Evaluation of Clonidine as an Additive to Bupivacaine for Central Neuraxial Blockade

Bhat Ravindra R[1], Mathew Jibin Sam[2], Balachander Hemavathy[3], Mishra Sandeep Kumar[4]

[1]Associate Professor, Department of Anaesthesiology, Indira Gandhi Medical College & Research Institute, Kathirkamam, Puducherry 605009, India. [2]Senior Resident [3]Senior Professor [4]Professor & Head, Department of Anaesthesiology, Jawaharlal Institute of Postgraduate Medical Education and Research, Dhanvantari Nagar, Puducherry 605006, India.

Abstract

Context: Advantages of Epidural anesthesia over spinal anesthesia like lesser incidence of hemodynamic instability and postdural puncture headache are offset by delayed onset time and unreliable motor blockade. Clonidine has been used as an additive in epidural and spinal anesthesia to prolong the duration of action. *Aims:* To compare the effect of Clonidine as an Additive in Epidural and Spinal Anesthesia. *Settings and Designs:* We designed this study to compare the effect of clonidine in epidural and spinal anesthesia in 75 adult patients scheduled for lower abdominal surgeries. *Materials and Methods:* Seventy five adult patients were randomized to receive intrathecal 0.5% hyperbaric Bupivacaine, 3 ml (Group ITB), 0.5% hyperbaric Bupivacaine + 30 µg clonidine, 3 ml (Group ITBC) or 16 ml 0.5% Bupivacaine with 75 µg clonidine at L3-L4 inter vertebral space, 16 ml (Group EDBC). Onset time of sensory blockade, duration and degree of sensory and motor blockade, heart rate, blood pressure and sedation were noted periodically. *Statistical Analysis:* Analysis was done by one way ANOVA (variables over time), Turkey's posttest (parametric variables), Kruskal-Wallis test (Nonparametric variables). *Results:* Group EDBC had similar onset time of Group ITB. Sensory blockade was increased by 37% in EDBC and 27% in ITBC compared to ITB (212.2 ± 12.4 min, 230.4 ± 13.6 min and 166.8 ± 8.5 min respectively). EDBC had motor blockade similar to that of ITB. Hypotension and bradycardia were more severe in ITBC. *Conclusions:* Epidural bupivacaine with clonidine has better hemodynamic stability compared to intrathecal bupivacaine with similar sensory and motor blockade characteristics.

Keywords: Additive; Clonidine; Epidural; Intrathecal; Spinal; Subarachnoid.

How to cite this article:
Bhat Ravindra R, Mathew Jibin Sam, Balachander Hemavathy et al. Evaluation of Clonidine as an Additive to Bupivacaine for Central Neuraxial Blockade. Indian J Anesth Analg. 2020;7(1 Part -II):311-318.

Introduction

Many drugs have been tested to prolong the highly desirous properties of single dose neuraxial block. Opioids have been most successful in this regard but respiratory depression, urinary retension and pruritis are annoying side effects. In this background, clonidine an α$_2$-adrenergic agonist, stands out but its propensity to cause bradycardia and hypotension and sedation is well-known. Besides this, neuraxially administered clonidine also has antihyperalgesic action which is highly beneficial in postoperative period.[1]

Epidural has certain advantages over intrathecal anesthesia in terms of the lesser chance of postdural puncture headache and the relatively slower onset

---

of hypotension. However, its failure to consistently ensure adequate muscle relaxation makes it a less attractive choice for many anesthesiologists in lower abdominal surgeries. Besides this, onset of blockade is delayed in epidural compared to intrathecal route. Addition of clonidine has been shown to improve the muscle relaxation. We designed this study to directly compare the effect of clonidine through epidural route with that with intrathecal route as there are very few studies addressing this.

Materials and Methods

After obtaining approval by the institutional research and ethics committee, 75 patients aged between 20 and 60 of ASA-I and ASA-II physical status scheduled for elective lower abdominal surgery were recruited. ASA-III and IV patients, those with significant cardiovascular, renal, hepatic dysfunction, morbidly obese, and those having an allergy to either clonidine or bupivacaine were excluded from the study.

After the informed consent the patients were randomly allocated into one of the following Groups: Group ITB (intrathecal bupivacaine 0.5% hyperbaric Bupivacaine, 3 ml), Group ITBC (0.5% hyperbaric Bupivacaine + 30 µg clonidine, 3 ml), Group EDBC (16 ml 0.5% Bupivacaine with 75 µg clonidine at L3-L4 inter vertebral space, 16 ml).

