Original Article

Effect of epidural clonidine on characteristics of spinal anaesthesia in patients undergoing gynaecological surgeries: A clinical study

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ABSTRACT

Background and Aims: Combined spinal–epidural (CSE) anaesthesia is being increasingly used for effective post-operative analgesia. This study was designed to evaluate the effect of epidural clonidine on characteristics of spinal anaesthesia for gynaecological surgeries. **Methods:** This was a prospective randomised, double-blind, controlled study involving sixty patients belonging to American Society of Anesthesiologists Physical Status I and II who underwent gynaecological surgeries were randomly divided into clonidine (C) group and saline (S) group of thirty each. All patients received CSE anaesthesia. Ten minutes before subarachnoid block (SAB), Group C received clonidine 150 μg diluted to 5 ml in normal saline (NS) and Group S received NS epidurally. Hyperbaric bupivacaine (15 mg) was administered intrathecally for both groups after epidural injection. Sensory and motor block characteristics, analgesia, sedation and haemodynamics were observed. Statistical analysis was performed using appropriate tests. **Results:** Epidural clonidine produced faster onset (37.83 ± 8.58 s in Group C compared to 50.33 ± 8.80 s in Group S, $P = 0.001$) and prolonged duration of sensory block (241.17±18.65 minutes in group C compared to 150.33±19.16 minutes in group S, $P = 0.001$). Time for two segment regression of sensory block was193.67 ± 19.82 min in Group C and 109.33 ± 18.56 min Group S ($P < 0.001$). The duration of analgesia was 299.00 ± 43.38 min in Group C and 152.50 ± 21.04 min in Group S ($P < 0.001$). Haemodynamics and sedation scores were comparable between two groups. **Conclusion:** Administration of clonidine epidurally, 10 min before SAB, caused early onset and prolonged duration of motor blockade and analgesia, without any significant post-operative complication.

Key words: Adjuvant, clonidine, epidural analgesia, gynaecological surgery, spinal anaesthesia

INTRODUCTION

Combined spinal–epidural (CSE) anaesthesia offers a safe and inexpensive technique with the advantage of both spinal and epidural anaesthesia. It provides faster onset of surgical anaesthesia and prolongs the duration of post-operative pain relief. Various adjuvants further increase its efficacy.[1]

The addition of opioids, which are the most commonly used adjuvants, to neuraxial anaesthesia is effective in prolonging the analgesic effect but has also been associated with adverse effects such as respiratory depression, nausea, urinary retention and pruritus, so various options including α_2 agonists are extensively evaluated as an alternative. α_2 agonists when used as adjuvant in central neuraxial blockade produce significantly lower post-operative pain scores without any of these opioid-related side effects.[2-5]

Studies comparing effects of the two α_2 agonists – dexmedetomidine and clonidine on

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spinal and epidural anaesthesia – have found that both produce a similar prolongation in the duration of the motor and sensory block with preserved haemodynamic stability and sedation.[5,6]

Clonidine, as an adjuvant with local anaesthetics, increases the duration of pain relief after intrathecal or epidural administration but is associated with significant hypotension and bradycardia.[7,8] Literature search revealed very few studies using clonidine and local anaesthetics sequentially via different routes in CSE to assess the influence of clonidine on characteristics of subarachnoid block (SAB). An attempt was made by this study to determine whether administration of clonidine alone as epidural adjuvant in CSE would provide prolonged analgesia without causing significant haemodynamic side effects.

METHODS

The study was undertaken in a tertiary teaching institute over a period of 7 months.

The sample size was calculated using duration of analgesia as primary criterion. Keeping power of study at 80% and confidence interval at 95%, to detect 30% difference in duration of analgesia, the sample size required was 25 in each group. We enrolled a total of 60 patients for better validation of results.

After obtaining the institutional ethical committee approval and written informed consent, 60 female patients undergoing elective gynaecological surgeries, aged 25–60 years, belonging to American Society of Anesthesiologists Physical Status I and II, were enrolled. Gynaecological surgeries included in this study were total abdominal hysterectomy, vaginal hysterectomy, myomectomy, open ovarian cyst excision and tubal recanalisation. Patients for whom central neuraxial block was contraindicated, those with neurological, cardiovascular, respiratory, endocrine disorders, psychiatric illness, antihypertensive therapy, with known allergy to study drugs and those who refused neuraxial block were excluded from the study. Patients enroled were randomly allocated into Group C (study) and Group S (control) of thirty each using a computer-generated random number sequence. The drug solution for both groups was prepared by an anaesthesiologist not involved in the study. The allocation sequence and the drug received by the patients were not revealed to the investigating anaesthesiologist until the end of data collection.

