ORIGINAL ARTICLE

COMPARISON BETWEEN THE ANALGESIC CHARACTERS AND HEMODYNAMIC CHANGES OF 2% LIGNOCAINE ALONE AND 2% LIGNOCAINE WITH CLONIDINE IN EPIDURAL BLOCKADE

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ABSTRACT: INTRODUCTION: Pain is as old as mankind and so is the quest for its control. It is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage”.¹ Pain relief is a growing concern to anaesthesiologist, since no single analgesia is free from side effect, so it is a challenge to provide pain relief without much side effect like sedation, respiratory depression or problem like nausea & vomiting.

Regional anaesthesia techniques generously offer adequate pain control for early mobilization and compliance with physiotherapy, they also provide additional benefits of decreased surgical stress response² improved myocardial stability,³,⁴ rapid recovery of bowel function⁵,⁶ and reduced risk of thromboembolic events like deep vein thrombosis and pulmonary embolism.⁷ As a result it is also associated with reduction in postoperative morbidity and mortality.⁸

Epidural anaesthesia has become increasingly popular in recent years for surgeries of lower abdomen, pelvis and lower limbs as it offer excellent operating conditions and is relatively safe for patients. It offers benefits in the form of greater hemodynamic stability and provision of postoperative analgesia via an epidural catheter.

Clonidine is a partial α-2 adrenergic agonist which, when administered by epidural route, has analgesic properties and potentiates the effect of local anesthetics.⁹

Clonidine has analgesic effect at spinal level mediated by alpha-2 adrenergic receptor situated in the postsynaptic dorsal horn of spinalcord.¹⁰ It works by blocking the conductance of C & A fibres, increases the potassium ion in isolated neurons in-vitro and intensifies conductance block of local anaesthetics.¹¹

The aim of our study was to compare the quality and duration of analgesia, to assess the hemodynamic effects and to assess the incidence of side effects (sedation, post-operative nausea and vomiting) when 2% lignocaine was used alone and in combination with clonidine in epidural blockade.

MATERIALS & METHODS: This study was undertaken to assess the degree of postoperative analgesia and hemodynamic changes produced by low dose (1mcg/kg) clonidine when added to lignocaine in epidural blockade.

After obtaining due approval of the Hospital Ethics Committee, a randomized, prospective, double blinded, control study on patients undergoing lower limb and lower abdominal surgery under epidural anaesthesia was designed.
Sixty patients were selected for the study. Written and informed consent was obtained from each patient at the time of including them in the study.

**INCLUSION CRITERIA:** age group 20-70 years, weighing 70-80kg belonging to ASA-I and ASA-II, posted for lower abdomen & lower limb surgeries.

**EXCLUSION CRITERIA:** Patient refusal, Patients with systemic disease like IHD/MI, respiratory, renal & hepatic disease. Patients with any contraindication for regional anaesthesia e.g: coagulation disorder, gross abnormality of spine, infection at site of needle insertion and patient with history of allergy to local anaesthetic.

The patients were randomly allocated into 2 groups with 30 patients each & randomization was done by a computer generated code.

**GROUP-A** (Control group n= 30) patients in this group received 15ml of 2% lignocaine with equivalent amount of distilled water to compensate for the volume of the study drug in the study group, through epidural catheter.

**GROUP-B** (Study group n= 30) patients in this group received 15ml of 2% lignocaine with clonidine (1 µg/Kg) through epidural catheter.

Once selected for the study, A methodical pre-anaesthetic check-up and assessment was performed. ASA grading was done during the pre-anaesthetic check-up. The visual analogue scale (VAS) was explained to all patients in the preoperative visit. They were premedicated with oral ranitidine (150 mg) on the night before and 2 hours before the surgery and diazepam (10 mg) at night before surgery.

On arrival in the operating room, standard monitors attached and baseline values were recorded. Patients were preloaded with lactated ringer’s solution in a dose of 15 ml/kg 15 minutes prior to intended time for epidural drug administration. Patients were placed in lateral position. The back was washed with savlon and betadine subsequently and then cleaned with spirit. The skin over the epidural site (L2-3 or L 3-4) was infiltrated with 3ml of lidocaine 1% plain. A 16 gauge epidural catheter was placed 3-5 cm into the epidural space and after a negative aspiration, 3ml of lidocaine 2% with 1:200,000 was injected. Provided there was no evidence of subarachnoid or intravascular injection the drug was introduced through catheter in epidural space. The time of injection was noted and patients were asked about feeling of numbness, tingling sensation, warmth in toes and feet after some time of injection.

All patients were monitored for analgesia and hemodynamic changes frequently and at regular interval of 15, 30, 45 & 60 minutes of drugs administration and postoperatively at 60 min in PACU.

