Original Research Article

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Comparative Study of Two Different doses of Intrathecal Clonidine with Bupivacaine for Postoperative Analgesia

Jayshri P. Prajapati

Associate Professor, Department of Anesthesiology, GMERS Medical College, Himmatnagar, Gujarat 383001, India.

Abstract

Background: α2-agonist prolongs the duration of intrathecally administered local anaesthetics. This study was planned to investigate the effects of 45 µg and 90µg clonidine added to 0.5% intrathecal hyperbaric bupivacaine for postoperative analgesia. *Materials and Methods:* This prospective study was conducted in 90 patients of ASA grade I and II, both sex and aged between 20-60years. Patients were randomly allocated to Group A receiving normal saline+bupivacaine, Group B receiving a combination of 45µg clonidine+bupivacaine and Group C receiving combination of 90µg clonidine+bupivacaine. Sensory block, Motor block, sedation score and hemodynamic parameters were recorded. *Results:* Time for onset of sensory block (2.9±0.78 min) and motor block (6.27±0.98 min) was significantly lowest in group C (2.9±0.78 min). ($p<0.01$) The duration of analgesia was significantly higher in group C (495.33±34.2 min) ($p<0.05$). The motor block was most prolonged and intense in group C (2.0±0.0 score at 1.5 hr). Maximum sedation was seen at the end of 3 hrs with mean score of 2.1±0.37 in group C as compared to 2.1±0.3 in group B and 1.06±0.2 in Group A. There was no significance difference between the groups for fall of blood pressure. Hypotension and bradycardia were significantly higher in group B and group C as compared to group A, but was within acceptable limits. *Conclusion:* Intrathecal 90 µg clonidine seems to be the optimum safe dose because it significantly prolongs postoperative analgesia and markedly decreases supplementary analgesic demand with minimum hemodynamic changes.

Keywords: Clonidine; Intrathecal; Analgesia; Bupivacaine.

Introduction

Regional anaesthesia techniques like subarachnoid block have got a definite and useful role in developing countries for various surgical procedures. To increase the duration of sensory anaesthesia and to prolong the duration of postoperative analgesia various drugs have been used in combination with local anaesthetics because postoperative analgesia is not only desirable but also is of utmost necessity for all surgical procedures [1]. Despite advances in the treatment of post-operative pain many patient still suffer from pain after surgery probably due to difficulties in balancing acceptable post-operative treatment regimen with acceptable side effect despite their efficacy, more wide use of opioid in intrathecal and epidural application had been limited by side effect. Various modalities had been used to provide optimum postoperative analgesia by various routes like oral, parenteral (i.m and i.v.) and neuraxia. Central mechanisms of pain relief which act by the inhibiting the release of neurotransmitters were always associated with at least theoretical possibility of respiratory depression.[2] Hence several forms of regional techniques were used more commonly for postoperative analgesia. Now a days use of intrathecal clonidine has its own advantages and disadvantages. The α2-agonist, clonidine prolongs the duration of intrathecally administered local anaesthetics by the activation of the α adrenoreceptor, located post synaptically in

Corresponding Author: Jayshri P. Prajapati, Associate Professor, Department of Anesthesiology, GMERS Medical College, Himmatnagar, Gujarat 383001, India.
E-mail: chaahathospital@gmail.com

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the dorsal horn of spinal cord and activating α adrenorecptors in the substansia gelatinosa which leads to analgesia [3]. Although such prolongation of the effects of local anaesthetics has been reported for oral and IV clonidine administration, the intrathecal route is more effective in prolonging bupivacaine spinal anesthesia [4].

Recent reports have established 1–2μg/kg intrathecal clonidine as an adequate dose for prolonging plain bupivacaine spinal anaesthesia in newborns, the optimal dose in adults in terms of effects versus side effects of intrathecal clonidine by itself is controversial. Clonidine, in the dose range of 150–450μg, causes marked hypotension, bradycardia and sedation. Because of this clinically relevant side effects, there is a tendency toward the use of smaller doses (<150μg)[5].

