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Effect of clonidine as an adjuvant to levobupivacainein epidural anesthesia

A Arumugam[1*], N Tandon[2], B Choudhary[3]
Senior Resident[1], Department of cardiac anaesthesia, Sri Ganga Ram hospital, New Delhi110060, India.
Associate Professor[2], Professor and Head[3] Department of Anesthesiology, Gajra Raja Medical College, Gwalior, M.P, India.

***Corresponding author:**drarunkumarpdy@gmail.com*

Background: Epidural anaesthesia is a safe alternative for general anaesthesia in patients undergoing infraumbilical surgeries. This study was conducted to evaluate the effect of clonidine as an adjuvant to levobupivacaine, an S (-) enantiomer of bupivacaine.

Material and Methods: Hundred patients of ASA grade I and II undergoing infraumbilical surgeries were randomized in two groups as L and LC. Group L received 0.5% levobupivacaine (1.5mg/kg) and group LC received 0.5% levobupivacaine (1.5mg/kg) with clonidine (2µg/kg). The onset time for sensory, motor blockade, duration of anaesthesia and duration of analgesia, VAS score were observed in both the groups. The haemodynamic variables such as heart rate, systolic and diastolic blood pressure, respiratory rate and SPO_2 at various time intervals were measured. Any untoward side effects were noted in both groups.

Results: The onset of sensory (7.8±1.7mins) and motor blockade (10.9±1.9mins) was significantly faster in clonidine group. Duration of anaesthesia and duration of analgesia was prolonged in group LC (234.5±16.1mins, 412.8±48.3mins) compared to group L (173.56±12.78 min, 269.2±24.2mins) which was statistically significant ($p<0.05$). Similarly clonidine group had less VAS score compared to control group. There was no significant change in the haemodynamic variables between the two groups. Hypotension and bradycardia was found more in clonidine group compared to the control group.

Conclusion: Clonidine as an adjuvant to levobupivacaine prolongs the post-operative analgesia and the duration of anaesthesia for infraumbilical surgeries.

Keywords: epidural; levobupivacaine; clonidine; analgesia; anaesthesia; infraumbilical surgeries

Introduction

Pain management during surgery and postoperative period is an uphill task for an anesthesiologist and many breakthroughs have happened to alleviate pain. Levobupivacaine, a long acting local anesthetic and an S (-) enantiomer of bupivacaine has recently emerged as a safer alternative for regional anaesthesia than its racemic parent bupivacaine. Levobupivacaine is preferred because of its less cardiotoxic effects.[1] Similarly the susceptibility for seizure activity with levobupivacaine is 1.5-2.5 times less than that of racemic bupivacaine.[2] Alpha -2- agonist exerts their analgesic activity in the spinal cord by activating the postganglionic alpha 2 receptors in the substantia gelatinosa of the spinal cord. This study was undertaken to evaluate the effects of clonidine as an adjuvant to levobupivacaine in epidural anaesthesia.

Material and methods

The present study was approved by the ethics committee of the institution. 100 patients of ASA grade I and II of either sex with age group between 25-60 years scheduled for elective infraumbilical surgeries were selected. Patients were explained about the procedure and verbal informed consent was taken. Randomization of patients was done by sealed envelope technique. This study was conducted as a double blinded study in which the anesthesiologist administering the drug was unaware of the drug he was administering to the patient and similarly the observer was also blinded. Patients were randomized into two equal groups as Group L and Group LC

Group L – Levobupivacine 0.5% 1.5mg/kg
Group LC – Levobupivacine 0.5% 1.5mg/kg + Clonidine 2 µg/kg.

Appropriate drugs were given to patients epidurally. Baseline values of heart rate, blood pressure, respiratory rate and SPO_2 were noted. Patients were monitored by systolic and diastolic blood pressure, heart rate, respiratory rate and oxygen saturation (SPO_2) at 5 min, 15, 30, 45, 60, 90,120,180, 240, 300 and 360mins. Sensory block was assessed using the pinprick method. Motor blockade was assessed using the modified Bromage Scale (Zero, bilateral sustained straightening of leg; 1, unable to straighten leg; 2, just able to flex knees; 3, foot movement only). Sedation was evaluated by Ramsay Sedation Score. (1- patient anxious and agitated or restless; 2- cooperative, oriented and tranquil; 3- responds to commands only; 4- brisk response to glabellar tap or loud auditory stimulus; 5-sluggish response to light glabellar tap or loud auditory stimulus;6- no response).