**ANALGESIC CHARACTERISTICS:**

a. **ONSET OF ANALGESIA:** It was described in terms of onset of sensory block. Sensory block was tested by pinprick along the mid-clavicular line till the block reached to level T10,
at which time the surgery was proceeded. The time between drug administration and onset of loss of pain to pinprick at T10 was taken as “onset of analgesia”.

b. QUALITY OF ANALGESIA: It was described in terms of intra operative pain and a feeling of discomfort, evaluated by the patient and recorded by an observer unaware of patient’s data using visual analogue scale. It was graded as. Excellent = No intra operative pain or discomfort (VAS = 0), Fair = Minimum pain/ discomfort, requiring supplemental analgesia (pentazocin, diazepam) (VAS ≤ 3), poor = Severe pain, requiring administration of ketamine or GA (VAS ≥ 4).

c. DURATION OF ANALGESIA: It was described as the time from epidural drug administration to the first request for supplemental analgesia in the postoperative period at which time rescue analgesia was provided by i. m inj diclofenac sodium 75mg.

Side effect like hypotension, bradycardia, sedation, post-operative nausea and vomiting if any were recorded.

STATISTICAL ANALYSIS: With the help of biostatistician the statistical calculations of present study were done. Different statistical aggregates like mean, standard deviation & standard error of the mean were used to analyse numerical parameters. For within the group comparison, paired t-test is applied and for one sample comparison, unpaired t-test is used for inter group comparison (two sample test). Chi-square test is used to test the significance of difference between two proportions of a qualitative data. p-value of less than 0.05 was taken as statistically significant.

RESULT:

| STATISTICAL PARAMETERS | Group- A (Control group) | Group – B (Study group) |
|------------------------|--------------------------|------------------------|
| Mean age (yrs) ± S.E   | 46.3 ± 2.742             | 46.20 ± 2.64           |
| Male: Female Ratio     | 1: 2.33                  | 1:1.73                 |
| Mean weight ± S.E      | 52.67 ± 2.36             | 55.20 ± 2.58           |

Table 1: DEMOGRAPHIC PROFILE OF PATIENTS

All the patients in both the group was comparable with respect to age, male-female ratio and weight.

| Group | Parameters | Preop | 15min | 30min | 45min | 60min | Post op |
|-------|------------|-------|-------|-------|-------|-------|---------|
| A     | Mean± S.E  | 98.87±| 97.06±| 86.93±| 84.00±| 84.47±| 82.6± 1.7|
|       |            | 2.26  | 2.38  | 2.56  | 2.03  | 2.19  |         |
| B     | Mean± S.E  | 96.33±| 92.93±| 86.17±| 81.60±| 79.93±| 75.73± 2.54|
|       |            | 3.12  | 2.59  | 2.29  | 1.92  | 1.79  |         |
| P I   | NS         | NS    | NS    | NS    | NS    | NS    | S       |
| t value | 0.659 | 1.259 | 0.221 | 0.859 | 1.605 | 2.248 |

Table 2: CHANGE IN MEAN PULSE RATE IN TWO GROUPS
Table 2 and Graph 1 evaluate the change in pulse rate between two groups pre, intra & post operatively. The difference in the pulse rate pre-op & intra op were statistically non-significant. The difference in the pulse rate post op were significant (p value <0.05).

| Group | Parameters | Pre op | 15 min | 30 min | 45 min | 60 min | Post op |
|-------|------------|--------|--------|--------|--------|--------|---------|
| A     | Mean ± S.E | 13.73± 3.37 | 127.07± 2.62 | 115.07± 2.84 | 109.07± 3.26 | 117.7± 2.98 | 123.2± 2.61 |
| B     | Mean ± S.E | 128.17± 2.78 | 122.8± 4.17 | 110.93± 3.53 | 112.2± 2.57 | 112.47± 2.12 | 114.33± 3.91 |
| P I   | NS         | NS     | NS     | NS     | NS     | S      |         |
| t value | 1.044  | 0.867  | 0.914  | 0.754  | 1.438  | 1.887  |         |

Table 3: Change in mean systolic blood pressure in two groups

Graph 1: Change in mean pulse rate in two groups

Graph 2: Change in mean systolic blood pressure in two groups

Table 3 and Graph 2 shows that the difference of systolic blood pressure between the groups was statistically non-significant throughout the operative period but difference is
statistically significant in the postoperative time. Lowest recording was at 45 min in control group and 30 min in study group.