Inside the OR, base line pulse rate, noninvasive blood pressure (Systolic BP, Diastolic BP and Mean BP) and oxygen saturation were recorded. Preloading was done with Ringer's lactate solution. Depending on the group allocated the anesthetic technique was performed. Noninvasive blood pressure, oxygen saturation, heart rate were monitored and recorded every five minutes. Onset of sensory level, maximum level of sensory blockade, duration of analgesia (the time of patient's first demand for analgesics) was also noted. Two segment regression level, degree of motor blockade by Bromage score (1-No impairment of movement of legs and feet, 2-Barely able to flex knees and no impairment of movement of legs, 3-unable to flex knees and barely able to move feet and 4-unable to move feet) and sedation Score 1–4 (1-agitated and uncomfortable, 2-awake and comfortable, 3-sleeping intermittently, 4-asleep wakes to touch) were assessed periodically during the surgery and 6 hours postoperatively.

The other parameters assessed were surgical relaxation as assessed by the surgeon, respiratory rate and oxygen saturation. The mephenteramine and atropine requirements were also recorded. Hypotension and bradycardia were treated with routine protocolized management measures.

Statistical Analysis

Statistical analysis was performed using SPSS version 17.0 and Graph Pad InStat 3.10. Statistical analysis of variables over time was evaluated by one way analysis of variance with repeated measures. Statistical analysis of parametric variables between groups was done by One Way ANOVA followed by Tukey's posttest. Intergroup comparisons between nonparametric variables were accomplished using Kruskal-Wallis test with posttest. Variation of nonparametric variables within a group was assessed by Friedman test.

Results

All three groups, were similar in their demographic characteristics. The three groups were similar with respect to baseline parameters *viz* heart rate, mean blood pressure, respiratory rate, hemoglobin oxygen saturation and sedation score.

Sensory Level

Addition of clonidine resulted in a faster onset of sensory level in both spinal and epidural group. The onset of sensory level to T10 was significantly faster in Group ITBC compared to Groups ITB and EDBC. There was no statistical difference between Groups ITB and EDBC in the time to onset of sensory level, (Table 1).

Table 1: Onset of sensory level in all three groups

Group	Onset of sensory level in minutes (Mean ± SD)
Group ITB	2.08 ± 0.5*
Group ITBC	1.52 ± 0.5*
Group EDBC	2.44 ± 0.6*

*$p < 0.05$.

ITB - Intrathecal Bupivacaine

ITBC - Intrathecal Bupivacaine with clonidine

EDBC - Epidural bupivacaine with clonidine

Duration of analgesia

Duration of analgesia was significantly prolonged in both the clonidine groups. Time to request for first analgesic was significantly more prolonged in Group EDBC when compared to the other Two Groups. Group EDBC > Group ITBC > Group ITB, (Table 2).

Bhat Ravindra R, Mathew Jibin Sam, Balachander Hemavathy / Evaluation of
Clonidine as an Additive to Bupivacaine for Central Neuraxial Blockade

313

Table 2: Duration of analgesia in all three groups

Group	Time to request for first analgesic (minutes) (Mean ± SD)
Group ITB	166.8 ± 8.5*
Group ITBC	212.2 ± 12.4*
Group EDBC	230.4 ± 13.6*

*p < 0.05.

ITB - Intrathecal Bupivacaine

ITBC - Intrathecal Bupivacaine with clonidine

EDBC - Epidural bupivacaine with clonidine

Two segment regression time

The two segment regression time was significantly longer in Group EDBC when compared to the other Two Groups. Group EDBC > Group ITBC > Group ITB. The regional block was successful in all patients and none of the procedures required conversion to general anesthesia, (Table 3).

Table 3: Two segment regression time in all three groups

Group	Two segment regression (minutes) (Mean ± SD)
Group ITB	83.6 ± 14.76*
Group ITBC	112.8 ± 17.45*
Group EDBC	135.4 ± 28.02*

*p < 0.05.

ITB -Intrathecal Bupivacaine

ITBC- Intrathecal Bupivacaine with clonidine

EDBC- Epidural bupivacaine with clonidine

Motor blockade

Motor blockade as assessed by the Bromage score was significantly more prolonged in the Group ITBC when compared to the other Two Groups, (Fig. 1).