Such doses of clonidine producing only minimal side effects would be a true alternative to other technical or pharmacological procedures aimed at prolonging spinal anesthesia and analgesia, such as combined spinal epidural anaesthesia or intrathecal opioids, both of which have adverse effects or risks.

Clinical research using clonidine in the dose range of 15–100 μg, however, has focused primarily on labour analgesia [6] and there are only a few clinical studies testing such doses, often in combination with intrathecal opioids, in surgical procedures. Therefore, present study was planned to investigate the effects of clonidine in the dose range of 45 μg and 90 μg, added to 0.5% intrathecal hyperbaric bupivacaine for postoperative analgesia.

Materials & Methods

This prospective study was conducted in 90 patients of either sex, between the age group 20-60year, of ASA-risk I, II; in whom spinal anaesthesia was planned for different types of surgery after approval from the institutional ethics committee. Written informed consent from all the patients was obtained. These patients were randomly divided into three treatment groups using the random number chart. Group A received bupivacaine H 0.5% 15 mg (3.0 ml) + 0.6 ml Normal saline, Group B received a combination of bupivacaine H 0.5% 15 mg (3.0 ml) + clonidine 45μg (0.3ml) + 0.3 ml normal saline and Group C received combination of bupivacaine H 0.5% 15 mg (3.0 ml) + clonidine 90μg (0.6ml). Patients with history of allergy to local anaesthetics, severe cardiac or respiratory disease, psychiatric illness, mental retardation, clinical evidence of significant dehydration, haemoglobin concentration less than 8g/dl, local infection, bleeding disorder eg. haemophilia were excluded from the study.

Standard monitoring like continuous electrocardiogram, pulse oximetry, non-invasive automated blood pressure measurements and visual assessment of respiration was done and recorded. In all the patients, under strict aseptic and antiseptic precautions, lumbar puncture was performed in the sitting position, after giving local anaesthesia 2ml of 2% lignocaine with a 22G needle, using a 23-gauge needle positioned midline at the L_{3-4} interspace. After checking clear free flow of CSF and confirming with aspiration test the drug was given according to their groups. Surgical anaesthesia was checked by using pin prick method.

Pulse rate, blood pressure, sensory level and SpO_2 were recorded at 2 min interval there after every 15 min interval intra-operatively. They were recorded upto 24 hours after surgery and thereafter post-op care in the post-surgical wards. Hypotension was defined a decrease of more than 20% from the baseline mean arterial pressure, was treated with an incremental intravenous bolus of mephentermine 6 mg or inj.ephedrine IV.

Bradycardia (defined as heart rate less than 20%) was treated with IV atropine, if it was associated with hypotension. Inadequate anaesthesia (patient complaint of pain) was treated with an additional bolus of intravenous fentanyl 1 μg/kg or Inj tramadol 1mg/kg or Inj diclofenac 1.5 mg/kg, with a second bolus allowable.

Total duration of sensory block, defined as, time to regress to L1 level (assessed with pinprick), total duration of motor block (assessed with modified Bromage Scale), total duration of analgesia defined as time of spinal anaesthesia to first request for analgesic, onset of sensory block, onset of motor block, effect on sedation as assessed by Ramsay Sedation Score, effect on blood pressure and heart rate, complications were recorded.

Pain was assessed by visual analogue score (VAS). Visual analogue score (VAS) for pain was measured every 15 minutes for 1 hour then 2 hourly till 6 hours and 6 hourly till 24 hours.

The observations were tabulated and analyzed using appropriate statistical tools ANOVA test and for inter group unpaired "t" test was used. P value <0.05 was considered significant.

Results

All the three treatment groups were comparable with respect to demographic variables or scheduled surgery (Table 1).