| Group | Parameters | Pre op | 15 min | 30 min | 45 min | 60 min | Post op |
|-------|------------|--------|--------|--------|--------|--------|---------|
| A     | Mean ± S.E | 83.93± 1.53 | 81.67± 1.30 | 74.87± 1.61 | 70.47± 1.61 | 76.60± 1.44 | 79.47± 1.40 |
| B     | Mean ± S.E | 81.67± 1.64 | 80.27± 1.37 | 75.20± 1.40 | 73.40± 1.40 | 72.73± 1.30 | 76.47± 1.24 |
| P I   | NS         | NS     | NS     | NS     | S      | NS     |         |
| t value | 1.008    | 0.741  | 0.155  | 1.124  | 1.995  | 1.604  |         |

Table 4: Change in mean diastolic blood pressure in two groups

Graph 3: Change in mean diastolic blood pressure in two groups

Table 4 and Graph 3 shows that the difference of diastolic blood pressure between the groups was statistically non-significant throughout the operative period and postoperative period time but difference was statistically significant at 60 min time interval. Lowest recording was at 45min in control group and at 60 min in study group.

| GROUPS | MEAN (min) ± S.E |
|--------|------------------|
| A      | 11.5±0.61        |
| B      | 9.07±0.52        |

Table 5: Mean onset of analgesia in two groups
Mean onset of analgesia with standard error is shown in Table-5. The difference in onset of analgesia between the groups is highly significant statistically (t-value = 3.032, p-value <0.01). Onset of analgesia in study group-B was earlier as compared to the control Group-A. (9.07 Vs 11.5 min) P value <0.01, is statistically highly significant.

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| Age (years) | Group A (n=30) (control group) | Group B (n=30) (study group) |
|-------------|---------------------------------|-----------------------------|
| No          | %                               | No                          | %                           |
| Excellent   | 18 60                           | 22 73.3                     |
| Fair        | 6 26.7                          | 6 20                        |
| Poor        | 4 13.3                          | 2 6.7                       |
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Table 6: Quality of analgesia in two group

The table 6 & graph 5 shows the quality of analgesia in two groups in terms of number and percentage. Quality of analgesia is improved in the study group-B than control.
group-A, i.e. lesser number of patients complaining of pain or discomfort. Study Group-B experienced better quality of analgesia than control Group-A (73% Vs 60%).

| Groups | Mean (min) ± S.E |
|--------|-----------------|
| A (control) | 78.47±4.52 |
| B (study) | 246.07±18.02 |

**Table 7: Mean duration of analgesia**

Table 7 & graph 6 shows the mean duration of analgesia with standard error of both groups.

The Group-B had a longer duration of analgesia as compared to Group-A. The difference between the mean duration of analgesia between the group is very highly significant (t value – 9.021, p value- <0.0001). The study Group-B experienced a painless period of more than three times than that of control group-A (246.07 Vs 78.47 min). P value <0.001. Showing very high statistical significant

| SIDE EFFECT | GROUP A | GROUP B |
|-------------|---------|---------|
| SEDATION    | NIL     | NIL     |
| PONV        | 6 (20%) | 4 (13.3%) |
| HYPOTENSION | 10 (33.3%) | 5 (16.67%) |

**Table 8: Incidence of side effect**

None of the patients in both the groups had sedation. There was no statistical difference in incidence of PONV in both Groups (p value >0.05). The patients in control group-A have 50% more incidence of hypotension than study group-B.

**DISCUSSION:** We have compared the Analgesic and Hemodynamic effects of a single dose of 2% lignocaine alone and 2% lignocaine with clonidine in epidural blockade. Clonidine, a partial α2
-- adrenergic agonist, has a variety of different actions, including antihypertensive properties and the ability to potentiate the effects of local anesthetics. This has been demonstrated in a rarity of clinical setting\textsuperscript{5,12} and has shown to result in the prolongation of the sensory blockade and a reduction in the amount or the concentration of local anaesthetic required to produce postoperative analgesia. Previous work with epidural infusion has shown that 150mcg of clonidine, when added to bupivacaine 0.25% approximately doubled the duration of the analgesia produced.\textsuperscript{4}

The result of the present study demonstrated that there is fall in pulse rate in both groups. The pulse rates were higher preoperatively due to atropine and anxiety which decreased as the effect of local anaesthetic increased. The fall was more uniform in study group-B due to clonidine than in control group-A. Similar result was obtained by Motsch J, et al\textsuperscript{13} where epidural clonidine produced a significant decrease (p<0.05) in heart rate. However in study of Yuan-shiou Huang, et al\textsuperscript{14} there was decrease in heart rate but the difference was not significant statistically. There was a fall in blood pressure in both the groups and later there was rise in blood pressure in both groups, but Group-B had a stable hemodynamic course as the rise was slow and uniform. This behaviour of the graph can be attributed to addition of clonidine to lignocaine, which prevented the steep fall and gave a stable hemodynamic intraoperative course for surgery. Similar result was obtained in the study by Motsch J, et al\textsuperscript{13} where epidural clonidine produced a significant decrease (p<0.05) in blood pressure. But in the study of Cigarini I, et al\textsuperscript{15} where epidural clonidine combined with bupivacaine was used for labor analgesia it was seen that fall in blood pressure was comparable in both groups. However in study of Yuan-shiou Huang, et al\textsuperscript{14} there was decrease in SBP but the difference was not significant statistically.