There was no statistical difference in the surgical relaxation score as assessed by the surgeon between the Group's p = 0.2219, (Table 4).

Table 4: Surgical relaxation as assessed by surgeon

Group	Surgical relaxation score (1–10) #
Group ITB	8 (7–9)
Group ITBC	9 (8–9)
Group EDBC	8 (7–10)

Median (range)

ITB - Intrathecal Bupivacaine

ITBC - Intrathecal Bupivacaine with clonidine

EDBC - Epidural bupivacaine with clonidine

Hemodynamics

Addition of clonidine resulted in a greater drop in heart rate. The drop in heart rate occurs earlier in the Group ITBC as compared to Group EDBC. In Group ITBC statistically significant drop in heart rate was observed from 10 min onwards. In Group EDBC drop in heart rate was observed from 60 min onwards. The heart rate in Group ITBC was significantly lower than in Group EDBC between 2 min and 20 min. Heart rate at 60 min was significantly lower in Group EDBC when compared to Group ITB. There was significant difference between the heart rate in Group ITB and Group ITBC from 30 min onwards. Fig. 2. In Group ITBC there were three episodes of bradycardia that required treatment with atropine (12%). In the other Groups, there was no significant bradycardia that required use of atropine.

A statistically significant drop in mean arterial pressure was observed in Group ITB and Group ITBC from 2 min while similar trend in Group EDBC from 5 min onwards. MAP was significantly lower in Group ITBC than in Group ITB at 2 min, 5 min and from 30 min up to 120 min. There was a statistically significant difference in MAP between Group ITBC and Group EDBC from 2 min onwards, (Fig. 3). Among patients in Group ITBC mean mephenteramine requirement was significantly more than those in Group EDBC (p < 0.05). Between other Groups there was no statistically significant difference in the usage of mephenteramine, (Table 5).

Table 5: Requirement of atropine and vasopressors

| Group	Atropine	Mephenteramine (mg/patient) #	Total me phen teramine (mg)
Group ITB	0 (0%)	4.6 ± 2.7	114
Group ITBC	3 (12%)	5.5 ± 2.9*	138
Group EDBC	0 (0%)	3.5 ± 2.1*	87

Mean ± SD

*p < 0.05

ITB - Intrathecal Bupivacaine
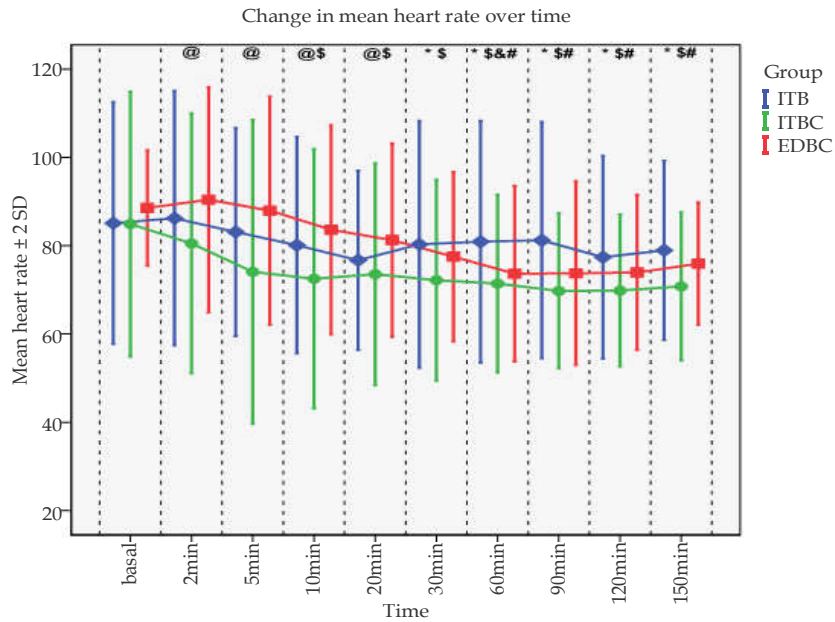
ITBC - Intrathecal Bupivacaine with clonidine