After intravenous (IV) access, the patients were preloaded with infusion of Ringer lactate (20 ml/kg). The epidural space was identified at L_2–L_3 interspace with 18 G Tuohy needle using loss of resistance technique under strict asepsis, and a 20 G epidural catheter was then advanced into the epidural space. Correct placement of epidural catheter was verified with a test dose of 3 ml of lignocaine (2%) with adrenaline (1: 200,000). Group C received injection clonidine 150 μg, diluted to 5 ml in normal saline (NS) via epidural catheter 10 min before SAB. Group S received 5 ml NS 10 min before SAB. Hyperbaric bupivacaine 0.5%, 15 mg (3 ml) was given intrathecally to both groups at L_3–L_4 interspace using 27G Quincke needle.

Sensory block was assessed bilaterally using loss of sensation to pinprick with a short hypodermic needle in midclavicular line. Motor blockade was assessed using modified Bromage scale[9] (0: No motor block; 1: Inability to raise extended legs; 2: Inability to flex knees; 3: Inability to flex ankle joints). Surgery was commenced after sensory block at T_6 dermatome was attained.

In this study, onset of sensory block was defined as time taken to achieve loss of sensation to pinprick at L_1 dermatome level following SAB. Time taken to achieve Bromage 3 following SAB was defined as onset of motor block. Time taken for two segment regression of sensory block was noted, and time taken for motor block to recede from Bromage 3 to Bromage 0 was recorded as the duration of motor block.

Basal heart rate (HR), respiratory rate, non-invasive arterial blood pressure and oxygen saturation were recorded before placement of epidural catheter and every 5 min till the end of surgery. Intra- and post-operative sedation was assessed using Ramsay Sedation Score[10] (1: Anxious or restless or both, 2: Co-operative, oriented and tranquil, 3: Responding to commands, 4: Asleep, brisk response to light, glabellar tap or auditory stimuli, 5: Asleep, sluggish response, 6: Asleep, unarousable).

Post-operatively, pain was assessed using visual analogue scale[11] (VAS) (0: No pain, 2–4: Mild pain, 5–7: Moderate pain, 8–10: Worst pain). Duration of analgesia was the time from onset of sensory block at L_1 till the patient complained of pain. Rescue analgesic injection tramadol 2 mg/kg was given via epidural catheter when patient requested for analgesic

or VAS >4. Sedation score, VAS and haemodynamic parameters were observed at 30 min, 60 min, 2nd, 3rd, 4th, 5th and 6th h post-operatively.

Hypotension was defined as systolic blood pressure <90 mmHg or >30% decrease in baseline mean arterial pressure, treated with IV crystalloid 250 ml bolus and injection mephentermine 6 mg IV. Bradycardia was defined as HR < 50/min and treated with injection atropine 0.6 mg IV. Other side effects such as nausea and vomiting, shivering and urinary retention were also looked for in both the groups.

Sensory and motor block characteristics and time to request for analgesics were recorded in both groups.

Parametric data are expressed as mean (standard deviation) and nominal data are presented in tabular format. Fischer exact test and Chi-square test were applied for nominal data. Student's *t*-test was used for parametric data. $P < 0.05$ considered statistically significant. All statistical analyses were performed using Statistical Analysis System 9.2 (manufactured by SAS Institute Inc, Cary, NC, USA), Statistical Package for the Social Sciences 15.0 (SPSS Inc. Chicago, IL, USA) and Stata 10.1(StataCorp LP, Texas, USA) statistical software.

RESULTS

All the enrolled patients completed the study. Demographic data were comparable between both groups [Table 1].

Onset of sensory block at L_1 was faster in Group C (37.83 ± 8.58 s) than Group S (50.33 ± 8.80 s). The highest dermatome level achieved in Group C was T_5 which was seen in 53.3% whereas the highest level achieved in Group S was T_6. Time to attain Bromage 3 block was 54.33 ± 7.74 s in Group C and 102.00 ± 73.17 s in Group S. Time to two-segment regression of sensory block in Group C was 193.67 ± 19.82 min and Group S was 109.33 ± 18.56 min ($P < 0.001$). Duration of motor block was 343.00 ± 32.92 min and 221.00 ± 29.17 min in Group C and Group S, respectively. All these differences were clinically significant ($P = 0.001$) [Table 2].

