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# A COMPARATIVE STUDY OF EPIDURAL FENTANYL AND CLONIDINE AS AN ADJUNCT TO BUPIVACAINE IN PATIENTS UNDERGOING ABDOMINAL HYSTERECTOMY.

Anesthesiology

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## ABSTRACT

**Background and Aims:** Regional anaesthesia is highly effective for both surgical procedure and postoperative pain management. In This Hospital Based Randomized Double Blind Interventional Study, We Compared The Effects Of epidural fentanyl and clonidine as an adjunct to bupivacaine in patients undergoing abdominal hysterectomy.

**Material and Methods :** After Obtaining Ethical Committee Approval, A Hospital Based Randomized Double Blind Interventional Study Was Conducted On 90 Patients With ASA Grade 1 And 2 In The Age Group 35 To 55 Years, Posted For abdominal hysterectomy. Divided Randomly Into 3 Groups, Group 1 received 0.5% bupivacaine 23ml plus 2ml of normal saline , Group 2 received 0.5% bupivacaine 23ml of 1.5ml of fentanyl plus 0.5ml of normal saline and Group 3 received 0.5% bupivacaine 23ml with 0.5ml of clonidine plus 1.5ml of normal saline. Onset of Sensory And Motor Block Along With Duration Of Analgesia And Adverse Effects Monitored, Hemodynamic Parameters Like Heart Rate (HR), Systolic Arterial Blood Pressure (SBP) And Diastolic Arterial Blood Pressure (DBP) Were Also **Monitored. Results:** Demographic Data And Surgical Characteristics Were Comparable In Both Groups. The Onset Time Of Sensory And Motor Block Were Significantly Shorter In Group 3 compared to Group 1 and 2. Duration Of Analgesia Was Significantly Longer In Group 3 compared to Group 1 and 2. Conclusion: Clonidine added as an adjuvant to bupivacaine for epidural anaesthesia has a shorter onset of analgesia and motor blockade and longer duration of analgesia.

## KEYWORDS

Fentanyl , Clonidine , Epidural , Bupivacaine , Analgesia .

## INTRODUCTION

Pain is defined by International Association for Study of Pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain is the most common and the most distressing complication of surgery. Regional anaesthesia is highly effective both for surgical procedure and postoperative pain management. The use of regional anaesthesia for major surgery can be advantageous as it provides not only good pain control extending into postoperative period but also early ambulation, feeding and possibly discharge. Epidural anaesthesia is a neuraxial technique which induces less physiological disturbances then spinal anaesthesia, besides it has low incidence of neurological sequelae, post-dural puncture headache and infection risk. Epidural techniques are widely used for operative anaesthesia , postoperative pain control, obstetric analgesia and chronic pain management. Epidural opioid analgesia is an effective and common method to control postoperative pain (Rawal et al. 1987)[1]. They provide more specific blockade of nociception by interacting with opioid receptors in central nervous system.

Fentanyl is a potent , short acting, highly lipophilic, synthetic opioid analgesic. The duration of postoperative analgesia is prolonged with the use of fentanyl than with spinal local anesthetics alone (Dahlgren et al. 1997)[2]. Use of epidural fentanyl with epidural bupivacaine provides quicker onset and spread anaesthesia , maintain hemodynamic stability and prolonged analgesia but with side effects notably nausea, vomiting, pruritus, urinary retention, respiratory depression (Ghos AA et al.2000)[3].

Clonidine is a partial alpha-2 adrenergic agonist which can provide pain relief by an opioid independent mechanism (Gabriel JS et al.2001)[4]. Preservative free clonidine administered into the epidural or subarachnoid space produces dose dependent analgesia and, unlike opioids, does not produce depression of ventilation, pruritus , nausea, vomiting or delayed gastric emptying (Filos et al.1994; Eisenach et al. 1996; Asai et al. 1997)[5][6][7]. The combination of epidural clonidine and bupivacaine provides satisfactory analgesia, and of longer duration than epidural bupivacaine –fentanyl combination (Kizilarslan S et al. 2000)[8].

The purpose of the study was to determine whether the combination of epidural bupivacaine and clonidine has better analgesic efficacy than combination of epidural bupivacaine and fentanyl. Also to study whether the epidural clonidine decreases the incidence of side effects compared with epidural fentanyl.

## REVIEW OF LITERATURE

Rucci et al (1985) studied the effect of fentanyl 0, 50, 100 or 200µg along with 0.5% bupivacaine in extradural blockade in patients undergoing lower abdominal surgeries. They concluded that the time to regression of analgesic blockade was significantly prolonged with mixture containing fentanyl 200µg.

Klimscha W et al (1995)[10] studied the hemodynamic and analgesic effects of clonidine added repetitively to continuous epidural and spinal blocks. In either spinal or epidural technique one- half of patients received clonidine (150µg) in addition to bupivacaine. They concluded that the addition of clonidine to bupivacaine yields long lasting, profound analgesia without significant alterations in the hemodynamic parameters.