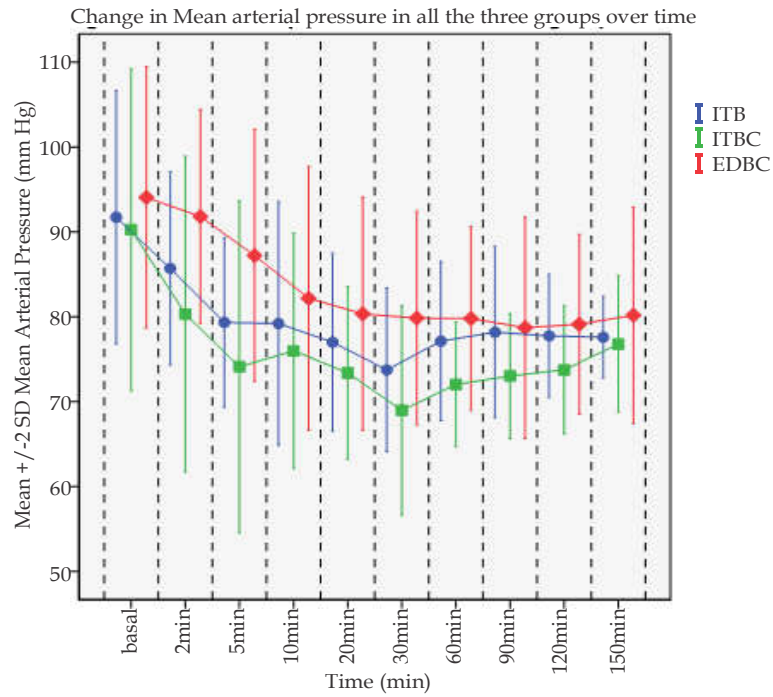EDBC- Epidural bupivacaine with clonidine

Sedation

Clonidine added to spinal or epidural bupivacaine makes the patient more sedated. Sedation is more intense in Groups ITBC and EDBC when compared to Group ITB as indicated by higher median sedation scores. Between Groups ITBC and EDBC more intense sedation is noted with Group ITBC. Statistically significant sedation is seen in Group EDBC till 3 hours after the block while it is seen in Group ITBC till 4 hours, (Fig. 4).
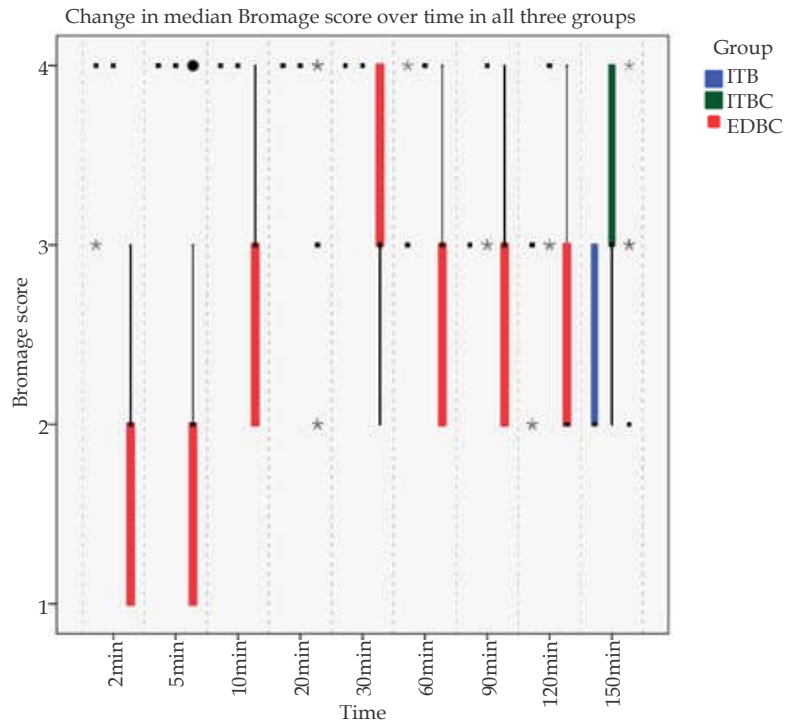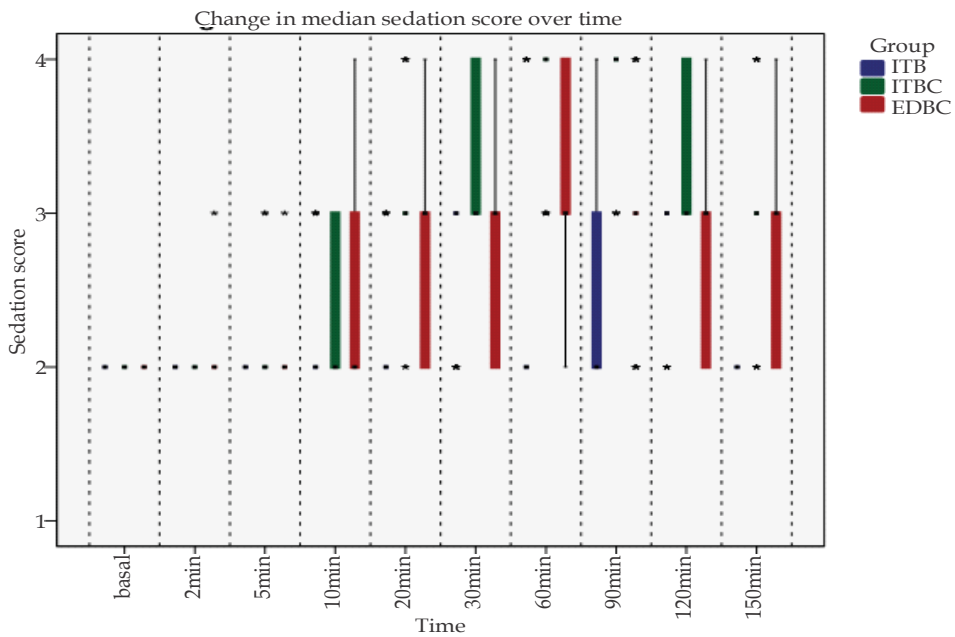
Fig. 1: Change in median Bromage score