The mean time of onset of sensory block was significantly lower (p<0.01) in both of the clonidine groups in a dose dependant manner compared to control (group A), lowest in group C (2.9±0.78 min) followed by group B (4.26±0.64 min). (Table 2)

Time to regression of spinal anesthesia below level L_1 was 140.1±16.8 min in Group A (control), 273.2±19.4 min in Group B and 315.8±19.1 min in Group C. The duration of sensory block was highly significant (p<0.01) in both clonidine groups compared to control (group A), and also between Group B and C. (Table 2)

The duration of analgesia was 179.67±19.6 min in Group A (control), 368±40.5 in Group B and 495.33±34.2 min in Group C and it was significantly higher (p<0.05) in both clonidine groups compared to control (group A), and also between Group B and C. (Table 2)

The mean time of onset of motor block was lowest in group C (6.27±0.98 min). Both clonidine groups (Group C - 6.27±0.98 min, group B - 6.63±0.99 min) had a significantly quicker onset (p<0.01), as compared to group A (7.77±0.93 min) (Table 2).

A complete motor blockade of the lower extremities was observed in all patients. The motor block was most prolonged and intense in group C as seen by scores at 1.5 hrs (2.0±0.0). The values were significantly higher (p<0.01) in all the clonidine groups compared to group A at all time points. The difference between group B and C was less significant (p<0.05), while the difference between A and C was found significant. (p<0.01) (Table 2)

Sedation was significantly greater in both clonidine groups as compared to control group A. Maximum sedation was seen at the end of 3 hrs with mean score of 2.1±0.37 in group C as compared to 2.1±0.3 in group B and 1.06±0.2 in Group A. (Table 2).

Table 1: Demographic profile of all the groups

	Group A (n=30)	Group B (n=30)	Group C (n=30)
Mean Age (yrs)	37.73 ± 7.70	37.4 ± 7.52	38.13 ± 7.52
Mean height (cms)	169.73 ± 6.82	170.2 ± 6.51	171.2 ± 4.80
Mean weight (kg)	67.36 ± 6.92	70.1 ± 6.42	69.7 ± 7.13
ASAI/II	2/28	6/24	7/23
M/F	13/17	17/13	15/15
Duration of Surgery	118.38±16.1	130±22.3	125.16±17.83

P value >0.05 (Non-significant)

Table 2: Comparison of block characteristics in all three groups

Parameter	Group A (n=30)	Group B (n=30)	Group C (n=30)
Onset of sensory block (mins)	5.7 ± 0.75	4.26±0.64*	2.9±0.78*
Onset of motor block (mins)	7.77 ± 0.93	6.63 ± 0.99*	6.27 ± 0.98*
Duration of Sensory Block (mins)	140.1 ± 16.8	273.2 ± 19.4*	315.8 ± 19.1*
Mean Bromage Score at 1.5 hrs	1.06 ± 0.25	1.93 ± 0.25*	2.0 ± 0.0*
Analgesia (min)	179.67 ± 19.6	368 ± 40.5**	495.33 ± 34.2**
Sedation	1.06 ± 0.2	2.1 ± 0.3	2.7± 0.5