## METHODS

After approval from hospital ethics committee and written informed consent from patients, 90 patients of ASA grade 1 and grade 2 were randomly selected by chit in the box method. All patients were of female gender, between 35-55 years, scheduled to undergo elective total abdominal hysterectomy with or without bilateral salpingo-oophorectomy under epidural block. Patients were randomized into 3 groups of 30 patients each , to receive 23ml of 0.5% plain bupivacaine with 2ml of normal saline (Group 1), 23ml of 0.5% plain bupivacaine with 1.5ml of fentanyl plus 0.5ml of normal saline (Group 2) and 23ml of 0.5% plain bupivacaine with 0.5ml of clonidine plus 1.5ml of normal saline (Group 3) . Exclusion criterias were any deformity or local sepsis in spinal or lumber region, severe hypovolemia , increased intracranial pressure, any major pre- existing neurological, cardiovascular, metabolic, respiratory or renal disease, any absolute or relative contraindication to study drug, any bleeding or coagulation abnormalities and any history of hypersensitivity to drugs.

The pre anesthetic examination comprised of detailed history and systemic examination to rule out any cardiopulmonary pathology and local examination of the lumbosacral region to look for the presence of any deformity or infection. Preoperative investigations included complete blood count (CBC), urine examination, blood sugar, serum electrolytes, coagulation indices, chest X-ray PA view, ECG and special investigation if required. All patients were kept fasting for at least 12 hours prior to surgery. Premedication included Tab. Alprazolam 0.5mg night before the surgery with sip of water .

Patient was taken on the operation table. Baseline Blood Pressure (BP), Pulse Rate (PR), Respiratory Rate (RR) were recorded and by 18G i. v. cannula preloading with 8-10 ml/kg of Ringer Lactate solution done.

Patient was positioned in left lateral decubitus position, with a pillow under the shoulder and asked to flex the knees and hips. Under all

aseptic technique, the back of the patient was painted with1% tincture iodine povidine solution then with spirit. Then selected site was draped with sterilized hole towel. Lumbar space between L2 - L3 vertebrae chosen by palpating the spine and anterior superior iliac spine. A subcutaneous wheal raised by injecting 5 ml of 2% lignocaine in supraspinous and interspinous ligaments. Lumbar epidural puncture was performed with 18 G Tuohy needle in L2- L3 inter space. A loss of resistance syringe with 5ml air connected to Tuohy needle was advanced slowly with pressure on piston. The resistance in the syringe disappeared dramatically – the loss of resistance sign. After confirming the position of the Tuohy needle, a test dose of 3 ml was given slowly, followed by the dose of the desired solution. The epidural catheter was inserted 4 cm. cephalad and fixed on the skin with sterile gauze and adhesive plaster. The time of injection, onset of analgesia (taken as the time to attain the highest level of sensory blockade), onset of motor block, level of sensory block, intensity of motor block and degree of sedation were noted. The sensory loss was tested by pin-prick test over the abdominal wall, perineum and legs by 25G disposable needle. Motor blockade was noted by using modified Bromage criteria.

Pulse rate (PR), Noninvasive blood pressure (BP), Respiratory rate (RR), and SpO2 were recorded at 5 minutes interval for first 20 minutes, at 10 minutes interval up to 40 minutes, at 60 minutes and then at 30 minutes interval till the operation was over. Time of commencement and end of surgery. In post operative period degree of sedation, grade of analgesia and motor blockade were noted at 30 minutes interval for the total duration of complete analgesia. Pain scoring was done by Visual Analogue Scale (VAS) and Verbal Ranking Scale (VRS). Duration of effective analgesia was measured as the time from onset of analgesia to the patient's first request for analgesia (or VAS score ≥3) either in the recovery room or the ward, and was recorded in minutes. Patient's demand for rescue analgesia constituted the end point of the study. Time when first dose of rescue analgesic was given, VAS score at that time and Modified Bromage scale score at that time were noted.

Adverse effects were observed and managed during intra operative or post operative period. Hypotension i.e., reduction in systolic blood pressure of more than 30% of the pre induction value was treated with incremental doses of intravenous mephentermine 5mg. Bradycardia was treated with intravenous administration of incremental doses of atropine 0.2mg. Nausea or vomiting was treated with intravenous administration of 4mg ondansetron.

A total of 120 patients were assessed for eligibility. Of these 26 patients did not fulfill the study of criteria and were excluded. A total of 94 patients, belonging to ASA grade 1 and grade 2, aged between 35 to 55 years, scheduled for elective total abdominal hysterectomy with or without bilateral salpingo-oophrectomy were randomly enrolled in the study. Four patients were excluded because of failed/partial epidural block, leaving a protocol- complaint sample size of 90 (effective sample size n=90).

Statistical Analysis- Categorical data i.e. ASA grade , type of surgery and the incidence of adverse events are presented as numbers and were compared among groups using Chi square test. P value < 0.05 was considered statistically significant. Groups were compared for demographic data , duration of surgery , total duration of motor block and analgesia by analysis of variance(ANOVA) and t- test. Probability was considered to be significant if less than 0.05.

## RESULT

The age, body weight and ASA status difference was not significant in the 3 groups. The Observations are presented as Mean ± Standard Deviation or as Percentages as is applicable.