Duration of analgesia was 299.00 ± 43.38 min in Group C and 152.50 ± 21.04 min in Group S ($P = 0.001$).

Haemodynamic parameters were comparable between the two groups and the difference was not clinically significant [Figure 1]. Clonidine group showed significantly lower pain scores as compared with saline group [Figure 2]. Sedation scores were significantly higher in clonidine group in the post-operative period [Figure 3].

Hypotension and bradycardia were comparable in both groups [Table 3]. Shivering, nausea and vomiting and urinary retention were not found in both the groups in our study.

DISCUSSION

The present study showed that clonidine (150 μg) administered via epidural route as adjuvant to SAB in CSE produced faster onset and prolonged duration of sensory and motor blockade. It significantly prolonged the duration of analgesia with improved sedation and pain scores in the post-operative period.

Clonidine is a centrally acting partial α_2 adrenoceptor agonist with selectivity ratio of 200:1. Its analgesic

Table 1: Demographic data

Demographic Variables	Group C	Group S
Age (years)	36.97±8.77	39.63±6.66
Height (cm)	157.5±3.15	158.26±3.07
Weight (kg)	62.9±7.58	58.5±6.54
Duration of surgery (min)	79.33±19.98	77.3±20.49

Table 2: Neuraxial blockade profile

Outcome variables	Group C	Group S	*P*
Onset of sensory block at L_1 (s)	37.83±8.58	50.33±8.80	<0.001**
Time to Bromage 3 (s)	54.33±7.74	102.00±73.17	0.001**
Time to 2 segment regression (min)	193.67±19.82	109.33±18.56	<0.001**
Duration of motor block (min)	343.00±32.92	221.00±29.17	<0.001**
Total duration of analgesia (min)	299.00±43.38	152.50±21.04	<0.001**

**Clinically significant if $P < 0.05$

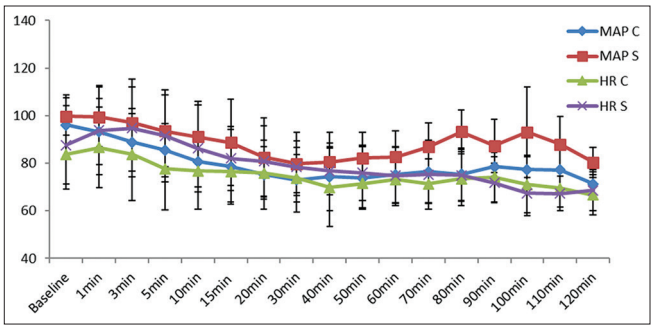

Figure 1: Comparison of heart rate (bpm) and blood pressure (mean arterial pressure) (mm Hg) between two groups

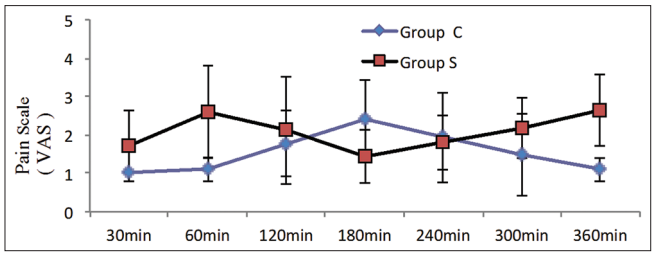

Figure 2: Comparison of post-operative pain scores between two groups

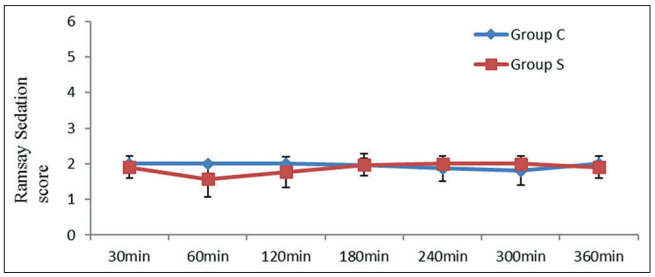

Figure 3: Comparison of post-operative sedation scores

Table 3: Comparison of side effects			
Side effect	**Group C**	**Group S**	***P***
Hypotension	3	9	0.21
Bradycardia	1	3	0.61
Shivering	0	0	

