Original Research Article

Comparison of two different doses of clonidine as adjuvant to intrathecal bupivacaine for prolongation of post-operative analgesia

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Abstract

Background: Postoperative pain relief is a growing concern for an anaesthesiologist as an uneventful postoperative period makes surgery a comfortable proposition of surgical patients. Clonidine is selective partial agonist of α_2- adrenoreceptors. It is known to increase both sensory and motor block of local anaesthetics. The purpose of this study was to compare the effects of 0.25µg/kg dose of clonidine along with 0.5µg/kg dose of clonidine added to intrathecal hyperbaric bupivacaine in evaluating prolongation of post-operative analgesia in patients undergoing surgeries below umbilicus. **Material and Methods:** Present study was single-center, prospective randomized double blind controlled comparative study, conducted in patients of 18-70 yrs, of either gender, of body weight 50-70 kilograms, belonging to ASA grade I and II, Undergoing elective major lower abdominal and lower limb surgeries, willing to participate 80 patients were randomly divided into 2 groups with 40 patients in each group as Group I Clonidine 0.25µg/kg with intrathecal hyperbaric Bupivacaine, Group II received Clonidine 0.5µg/kg with intrathecal hyperbaric bupivacaine **Results:** Both groups were similar with respect to age and gender distribution, ASA Grade, type of surgeries, onset of sensory blockade (min), onset of motor blockade (min), time taken for 2 segment regression (min), duration of sensory block (min), duration of rescue analgesia (min), duration of analgesia (min) and visual analogue score were compared between groups and difference was not significant statistically. Two patients in Group I and nine patients in Group II developed bradycardia requiring treatment. This is statistically significant between the two groups. Patients in Group I were observed to have better hemodynamic stability compared to patients in Group II. Conclusion**:** 0.25µg/kg dose of intrathecal clonidine provides maximum benefit and minimum side effects. It is recommended when prolongation of spinal anaesthesia is desired.

Keywords: intrathecal clonidine, bupivacaine, postoperative analgesia, spinal anaesthesia

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INTRODUCTION

Postoperative pain relief is a growing concern for an anaesthesiologist as an uneventful postoperative period makes surgery a comfortable proposition of surgical patients. In recent years, 0.5% bupivacaine has replaced 5% lignocaine for spinal anesthesia for its obvious advantages over the latter. Bupivacaine is three or four times more potent than lignocaine and has longer duration of action. Its disadvantages are slow onset of action and decreased motor block. Though the duration of anesthesia of bupivacaine is prolonged, it will not produce prolonged post operative analgesia. An adjuvant is required for prolonged post operative analgesia. Opioid analgesics produce intense, prolonged analgesic action without gross autonomic changes, loss of motor power or impairment of sensation other than pain when injected into subarachnoid or epidural space. Opioid analgesics can produce serious side effects like late and unpredictable respiratory

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depression, post operative nausea and vomiting, pruritis, urinary retention and activation of herpes labialis.[1] Clonidine (α_2 agonist) act on adrenoreceptors in the spinal cord and block the conduction of C and Aδ fibres, increasing potassium conductance and intensifies conduction block of local anaesthetics. Less than 150µg of clonidine has been shown to significantly prolong the anaesthetic and analgesic effect of bupivacaine in a dose depended manner. The purpose of this study is to compare the effects of 0.25µg/kg dose of clonidine along with 0.5µg/kg dose of clonidine added to intrathecal hyperbaric bupivacaine in evaluating the safety, efficacy, onset and duration of sensory and motor blockade as well as prolongation of post-operative analgesia in patients undergoing surgeries below umbilicus.

MATERIAL AND METHODS

Present study was single-center, prospective randomized double blind controlled comparative study, conducted in department of anaesthesiology, at Bharati Hospital attached to Bharati Vidyapeeth Deemed University Medical College, Sangli, Maharashtra, India. Study duration was of 18 months (December 2014 and May 2016). Study was approved by institutional ethical committee.

Inclusion criteria: Patients of 18-70 yrs, of either gender, of body weight 50-70 kilograms, belonging to ASA grade I and II, Undergoing elective major lower abdominal and lower limb surgeries, willing to participate

Exclusion criteria: Patient refusal for procedure. ASA grade III and IV. Emergency surgery. Physiological status in women subjects eg: Menstruating, pregnant or lactating women. Minor pathological status like under nutrition(BMI < 18.5 kg/m2), significant anemia (Hb <10 gm/dl). All contra-indications for regional anaesthesia