The increase in efficacy of the combination of clonidine and lignocaine compared with lignocaine alone was demonstrated in the analgesic characters. The mean onset of analgesia in Control Group-A was 11.5 ± 0.61 min and 9.07 ± 0.52 min in Study Group-B. The difference of mean onset of analgesia in both groups was found to be statistically highly significant t-value 3.032 & p-value < 0.01. Early onset of analgesia with addition of clonidine may be due to its own intrinsic analgesic activity by causing inhibitions of substance P at the posterior horn cells of spinal cord. (Table- 6 & Graph-9). Quality of analgesia improved in the Study Group-B than Control Group-A. That is, lesser number of patients complained of pain or discomfort in Study Group-B. The Study Group-B had 73% of patient with excellent analgesia as compared to 60% in Control Group-A. Fair and poor analgesia was more common in Control Group-A (Table -7 & Graph-10). The mean duration of analgesia in Control Group-A was 78.47 ± 4.52 min and Study Group-B it was 246.07 ± 18.02 min. The Study Group-B had more than three times (3.19) the painless period than that of Control Group-A (t-value 9.021 & p-value < 0.001) statistically very highly significant. This is mainly due to vasoconstrictor effect of clonidine which delays the systemic spread of local anaesthetic. This also helps in decreasing the systemic side effects of local anaesthetic (Table-8 & Graph-11).

Bouquet D, et al (1994)\textsuperscript{16} showed that Clonidine produces analgesia beyond the duration of local anaesthetic effect as judged by the time to first analgesic requirement (13±4 h vs. 7±5 h) with 150µgm clonidine added to a caudal lignocaine/ bupivacaine/ epinephrine mixture for anal surgery. Gabrile JS and Gordin (2001),\textsuperscript{17} Cigarini I, et al\textsuperscript{15} and Anzai Y and Nishikawa T (1995)\textsuperscript{18}
had the similar result and showed that when clonidine is added to a fentanyl-bupivacaine mixture for epidural labour analgesia, it seems to provide satisfactory analgesia of a longer duration than that produced by the fentanyl-bupivacaine combination alone. Schnabel A, et al (2001)\(^1\) had similar result of longer duration of postoperative analgesia and less requirement of rescue analgesia and so was the result in Francis Bonnet, et al (1989).\(^2\)

Clonidine stimulates the alpha-2 receptors in the Reticular activating system (Locus Ceruleus) which has an inhibitory effect on the sleep wake cycle. This causes sedation but no sedation was recorded in both groups, as low dose of clonidine was used. In the study of Filos KS, et al (2006)\(^2\) and Grabrile JS, et al\(^\text{17}\) sedation was seen in group who received higher dose of clonidine. Yuan-shiou Hang, et al (2007)\(^4\) showed that sedation was present in group who received 4µg/ml and not in group which received a dose of 1µg/ml.

The incidence of PONV was more in Control Group-A as compared to Study Group-B, but was statistically insignificant. Dobrydnjov I, et al (1999)\(^2\) found that there is no evidence after multiple studies that risk of PONV increases after addition of clonidine to LA. Clonidine is a partial \(\alpha\)-2 adrenergic agonist that has a variety of different action including antihypertensive effect as well as the ability to potentiate the effect of local anaesthetics.\(^23,24,25\) This was attributed to a more stable hemodynamic course of anaesthesia after adding clonidine to local anaesthetic.

**CONCLUSION:** Clonidine is a very useful adjunct to the pharmacological armamentarium of the Anaesthesiologists. Appropriate use of clonidine in clinical practice would help in the producing excellent quality of analgesia and stable hemodynamics in the peri-operative period. The extensive experience with clonidine is consistent with effect of alpha-2 adrenergic agonists in regional anaesthesia and with our knowledge of the pharmacology of these agents.

In summary clonidine will definitely expand scope and improve the reliability and efficacy of epidural anaesthesia. The major clinical place of clonidine is as an adjuvant to other analgesics and local anaesthetic as shown in number of studies. The clinical experiences of clonidine deserve to be more widely used in clinical practice and every anaesthesiologist should become more familiar with the various facets of this interesting drug. Finally “IT IS A VERSATILE ADJUVANT TO LOCAL ANAESTHETIC”.

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