ITB -Intrathecal Bupivacaine

ITBC- Intrathecal Bupivacaine with clonidine

EDBC- Epidural bupivacaine with clonidine

Fig. 2: Change in mean heart rate over time

ITB -Intrathecal Bupivacaine

ITBC- Intrathecal Bupivacaine with clonidine

EDBC- Epidural bupivacaine with clonidine

@ $p < 0.05$ between group ITBC and group EDBC

* $p < 0.05$ between group ITB and group ITBC

& $p < 0.05$ between group ITB and group EDBC

# $p < 0.05$ within group EDBC when compared to basal heart rate

$ $p < 0.05$ within group ITBC when compared to basal heart rate

Fig. 3: Change in Mean Arterial Pressure

ITB -Intrathecal Bupivacaine

ITBC- Intrathecal Bupivacaine with clonidine

EDBC- Epidural bupivacaine with clonidine

@p < 0.05 between group ITBC and group EDBC

* p < 0.05 between group ITB and group ITBC

& p < 0.05 between group ITB and group EDBC

# p < 0.05 within group EDBC when compared to basal heart rate

$ p < 0.05 within group ITBC when compared to basal heart rate

Fig. 4: Change in median sedation score

ITB -Intrathecal Bupivacaine

ITBC- Intrathecal Bupivacaine with clonidine

EDBC- Epidural bupivacaine with clonidine

Respiratory rate and Oxygen saturation

There was no significant drop in respiratory rate or oxygen saturation in the intraoperative or immediate postoperative period in all Three Groups. There were no intergroup differences in the blood pressure and the heart rate in the immediate postoperative period (6 hours).

Discussion

We observed that the addition of clonidine to epidural or intrathecal bupivacaine increased the duration of analgesia as assessed by the first request for analgesia by about 37% in Epidural Group and 27% in Intrathecal Group compared to bupivacaine - only intrathecal group (212.2 ± 12.4 min in Group ITBC, 230.4 ± 13.6 min in Group EDBC when compared to 166.8 ± 8.5 min in Group ITB), Table 2. Similarly the two segment regression time was significantly increased ($p < 0.05$) in groups receiving clonidine with 60% increment in epidural group and 37% increase in intrathecal group compared to plain bupivacaine intrathecal group (112.8 ± 17.45 min in Group ITBC, 135.4 ± 28.02 min in Group EDBC as compared to 83.6 ± 14.76 min in Group ITB), Table 3. Onset of sensory block is generally slower with epidural than with intrathecal anesthesia. However, we found that the onset of blockade when clonidine was added in the epidural group was comparable to the control intrathecal group, Table 1. This would reduce the time lost in waiting for the epidural anesthesia to take effect.