Visual analogue scale was used to assess pain. Patients were educated about the scale (0 being no pain and 100 being the worst possible pain). Any side effects that occurred during the surgery or during the post-operative period were noted. After the surgery the patients were shifted to the post-operative ward and the monitoring was continued. Time to two segment regression of analgesia to pin prick from the highest level achieved was considered as duration of anaesthesia. Time to rescue analgesia was considered as duration of analgesia. Episodes of nausea, vomiting, bradycardia, hypotension and respiratory depression were observed.

Statistical analysis

The data was analyzed using student 't' test as applicable for comparison of different parameters in group L and group LC using EpiCalc 2000. P value of < 0.05 was considered as statistically significant and p value of > 0.05 was considered as statistically insignificant.

Results

The age, weight, height and duration of surgery were comparable in both groups (Table 1). The mean time for onset of sensory blockade in control and clonidine group was 15.9±2.3mins and 7.8±1.7mins (CI 7.2-8.9, p-0.0001). Similarly the mean time for onset of motor blockade in control group was 19.8±2.3mins whereas clonidine group was 10.9±1.9mins (CI-8.6-9.7, p-0.0001) (Table:2) where clonidine group had a faster onset of action.

Table 1: Demographic data

Variables	Group L (Mean±SD)	Group LC (Mean±SD)	P value	95% confidence interval
Age (in years)	37.4 ± 11.8	37.7 ± 13.0	0.90(#)	-5.2 to 4.6
Weight (in Kg)	63.8 ± 5.0	65.3 ± 5.4	0.15(#)	-3.5 to 0.5
Height (in cm)	165.9 ± 5.4	167.3 ± 4.9	0.17(#)	-3.4 to 0.6

(#)- not significant[p>0.05] ($) – significant [p<0.05]

Table 2: Onset time for sensory and motor blockade

Parameters	Group L	Group LC	P value	95% confidence interval
Onset time of sensory blockade (mins)	15.9±2.3	7.8±1.7	0.0001($)	7.2 to 8.9
Onset time of Motor blockade (mins)	19.8±2.3	10.9±1.9	0.0001($)	8.0 to 9.7

(#)- not significant[p>0.05] ($) – significant [p<0.05]

The duration of anaesthesia in group L and group LC was 173.5±12.7min and 234.5±16.1mins (CI-66.7-55.2).The difference in the total duration between the two groups was significantly higher in clonidine group (p-0.0001). Similarly the total duration of analgesia in the clonidine group (412.8±48.3mins) was significantly higher when compared to the control group (269.2±24.2mins) (CI-158.7-128.4, p-0.0001). (Table 3)

Table 3: Duration of surgery, anaesthesia and analgesia

Parameters	Group L	Group LC	P value	95% confidence interval
Duration of surgery (mins)	80.2±19.9	80±22.0	0.96(#)	-8.1 to 8.5
Duration of sensory blockade (mins)	173.5±12.7	234.5±16.1	0.0001($)	-66.7 to -55.2
Duration of analgesia (mins)	269.2±24.2	412.8±48.3	0.0001($)	-158.7 to -128.4

(#)- not significant [p>0.05] ($) – significant [p<0.05]

Table 4: Differences in haemodynamic variables compared to the pre op variables.

Time	HEART RATE			
	Group L	Group LC	P value	Confidence interval
Pre op	89.5±10.9	89.6±10.7	0.96(#)	-4.3 to 4.1
5 min	87.7±10.9	87.1±10.1	0.77(#)	-3.5 to 4.7
15 min	85.0±10.1	85.9±10.1	0.65(#)	-4.9 to 3.1
30 min	83.0±10.1	84.5±9.5	0.44(#)	-5.3 to 2.3
45 min	82.0±10.0	80.9±9.2	0.56(#)	-2.7 to 4.9
60 min	79.7±9.2	77.6±9.1	0.25(#)	-1.5 to 5.7
90 min	78.6±9.9	77.0±9.8	0.41(#)	-2.3 to 5.5
120min	77.1±9.9	75.2±11.3	0.37(#)	-2.3 to 6.1
180min	76.1±9.4	74.2±10.4	0.34(#)	-2.0 to 5.8
240min	78.4±8.6	77.2±9.0	0.49(#)	-2.2 to 4.6
300min	80.0±7.9	80.5±7.2	0.74(#)	-3.5 to 2.5
360min	83.04±7.5	85.96±8.5	0.07(#)	-6.0 to 0.2

