0.8 hr 7.3± 0.9hr	Bromage grade3	142± 37.1 min 191.7 ±38.5 min	Hypotention 10/15 patient Hypotention 8/15 patients
Saxena H *et al*[18]	2010	15µg 30 µg 37.5 µg	1.48± 0.39min 0.95± 0.09min 0.92± 0.08min	–	164.53± 23.9 min 264.75± 44.3 min 285.6± 36.5 min	Bromage grade3	206.75 ±20.16 min 220 ±47.a min 235 ±31.9 min	Mean arterial BP decrease 2% in clonidine group 37.5 µg
Our study	2012	1 µg/kg	2.2±0.5 min	T_6	346.83± 79.8min	III	307.34±46 min	Hypotension Bradycardia Nausea
Khnadelwal M *et al*[11]	2018	30 µg 50 mg Magnesium	6±1.2 7.1±2.5	--	330.7±47. 246.2± 55.9	--	218.5 ± 52.7 138.3±25.7	Nausea ,Vomitting

Similarly In a study conducted incidence of bradycardia to be 30% in clonidine group (2µg/kg) which is higher than compared to our study and this may be due to larger dose of clonidine (2µg/kg) used[17]. Sedation was an additional advantage as patients were calm and comfortable intaraoperatively without any respiratory depression. More sedation observed in clonidine group. None of the patients in whom clonidine was used had a sedation score of more than 3. Similar observations found in a study conducted by Saxena H *et al*[18] How. But some studies reported no significance in mean sedation scores among the groups[9]. Incidence of bradycardia, nausea vomiting and respiratory depression was insignificant in both the groups. Also there was no any patient

complaining of postdural puncture headche in either group. Overall the occurrence of side effects was very less with the selected dose in study group. Thus it is concluded that intrathecal low dose Clonidine is effective regarding enhancing the quality of sensory blockade and duration of analgesia without significant complications. However further studies are recommended multi insttutional level in all age group and different surgeries to confirm its intrathecal efficiency and to evaluate the long term side effects if any.

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