Motor blockade as assessed by Bromage score was significantly more in patients who had received intrathecal clonidine when compared to the other two groups till four hours postoperatively ($p < 0.05$). In Group ITBC the motor blockade outlasted the sensory blockade as assessed by the request for systemic analgesics. Therefore, we infer that addition of clonidine to bupivacaine to intrathecal space results in intense motor blockade which outlasts the sensory blockade. Several studies have reported similar finding of improved sensory and motor blockade.[2,3]

Clonidine by itself does not cause any motor blockade.[4] However, it potentiates the motor blockade caused by intrathecal local anesthetic.[5] Epidural clonidine exerts its effect through its escape into the intrathecal space and action in the spinal cord, direct action on the Aδ and C nerve fiber in the epidural space and through the vasoconstrictor effect which potentiates and augments the action of local anesthetic by increasing the effect site concentration.[6] The CSF concentration of clonidine after epidural and intrathecal administration is similar after 2 hrs.[7] So, the greater sensory and motor blockade observed in epidural group in our study may have been because of the other two actions.

As expected after a neuraxial block, there was a drop in mean arterial pressure in all the three groups, Fig. 3. This drop due to sympathetic blockade occurred later in the epidural group compared to the other Two Groups. Mean blood pressure in Group EDBC was significantly higher than in Group ITB during the first 10 min. This is as expected because epidural anesthesia is slower to set in compared to intrathecal blockade. After 10 minutes there was no significant difference in blood pressure between Groups ITB and EDBC. This shows that the addition of clonidine does not negate the better hemodynamic profile in epidural route.

Between the intrathecal groups, addition of clonidine resulted in lower blood pressure at 2 min, 5 min and from 30 min onwards till 120 min. Between the clonidine groups, epidural group had significantly higher mean arterial pressure than intrathecal group at all-time intervals. Addition of clonidine to intrathecal or epidural space is known to cause hypotension but the degree of hypotension is more severe in the case of intrathecal clonidine.[7] Clonidine produces hemodynamic effects due to their action in the brain stem and peripheral blood vessels after systemic absorption as well as the direct inhibition of sympathetic preganglionic neurons in spinal chord.[8,9] Epidural clonidine rapidly penetrates into the intrathecal space with peak concentration in the CSF is observed at 30–60 min.[9] In our study, the peak reduction in mean arterial pressure in epidural clonidine group occurred at 60–90 minutes after the procedure, (Fig. 3).

However, in the immediate postoperative period (6 hours) there was no significant drop in blood pressure in all the Three Groups from the baseline. This makes clonidine a safe additive for neuraxial blockade if the intraoperative hypotension is managed well.

Heart rate was significantly lower in clonidine groups compared to control, Fig. 2. Intrathecal route caused lower heart rate than epidural route. Decrease in heart rate which occurred earlier in intrathecal group as compared to epidural clonidine. In 3 out of the 25 patients (12%) receiving intrathecal clonidine, there was a significant drop in heart rate which required the use of atropine, (Table 5).

Bhat Ravindra R, Mathew Jibin Sam, Balachander Hemavathy / Evaluation of
Clonidine as an Additive to Bupivacaine for Central Neuraxial Blockade

317

The patients in groups receiving clonidine were more sedated than the control group, Fig. 3. Sedation to some extent with anxiolysis is a desirable property in a patient undergoing neuraxial blockade. Sedation commonly accompanies the use of clonidine for regional anesthesia due to its systemic absorption and action in the locus coeruleus in brain.[10] Contrary to expectation, cephalad migration in CSF producing delayed sedation does not happen. As a result, the amount of sedation should be regardless of the route of administration.[9] However, this was not what we observed. Intrathecal route produced more sedation due to clonidine than epidural group in our study, (Fig. 4). We could not find many studies comparing epidural clonidine to intrathecal clonidine to compare our observation.

Despite the increased sedation in clonidine groups, there was no statistically significant difference in the respiratory rate and the oxygen saturation between the three groups nor were these parameters significantly lower than the baseline in any of the groups. This reiterates the safety of neuraxial clonidine through neuraxial route. However, caution must be observed in patients who are prone for airway obstruction or when sedation is not desirable.