*p value <0.01, **p value <0.05

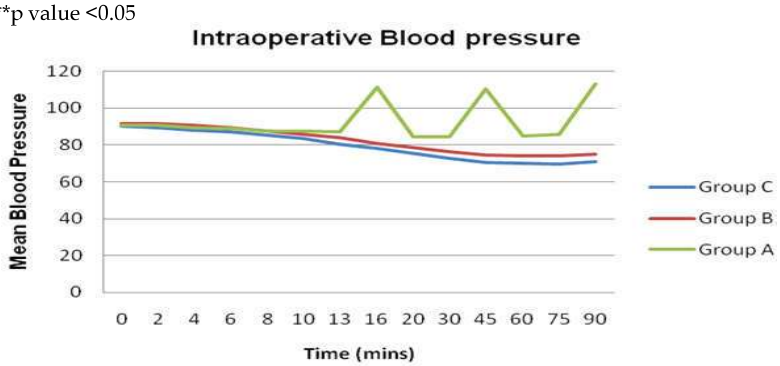

Fig. 1: Mean blood pressure changes in all the groups

Intragroup comparisons revealed a reduction of mean arterial BP in all three groups. However, a significant reduction was seen in group B and group C as compared to baseline. The mean of fall in mean blood pressure at the end of 60 min was 8.03±4.70, 19.93±5.99 and 23.1±5.43 mm of Hg in group A, group B and group C respectively (Figure 1).

The mean decrease in heart rate at the end of 60 min was 13.53±7.62, 26.16±12.19 and 28.96±15.39 bts/min in group A, group B and group C respectively. At the end of 60 mins there was significant ($P<0.05$) difference in decrease in heart rate between group A and other two groups. However, no patient in any group was treated for bradycardia throughout the period of observation (Figure 2).

The incidence of hypotension was significantly higher in group B and group C as compared to group A. The incidence of bradycardia was higher in group B and group C; but was within acceptable limits. 3 patients in group A, 5 patients from group B and 6 from group C suffered from vomiting (Table 3).

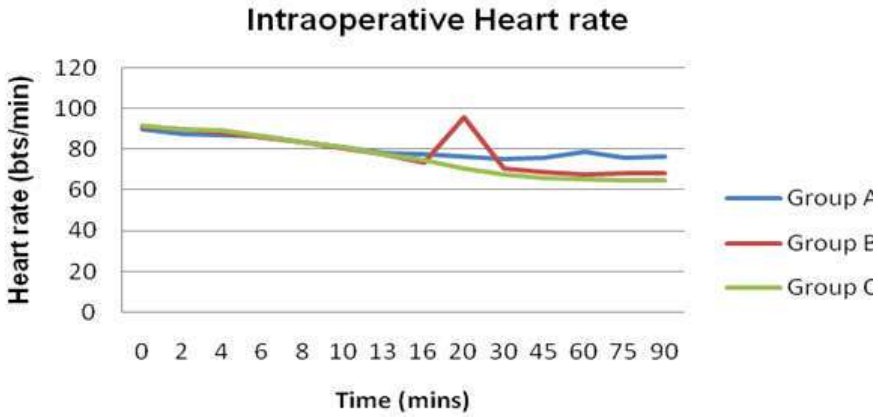

Fig. 2: Heart rate in all the groups

Table 3: Complications in all the groups

Complication	Group A (n=30) N (%)	Group B (n=30) N (%)	Group C (n=30) N (%)
Hypotension	3(10)	7(20.33)	9(30)
Bradycardia	0	9(30)	10(33.33)
Respiratory depression	0	0	0
Vomiting	3(10)	5(16.66)	6(20)
Shivering	7(20.33)	5(16.66)	6(20)
Urinary retention	3(10)	2(6.66)	2(6.66)

Discussion

Nowadays, various drugs are being used in combination with local anaesthetic drugs in spinal anaesthesia to increase the duration of postoperative analgesia with their own merits and demerits.[1] Enthusiastic efforts are still going on in this area of regional anaesthesia practice in search of an ideal agent and its optimum dose as adjuvant of local anaesthetics in spinal anaesthesia.

All the groups in present study were comparable. On intergroup comparison the early onset of sensory block was statistical significant between group C and control group A and between group B and control group while it was not significant between group B and group C indicating that the onset of anaesthesia is not dose dependent. On intergroup comparison there was significant difference between group C and control group; and group B and control group in mean time for onset of motor block. However there was no significant difference between group B and group C indicating that onset of motor block is also not dose dependent. Larsen et al found that there was no effect of addition of clonidine 45 µg and 90 µg to spinal mepivacaine 4% on time of onset and spread of anaesthesia [7].