After explaining the anesthetic procedure to the patients, informed written consent was taken to include them in the study. A thorough pre-anaesthetic evaluation with general physical and systemic examination was done prior to the proposed surgery. History, general examination including recording pulse rate, blood pressure, airway assessment, examination of the respiratory and cardiovascular systems, spinal deformities and local infection at lumbar puncture site. Investigations Hemoglobin %, Bleeding and clotting time, Random or fasting blood sugar, Blood urea , Serum creatinine, Urine analysis for albumin, sugar and microscopy, Electrocardiogram, HIV and HbsAg status, Chest X-ray were carried out in all patients: In operation theater, 80 patients undergoing elective operative procedures under spinal anesthesia for lower abdominal and lower limb surgeries were randomly divided into 2 groups with 40 patients in each group

Group I (study group) (n=40) - received Clonidine 0.25µg/kg body weight with intrathecal hyperbaric Bupivacaine (total volume = 3ml)

Group II (control group) (n=40) – received Clonidine 0.5µg/kg body weight with intrathecal hyperbaric Bupivacaine (total volume = 3ml) All patients were prescribed 0.5 mg of alprazolam and ranitidine 150 mg orally the previous night. Patients were advised to be nil orally from 10pm onwards on the previous day of surgery. On the day of surgery intravenous access was secured with 18 gauge venous canula for fluid administration before the block. NIBP, ECG, Pulse oximeter monitors were connected and base line pulse rate, systolic and diastolic blood pressure, Mean arterial pressure and SpO_2 were recorded. A lumbar subarachnoid block was performed under strict aseptic precautions with the patients in the left lateral position with a pillow under the head and the table flat, in the L_3- L_4 interspace, midline approach, using 25 gauge Quincke's needle, after local infiltration of skin using 2 ml of 2% lignocaine. After obtaining free flow of clear CSF, drug was administered slowly, making sure of negative aspiration for blood. Patients were made to lie supine immediately after the completion of injection. The time of injection of the drug was recorded as 0 minute. During surgery, all patients were given intravenous fluids- Isotonic saline and Ringer lactate solution. Heart rate, Systolic Blood pressure, diastolic blood pressure, mean arterial pressure and SPO2 were monitored at 0min, 5min, 10min, 15min, 30min, 1hr, 2hr and 3hr Parameters such as time of onset of sensory blockade, time of onset of motor blockade, height of sensory blockade, duration of sensory blockade, duration of motor blockade, degree of fall in heart rate, Degree of fall in BP, two segment regression of sensory blockade, duration and quality of post-operative analgesia (by visual analogue scale) were studied. Intraoperative and postoperative complication were noted and managed accordingly. Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi- square test or Fisher exact test as applicable. P value less than 0.05 was considered as statistically significant.

RESULTS

Both groups were similar with respect to age and gender distribution. The mean age of the patient in group I was 47.9 ± 12.26 and group II was 48.33 ± 11.95. There was no statistical significance between the mean age, gender distribution of the patient between the groups.

Table 1: Age and gender Distribution

Age (Years)	Group I		Group II	
	Male	Female	Male	Female
< 25	2 (5%)	0	2 (5%)	0
26 – 35	1 (2.5%)	2 (5%)	3 (7.5%)	2 (5%)
36 – 45	4 (10%)	6 (15%)	1 (2.5%)	7 (17.5%)
46 – 55	7 (17.5%)	7 (17.5%)	6 (15%)	6 (15%)
56 – 65	4 (10%)	4 (10%)	6 (15%)	5 (12.5%)
> 65	2 (5%)	1 (2.5%)	0	2 (5%)
Total	**20**	**20**	**18**	**22**

47.5% of the patients in group I and 42.5% patients in group II belong to ASA Grade I, while 52.5% in group I and 57.5% in group II belong to ASA Grade II. The difference between the groups with regard to distribution of ASA physical status is not statistically significant. (P value > 0.05) Majority of patients (75% in group I and 85% in group II) underwent gynaecological and orthopaedic surgeries. The difference in the type of surgery between the two groups is statistically not significant. (P value > 0.05)

Table 2: Other characteristics

Characteristics	Group I		Group II	
	No. Of patients.	Percentage	No. Of patients.	Percentage
ASA Group				
ASA I	19	47.5%	17	42.5%
ASA II	21	52.5%	23	57.5%
Type of surgery				
Gynaecology	14	35%	17	42.5%
Orthopaedics	16	40%	17	42.5%
Urology	6	15%	2	5%
General surgery	4	10%	4	10%

Height, onset of sensory blockade (min), onset of motor blockade (min), time taken for 2 segment regression (min), duration of sensory block (min), duration of rescue analgesia (min), duration of analgesia (min) and visual analogue score were compared between groups and difference was not significant statistically.