(#)- not significant[p>0.05] ($) – significant [p<0.05]

Time	SYSTOLIC BLOOD PRESSURE			
	Group L	Group LC	P value	Confidence interval
Pre op	124.4±9.1	127.4±9.8	0.11(#)	-6.7 to 0.7
5 min	123.5±9.1	125.2±9.8	0.37(#)	-5.4 to 2
15 min	121.2±7.9	122.7±8.5	0.36(#)	-4.7 to 1.7
30 min	119.5±8.3	117.7±9.1	0.30(#)	-1.6 to 5.2
45 min	117.7±7.8	115.0±10.8	0.15(#)	-1 to 6.4
60 min	116.5±9.5	112.4±11.2	0.05(#)	-0 to 8.2
90 min	115.9±8.4	113.2±8.5	0.11(#)	-0.6 to 6
120min	114.0±8.4	112.3±7.8	0.29(#)	-1.5 to 4.9
180min	113.6±7.6	112.6±6.1	0.46(#)	-1.7 to 3.7
240min	114.6±6.5	114.8±5.3	0.86(#)	-2.5 to 2.1
300min	116.5±6.9	116.3±5.1	0.86(#)	-2.2 to 2.6
360min	118.9±6.3	120.8±6.0	0.12(#)	-4.3 to 0.5
	DIASTOLIC BLOOD PRESSURE			
Time	**Group L**	**Group LC**	**P value**	**Confidence interval**
Pre op	81.0±6.2	82.9±5.0	0.09(#)	-4.1 to 0.3
5 min	79.0±6.7	81.2±7.6	0.12(#)	-5 to 0.6
15 min	77.6±5.4	80.0±6.8	0.05(#)	-4.8 to 0
30 min	75.2±6.4	76.4±8.3	0.42(#)	-4.1 to 1.7
45 min	73.5±6.8	74.4±9.6	0.58(#)	-4.2 to 2.4
60 min	73.4±6.8	72.4±8.6	0.52(#)	-2 to 4
90 min	71.7±5.8	72.2±8.6	0.73(#)	-3.4 to 2.4
120min	69.7±6.8	72.1±6.5	0.07(#)	-5 to 0.2
180min	71.3±6.9	70.9±7.0	0.77(#)	-2.3 to 3.1
240min	71.6±6.3	73.2±6.5	0.21(#)	-4.1 to 0.9
300min	73.3±4.8	74.7±5.8	0.19(#)	-3.5 to 0.7
360min	77.3±6.7	79.4±5.5	0.08(#)	-4.5 to 0.3

Haemodynamic parameters such as heart rate, SBP, DBP, respiratory rate and SPO_2 showed no significant changes at various time intervals between the two groups. Though there was a greater fall in systolic blood pressure and diastolic blood pressure in the clonidine group the change was insignificant. (Table 4)

The VAS score at the time of first analgesic request was 48.7± 10.1 in control group and 41.5± 7.3 in clonidine group. There was a significant lower VAS score in clonidine group compared to the control group (p-0.0001).

56% of patients in group LC and only 16% of patients in group L had Ramsay sedation score of 2.84% of patients in group L and 44% of patients in group LC had a sedation score of 1.
This study also observed that the incidence of hypotension and bradycardia was more in clonidine group (8%, 4%) compared to the control group (2%, 0%). Shivering was more common in the control group (8%) compared to the clonidine group (2%).

Discussion
Regional anaesthesia is a safe alternative to general anaesthesia with an advantage of postoperative pain relief. Clonidine in epidural administration along with local anaesthetics produces sedation, analgesia, anxiolysis, hypnosis and sympatholysis.[3,4] The faster onset of action of local anaesthetics, rapid establishment of both sensory and motor blockade, prolonged duration of analgesia into the post-operative period, and stable cardiovascular parameters makes alpha-2 agonists a very effective adjuvant in regional anaesthesia.[5-9]

Clonidine is a mixed agonist that stimulates α_1, α_2 and imidazoline receptors while it has agonistic effects on α_2/α_1adrenoreceptorswith a relationship of approximately 200:1.[10] Clonidine stimulates α_2 adrenergic inhibitory neurons in the medullary center decreasing the sympathetic outflow from CNS to peripheral tissue, and the decrease in the sympathetic outflow causes decrease in BP, HR and cardiac output. On spinal cord the activation of post ganglionic α_2 receptors in the substantia gelatinosa produces analgesia. Neuraxial placement of clonidine inhibits the spinal substance P release and the nociceptive neuron firing produced by noxious stimulation. The sedative and anxiolytic effects may be mediated by the post synaptic α_2a subtype adrenoreceptors located in the locus coeruleus.[11]