effect is mediated by binding to postsynaptic α_2 receptors (G-protein coupled inhibitory receptors) in the dorsal horn of the spinal cord. This mimics the effects of noradrenaline which is released from the descending inhibitory pathways in the central nervous system. Thus, decreased activity of the second-order neurons and wide dynamic range neurons in the dorsal horn occurs which in turn attenuates the input from peripheral nociceptive A_δ and C fibres. It does not affect proprioception or produce motor blockade. Studies in rats show that clonidine partially inhibits voltage-gated sodium and potassium channels and suppresses generation of action potentials in tonic firing spinal dorsal horn neuron.[12]

Studies have demonstrated potentiation of analgesic effects of local anaesthetics by clonidine through oral, IV, intrathecal and epidural routes. As clonidine-induced analgesia is mediated by activation of adrenergic receptors on the dorsal horn of the spinal cord, intrathecal or epidural administration of the drug close to its action site seems to be logical. Clonidine is rapidly and extensively absorbed into the spinal cerebrospinal fluid compartment after epidural administration, with concentrations peaking 30–60 min after injection and coincides with near-maximal analgesia. After epidural administration, clonidine produces peak concentrations in arterial blood within 10 min and venous blood within 30–45 min.[13] As side effects, such as sedation, hypotension or bradycardia, are at least partly related to systemic absorption, the route that provides the best balance between analgesia and side effects is more acceptable.

In this study, we used 150 μg clonidine (3–4 μg/kg body weight) epidurally as some studies have shown increased incidence of adverse effects such as bradycardia, hypotension and sedation with higher doses (>600 μg) of clonidine .[13]

In the present study, duration of analgesia was very much prolonged in clonidine group (299.00 ± 43.38 min) as compared to saline group (152.50 ± 21.04 min). We also observed that epidurally administered clonidine reduced post-operative analgesic requirements. A previous study found that epidural clonidine (150 μg) prolonged anaesthesia duration along with significant sedation,[14] similar to what was observed in our study. Motor and sensory blockade effects of local anaesthetics are enhanced by clonidine. The effects of clonidine on the prolongation of nerve blockade are dose-dependent [15,16].

After neuraxial administration, clonidine affects arterial blood pressure in a complex manner because of opposing actions at multiple sites. The α_2-adrenergic agonists produce sympatholysis and reduce arterial blood pressure through effects at specific brainstem nuclei and sympathetic preganglionic neurons in the spinal cord, effects that are counteracted by direct vasoconstriction resulting from the α_2-adrenergic agonists on the peripheral vasculature.[17] Eisenach *et al*. showed that 160 μg clonidine decreases arterial blood pressure by 18% and reduces HR by 5–20% and concluded that epidural clonidine does not induce haemodynamic instability.[18] The current study showed relatively low incidence of hypotension and bradycardia with epidural clonidine at dose of 150 μg.

The α_2 agonists when used in regional anaesthesia are shown to hasten onset of action of local anaesthetics with rapid establishment of both sensory and motor blockade, prolongation of analgesia into the post-operative period, with dose-sparing action of local anaesthetics and stable cardiovascular parameters.[6] The current study also showed similar findings.

Sedation is another central effect of clonidine due to its action on locus ceruleus. Sedation after epidural

clonidine is due to its systemic absorption and vascular redistribution to higher centres.[19] In our study, we found that epidural clonidine produced arousable sedation in intra- and post-operative periods. Patients rested quietly in beds with eyes closed but were able to respond to oral commands. Duration of sedation corresponded with duration of analgesia but did not hinder VAS measurement.

Epidural clonidine and neostigmine[20,21] have been used as adjuvants following intrathecal labour analgesia with local anaesthetic and found to be associated with improved quality of analgesia, reduced the local anaesthetic requirement and higher patient satisfaction. In the current study, we administered epidural clonidine before SAB in gynaecological surgery and found improved quality of analgesia, along with the early onset of sensory and motor blockade.

CONCLUSION

Epidural clonidine when administered 10 min prior to SAB during CSE, produces prolonged analgesia and arousable sedation. It increased the speed of onset and prolonged the duration of sensory and motor blockade of intrathecal bupivacaine without significant haemodynamic adverse effects.

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Conflicts of interest

There are no conflicts of interest.

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