Table 3: Anaesthesia Characteristics

Characteristics	GROUP I (Mean ± SD)	GROUP II (Mean ± SD)	P VALUE
Height	160.5 ± 7.07	160.08 ± 6.6	0.7843
Onset of sensory blockade (min)	2.13 ± 0.76	1.98 ± 0.62	0.3364
Onset of motor blockade (min)	3.25 ± 0.78	3.03 ± 0.66	0.1772
Time taken for 2 segment regression (min)	140.8 ± 10.82	144.38 ± 12.08	0.1666
Duration of sensory block (min)	318.6 ± 14.9	324.85 ± 14.96	0.0649
Duration of rescue analgesia (min)	313.48 ± 28.04	320.1 ± 26.85	0.2841
Duration of analgesia (min)	287.53 ± 24.56	295 ± 26.93	0.1987

With regard to the maximum level of sensory blockade attained, patients of group I, 27.5% attained T4 level, 32.5% achieved T6, 40% achieved T8. In group II, 30% attained T4 level, 32.5% achieved T6 level and 37.5% achieved T8 level. This data was not statistically significant as the P value > 0.05 as shown in table 4.

Table 4: Maximum level reached

Max. level reached	Group I		Group II		PValue
	No. Of patients.	Percentage	No. Of patients.	Percentage	
T4	11	27.5	12	30	0.8026
T6	13	32.5	13	32.5	1
T8	16	40	15	37.5	0.8181

The mean heart rate from basal to 5th minute recording is statistically not significant, between the groups (P value > 0.05). the mean heart rate from 10th min to 2hr is statistically highly significant between the groups (P value < 0.05). The

mean MAP from basal to 5th minute recording is statistically not significant, between the groups (P value > 0.05). the mean MAP from 10th min to 2hr is statistically significant between the groups (P value < 0.05).

The mean SBP at basal recording is statistically not significant, between the groups (P value > 0.05). The mean SBP from 5th min to 2hr is statistically significant between the groups (P value < 0.05). The mean DBP from basal to 5th min recording is statistically not significant, between the groups (P value > 0.05). The mean DBP from 10th min to 2hr is statistically highly significant between the groups (P value < 0.05). There was no significant difference pertaining to oxygen saturation between the two groups.

Table 5

Visual Analogue Scores	Group I	Group II	P Value
0 HR	0	0	
1 HR	0	0	
2 HR	1.05 ± 1.01	0.9 ± 1.01	0.5085
4 HR	3 ± 1.01	2.95 ± 1.01	0.8254

Table 6: Intra – operative side effects

Side-Effects	Group I		Group II		p value
	No. Of patients.	Percentage	No. Of patients.	Percentage	
Bradycardia	2	5%	9	22.5%	0.0232
Hypotension	3	7.5%	10	25%	0.034
Nausea and vomiting	1	2.5%	2	5%	0.5552
Shivering	3	7.5%	5	12.5%	0.4533

In group I, two out of forty patients and in group II nine out of forty patients developed bradycardia which is statistically significant. (P value < 0.05). In group I, three out of forty patients and in group II ten out of forty patients developed hypotension which is statistically significant. (P value < 0.05).

DISCUSSION

Spinal anesthesia consists of the temporary interruption of nerve transmission within the subarachnoid space produced by the injection of a local anesthetic solution into the cerebrospinal fluid. Used widely, safely and successfully for almost 100 years, spinal anesthesia has many potential advantages over general anesthesia, especially for operations involving the lower abdomen, the perineum and the lower extremities. Clonidine is a selective partial agonist of α_2– adrenoreceptors (α_2:α_1 =220:1). It is known to increase both sensory and motor block of local anesthetics. The analgesic effect following its intrathecal administration is mediated spinally through activation of postsynaptic α_2 receptors in substantiate gelatinosa of the spinal cord and it works by blocking the conduction of C and A delta fibers, increases potassium conductance in isolated neurons in vitro and intensifies conduction block of local anesthetics.[2] It also activates the descending inhibitory pathways (medullospinal pathways) and there by decreases the release of nociceptive substances from substantia gelatinosa. Roh *et al.*,[3] recently suggested that one of the mechanisms for the enhanced potency of intrathecal clonidine administration in a rat model of neuropathic pain is its ability to suppress phosphorylation of NMDA receptor subunit NR_1 in spinal dorsal horn neuron of rats. In our study, the mean duration of analgesia in group I was found to be 287.53 ± 24.56 minutes, and in group II was 295 ± 26.53 minutes. Though there is slightly more prolongation in group II but it was not statistically significant. Our study concurs with the study conducted by Strebel S *et al.*[4] who observed the mean duration of analgesia to be 381±117 mins when using clonidine of 75 µg and Grandhe PR *et al.*[5] observed the mean duration of analgesia of 6.3±0.8 hours when using clonidine of 1µg/kg with a mean weight of 60.6±19.4 kg. In a study conducted by Shilpashri A. M *et al.*,[6] authors observed the mean duration of analgesia was 240.8 minutes in clonidine group (30µg) which is comparable with our study. The slightly lower value of the mean duration of analgesia in their group is due to lower dose of bupivacaine (12.5mg) used compared to our study. In a study conducted by van Tuijl I *et al.*[7] authors observed the duration of analgesia to be 55 mins in control group (2.2ml bupivicaine, 0.5%,heavy) and 129 mins in clonidine group (75µg) which is less than that in our study. This difference could be probably due to the study population being pregnant women in whom there is rich vascularity of the spinal cord which can absorb the study drug to circulation very fast and gets eliminated and also due to the lesser mass of drug (11 mg bupivacaine) used compared to our study. The mechanism of clonidine induced potentiation of sensory block in spinal anaesthesia is reported to be mediated by presynaptic (inhibition of transmitter release) and post synaptic (enhancing hyperpolarisation) affects. Adding clonidine to intrathecal bupivacaine prolongs postoperative pain free period, appreciated by all the patients. These effects of clonidine are valuable in prolonged procedures such as repeat caesarean section.