In this study both the groups were comparable with regard to age, duration of surgery. Clonidine combined with levobupivacaine has a faster onset of sensory and motor block which was in accordance with Milligan KR et al[12], Gupta S et al[13] and Jain A et al.[14] Clonidine being a lipophilic drug is rapidly absorbed into the spinal compartment and blocks the conduction of C and Aδ fibres.[15] Chalkiadis DS et al[16] in their study demonstrated the absorption characteristics of epidural levobupivacaine with clonidine and adrenaline via caudal epidural route and showed that clonidine mixed with levobupivacaine had a faster absorption compared to adrenaline mixed with levobupivacaine.

In the present study, duration of anaesthesia was prolonged significantly in clonidine group compared to the control group. Alves TCA and Braz JRC[17] in their study demonstrated that the duration of sensory blockade was significantly prolonged when clonidine was added to ropivacaine epidurally. Similarly clonidine prolonged the duration of post-operative analgesia (412.8±48.33mins) when compared to the control group (269.2±24.23mins) which was statistically significant. Milligan KR et al[11], found in their study that the time to rescue analgesia was significantly delayed in group LC (levobupivacaine with clonidine) compared to group L (levobupivacaine) and group C (clonidine). Other studies by Gupta S et al[13], Ghatak T et al[18], Alves TCA and Braz JRC[17] also showed a significant prolongation of duration of analgesia in their respective studies when clonidine was used as an adjuvant to local anaesthetics in epidural administration. Disma N et al [19]showed that a dose of 2μg/kg of clonidine increases the duration of post-operative analgesia in caudal anaesthesia for lower abdominal surgery. Clonidine produces analgesia by blocking the

conduction of C and Aδ fibers and increasing potassium conductance in isolated neurons in vitro and thereby intensifying conduction block of local anaesthetics. Because systemic pharmacokinetics are not a factor in these in vitro experiments, these data support a direct effect of clonidine on neural transmission in high local concentrations, such as may occur after local injection. Secondly, clonidine may cause local vasoconstriction in the clinical setting, thereby reducing vascular removal of local anaesthetic surrounding neural structures. Although clonidine and other $\alpha_2$adrenergic agonists can vasoconstrict in high concentrations, there is little evidence for this mechanism with clinically used concentrations.[11]

The VAS score was lower in clonidine group LC compared to the control group L which was statistically significant ($p<0.05$). Alves TCA and BrazJRC[17]also showed a significant lower VAS score compared to the control group. However Milligan Kr et al[12]demonstrated a lower VAS score in levobupivacaine with clonidine group but it was not statistically significant compared to the levobupivacaine only group.

In the present study, the haemodynamic parameters such as systolic blood pressure and diastolic blood pressure that were recorded showed a decreasing trend after the administration of epidural anaesthesia in both groups. While the clonidine group showed a greater fall in systolic and diastolic blood pressure compared to the control group this change was statistically insignificant. Similarly the studies conducted by Ghatak T et al**[19]** and Alves TCA and Braz JRC[17] showed no significant decrease in blood pressure between the clonidine and the control groups in their respective studies.

Gupta S et al[13]**,**Alves TCA and Braz JRC[17]in their studies showed the sedative effect of clonidine after epidural administration in more than 50% of patients when compared to the control group which was in accordance with our study too. The sedative effect of clonidine can be explained by the agonistic action of clonidine on locus coeruleus.

Hypotension and bradycardia were the major side effects that we observed in our study which was also reported by the studies conducted by Gupta S et al[13]**,** Alves TCA and Braz JRC.[17]

Conclusion

Levobupivacaine being an S (-) enantiomer to bupivacaine with a less cardiotoxic and neurotoxic profile has a promising safety profile for the patients. Clonidine, α_2 agonist has an excellent analgesic potential when added as an adjuvant to local anaesthetics and reduce the requirement of rescue analgesics and in general the postoperative outcome of patient is good. This study concluded that levobupivacaine and clonidine when administered together epidurally can provide a prolonged duration of anaesthesia and analgesia with a faster onset of action.

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