In present study the prolongation of the duration of postoperative analgesia was statistical significant in group C when compared with control group A. Also, there was statistical significant difference between group B and group A. These finding suggests that the prolongation of the duration of postoperative analgesia by addition of clonidine intrathecally is dose related with the dose 90 µg

clonidine having maximum desirable effect. One study have also observed that the duration of pain relief was significantly prolonged in a group of patients receiving 150 µg in addition to bupivacaine as compared to group receiving less dose of clonidine [8]. Thus there was dose dependent prolongation in duration of postoperative analgesia when different dose of clonidine was added to bupivacaine in spinal anaesthesia. They concluded that 150 µg of clonidine seems to be preferred dose in terms of effect versus unwarranted side effect when prolongation of spinal anaesthesia was desired. Similar findings were found in Kaabachi et al. and Dobrydnjov et al. study [9,10].

In present study, the prolongation of sensory anaesthesia was statistically significant between group C and control group A. Also there was significant difference between group B and group A. These findings suggest dose related prolongation of spinal anaesthesia associated with intrathecal administration of clonidine which correlates well with the studies of Niemi et al and Bonnet et al. [11,12]. Similar results were also found in other studies [7,13].

Larsen et al and Bonnet et al observed decreases in heart rate intraoperativly in the group who received clonidine as compared to control group [7,12]. Similar findings intraoperatively found in present study also. And it was more in group C who received large dose of clonidine. In can be concluded that large dose of clonidine is related with higher incidence of bradycardia but was within acceptable limits [9,11].

In present study fall in MAP was statistically significant in group C compared to group A and group B at 30 min intraoperatively. This falls in MAP in group B remained significant up to 120 min intraoperatively when it became non-significant in comparison with control group. While the fall in group C remained significant throughout intraoperative period and in postoperative period up to 6th hour when it became non-significant in comparison to group A and group B. Similar results were found in other studies [7,9,11,12]. These findings suggests fall in MAP was dose related and also patients of Group C developed long lasting fall in MAP within acceptable limits.

Sedation was more pronounced in a group of patients receiving intrathecal clonidine 90 µg in addition to lidocaine in comparison with control group receiving only lidocaine in a clinical study done by Dobrydnjov et al [13]. In their study the most intense sedation was recorded in patients who received oral clonidine 300 µg (sedation 2.4±0.9). Niemi et al. had recorded in his study that patients receiving intrathecal clonidine 3 µg /kg mixed with 15 mg of 0.5% hyperbaric bupivacaine remained sedated for 3-6 hours after the injection compared to control group receiving only 0.5% hyperbaric bupivacaine [11]. In present study more patients in group C were having sedation score 3 postoperatively compared to group B and none in group A, while there was no significant difference in the sedation level between group B and Group C intraoperatively. Higher level of sedation was found in group who received large dose. Other studies have also shown similar results [13-15].

Intraoperatively respiratory rate was decreased in all three groups but there was no significant respiratory depression in any patient nor there statistically significant change in respiratory rate between the three groups. In our study the mean SpO_2 remained unchanged, in all the groups intraoperatively. Similarly results were found in Dobrydnjov et al study [13]. Post operative vomiting was found in all groups. This suggests that there was no increase in the incidence of postoperative vomiting by addition of intrathecal clonidine. Incidence of urinary retention was found less in clonidine group compared to control group while there was no significant difference between groups. Bonnet et al. have concluded that spinal clonidine produces significantly less urinary retention than intrathecal morphine [12].

Conclusion

In conclusion intrathecal clonidine (45 µg and 90 µg) with bupivacaine prolonged sensory blockage of spinal anaesthesia and post operative analgesia. Intrathecal clonidine 90 µg significantly, prolonged postoperative analgesia and markedly decrease supplementary analgesic demand with minimum hemodynamic instability. So, Intrathecal clonidin 90 µg seems to be the optimum safe dose for postoperative analgesia.

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