When a procedure unexpectedly takes more time, it is reassuring to use a technique that results in an extended duration of analgesia and motor block, without serious side effects.[7] The mean duration of sensory block in group I was 313.48 ± 28.04 minutes varying from 253 to 364 minutes, and in group II was 320.1 ± 26.85 minutes, varying from 259 to 373 and found to be statistically not significant as the P value is > 0.05. B.S.Sethi *et al.*,[8] In his study found that the mean time of rescue analgesia in clonidine group was 614 minutes and in control group 223 minutes. These findings were comparable to our study but higher value of time of rescue analgesia in their study is attributed to the higher dose of clonidine (1µg/kg) used compared to our study. In a study conducted by Shilpashri A. M *et al.*[6], authors observed the mean time of rescue analgesia was 362.84 minutes in clonidine group (30µg) which is comparable with our study. Thus we can conclude that low dose intrathecal clonidine along with bupivacaine prolongs the duration of analgesia thus prolonging the first request of supplemental analgesics in the post operative period.

In the present study, there is no significant statistical difference in the visual analogue score of the patients in group-I in comparison with VAS in group-II recorded at 0 hours, 1 hour, 2 hours and 4 hours after giving spinal anesthesia. Brian D. Sites, *et al.*[9] concluded that the co administration of intrathecal clonidine and morphine decreases the 24-h IV morphine consumption and improves the 24-h VAS score when compared with intrathecal morphine alone. Since the difference in maximum decrease in mean heart rate between the groups is 2.37 bpm, it is clinically not significant. Two patients developed bradycardia in group I and nine patient in control group which is statistically highly significant (P = 0.0232). Bradycardia is easily reversed with 0.6mg IV atropine in all the patients in both the groups. In our study we noticed a prolonged decrease of heart rate in group II compared to group I. In a study conducted by Kaabachi O *et al.*[10] the authors observed the incidence of bradycardia to be 30% in clonidine (2 µg/kg) group which is higher compared to our study and this may probably due to larger dose of clonidine (2µg/kg) used compared to our study. Clonidine reduces heart rate partly by a presynaptically mediated inhibition of norepinephrine release at the neuroreceptor junction and partly by a vagomimetic effect. And also by direct depression of atrioventricular nodal conduction. In a study conducted by Dobrydnjov I *et al.*[11] the MAP was significantly lower during the first 45-120 min after spinal injection in clonidine group. The maximum changes from baseline values in MAP during this time varied from 11 to 19 mmHg for patients in clonidine group (15µg) and 15 to 20 mmHg for patients in clonidine group (30µg), which concurs with our study where in we noticed in group II that the MAP is significantly lower at 30th min (13.83 mmHg fall in mean MAP, 15.41% from basal). In a study conducted by Strebel S *et al.*[4] the maximum decrease in MAP was 25%±14%, 26%±12% and 25±13%, who received clonidine 37.5 µg, 75 µg and 150 µg respectively. In a study conducted by Kaabachi O *et al.*[10] the incidence of hypotension was 54% in clonidine group (2 µg/kg) probably this may be due to higher dose of clonidine used compared to our study.

Patients were observed for urinary retention, respiratory depression, dry mouth, sedation and other effects postoperatively for 24 hours. Both the groups have none of these effects.

CONCLUSION

Addition of intrathecal clonidine to bupivacaine even in very small doses significantly hastens the onset of sensory and motor block, provides excellent surgical analgesia, prolongs the duration of superior quality postoperative analgesia and reduced postoperative analgesic requirements with relative hemodynamic stability. 0.25µg/kg dose of intrathecal clonidine provides maximum benefit and minimum side effects. It is recommended when prolongation of spinal anaesthesia is desired as for example in patients scheduled for long lower abdominal or lower limb surgeries.

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