The 30 μg of clonidine used in the intrathecal group in our study might sound very small compared to the other studies where up to 150 μg were used.[1] However, despite a large number of trials, the optimum dose of intrathecal clonidine remains unknown.[11] Clonidine comes in 100–150 μg/ml preparations. 150 μg of clonidine will have a volume of 1–1.5 ml. When this volume is added to the local anesthetic, it dilutes the local anesthetic. The diminished action due to the dilution is made up by the addition of clonidine! Besides this, many studies comparing varying doses of intrathecal clonidine, topped up the final drug solution to a constant volume in order to ensure blinding between the groups. However, this is not how drug is administered in general practice. For example 2 ml of bupivacaine 0.5% heavy added with 50 μg of clonidine (0.3 ml of 150 μg/ml preparation) and made up to the final volume of 3.2 ml with saline (0.9 ml of saline)[10] is not same as the same preparation without saline. This factor should not be forgotten when applying the findings of these studies to practice. In our study, we did not use any saline to make up the volume. The total volume in the intrathecal groups were maintained at 3 ml by sacrificing the bupivacaine dose in the ITC Group. This factor should be kept in mind in attempting to replicate the finding we observed.

Epidural has certain advantages over intrathecal anesthesia in terms of the lesser chance of postdural puncture headache and the relatively slower onset of hypotension. However, its failure to consistently ensure adequate muscle relaxation makes it a less attractive choice for many anesthesiologists in lower abdominal surgeries. Our study reveals that this short coming of epidural can be circumvented by the addition of clonidine which makes it at par with intrathecal route with distinct advantages.

Conclusion

We observed that low-dose clonidine as an additive to bupivacaine in central neuraxial blocks improves the analgesic efficacy and block characteristics (onset of sensory level, muscle relaxation) but intrathecal clonidine was associated with more hemodynamic alterations. Addition of 75 μg Clonidine in epidural makes the onset comparable to intrathecal route, sensory and motor blockade longer while preserving the hemodynamic stability and maintaining optimum level of sedation.

Key Messages

Addition of clonidine to epidural bupivacaine makes it similar to intrathecal bupivacaine with better hemodynamic stability.

Source(s) of support: NIL

Presentation at a meeting: NIL

Conflicting Interest (If present, give more details): NIL

References

1. Lavand'homme PM, Roelants F, Waterloos H, Collet V, De Kock MF. An evaluation of the postoperative antihyperalgesic and analgesic effects of intrathecal clonidine administered during elective cesarean delivery. Anesth Analg. 2008;107(3):948–95.

2. Strebel S, Gurzeler JA, Schneider MC, et al. Small-dose intrathecal clonidine and isobaric bupivacaine for orthopedic surgery: A dose-response study. Anesth Analg 2004;99(4):1231–238.

3. Dobrydnjov I, Axelsson K, Thörn SE, et al. Clonidine combined with small-dose bupivacaine during spinal anesthesia for inguinal herniorrhaphy: A randomized double-blinded study. Anesth Analg 2003;96(5):1496–503.

4. Filos KS, Goudas LC, Patroni O, et al.

Hemodynamic and analgesic profile after intrathecal clonidine in humans. A dose-response study. Anesthesiology 1994;81:591–601.

5. Dobrydnjov I, Samarütel J. Enhancement of intrathecal lidocaine by addition of local and systemic clonidine. Acta Anesthesiol Scand 1999;43:556–62.

6. Nishina K, Mikawa K. Clonidine in pediatric anesthesia. Curr Opin Anesthesiol 2002 Jun;15(3):309–316.

7. Castro MI, Eisenach JC. Pharmacokinetics and dynamics of intravenous, intrathecal, and epidural clonidine in sheep. Anesthesiology 1989;71:418–25.

8. Guyenet PG, Cabot JB. Inhibition of sympathetic preganglionic neurons by catecholamines and clonidine: A mediation by an alpha-adrenergic receptor. J Neurosci Off J Soc Neurosci 1981;1:908–17.

9. Eisenach JC, Kock MD, Klimscha W. α_2-Adrenergic agonists for regional anesthesia: A clinical review of clonidine (1984–1995). Anesthesiol J Am Soc Anesthesiol 1996 Sep;85(3):655–74.

10. Maze M, Tranquilli W. Alpha-2 adrenergic receptor agonists: Defining the role in clinical anesthesia. Anesthesiology 1991;74:581–605.

11. Elia N, Culebras X, Mazza C, et al. Clonidine as an adjuvant to intrathecal local anesthetics for surgery: Systematic review of randomized trials. Reg Anesth Pain Med 2008 Mar-Apr;33(2):159–67.