*Table 1 Demographic Data*

| Variables | Group 1 | Group 2 | Group 3 | P value |
|---|---|---|---|---|
| Age (years) | 42.40 ± 4.74 | 41.70 ± 5.17 | 42.00 ± 5.39 | P>0.01 |
| Weight (kg) | 57.33 ± 3.32 | 56.57 ± 3.77 | 57.23 ± 3.31 | P> 0.01 |

*Table 2 Hemodynamic Parameters*

| Variables | Group 1 | Group 2 | Group 3 | P value |
|---|---|---|---|---|
| Pulse Rate (per min.) | 72.87 ± 5.24 | 72.40 ± 5.39 | 70.23 ± 5.25 | P>0.05 |
| Systolic BP (mm Hg) | 117.67 ± 4.95 | 118.53 ± 7.53 | 116.67 ± 6.18 | P>0.05 |
| Diastolic BP (mm Hg) | 75.20 ± 4.71 | 73.87 ± 5.12 | 73.07 ± 4.78 | P>0.05 |
| Respiratory (per min.) | 17.63 ± 1.32 | 17 ± 1.14 | 17.36 ± 1.38 | P>0.05 |

Intraoperative hemodynamic parameters did not differ in the two groups during the course of anaesthesia.

*Table 3 Onset of Analgesia (in min.)*

| | Group 1 | Group 2 | Group 3 |
|---|---|---|---|
| Mean ± SD | 15.97 ± 1.99 | 11.83 ± 1.51 | 11.90 ± 1.45 |

Table 3, show the mean onset of analgesia along with standard deviation. The mean time of onset of analgesia in clonidine group was 11.90± 1.45 minutes which was same (11.83±1.51 minutes) as in fentanyl group (P >0.05). These values were significantly different from the bupivacaine group in which onset time of analgesia was 15.97 minutes (P< 0.001).

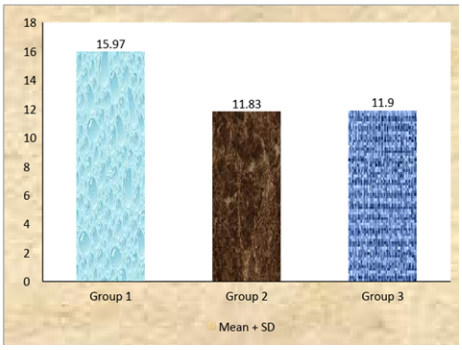


*Table 4 Onset of Motor Block (in min.)*

| | Group 1 | Group 2 | Group 3 |
|---|---|---|---|
| Mean ± SD | 16.93 ± 2.08 | 15.96 ± 1.65 | 13.63 ± 1.49 |

Table 4, shows the mean onset of motor block with standard deviation. The mean time of onset of motor block was shorter in clonidine (13.63± 1.49 minutes) group compared to fentanyl group (15.96± 1.65minutes) and bupivacaine group (16.93± 2.08 minutes) which was significantly less (p <0.001) from the bupivacaine group

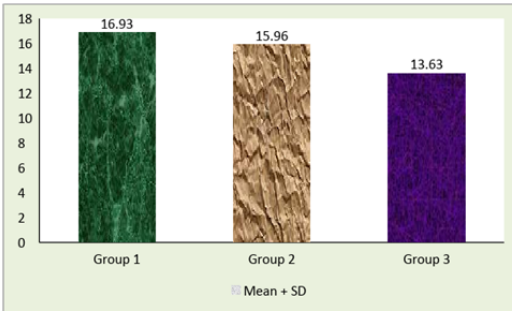


*Table 5 Intensity of Sensory Block*

| Group | Clinical Impression | | | Total |
|---|---|---|---|---|
| | Good | Fair | Unsatisfactory | |
| 1 | 24 (80%) | 6 (20%) | | 30 |
| 2 | 26 (86.66%) | 4 (13.33%) | | 30 |
| 3 | 28 (93.33%) | 2 (6.66%) | | 30 |

Table no 5 shows that 24 out of 30 patients in group 1, 26 patients in group 2 and 28 patients in group 3 showed no signs of reaction to stimuli from the site of operation, the sensory block was graded as good. 6 patients in group 1 , 4 patients in group 2 and 2 patients in group 3 showed slight reflex response at sometime during the procedure and were supplemented with propofol , the block was described as fair.

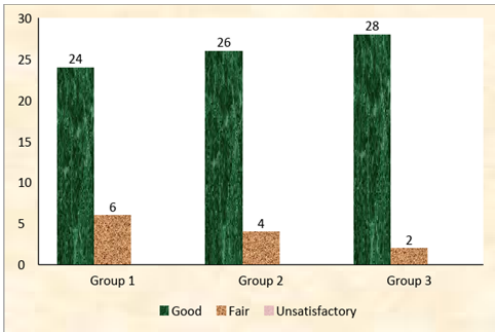

*Table 6 Intensity of Motor Block*

| Group | Clinical Impression | | | Total |
|---|---|---|---|---|
| | Complete (1) | Almost Complete | Partial (3) | |
| 1 | 21 (70%) | 9 (30%) | | 30 |
| 2 | 20 (73.33%) | 9 (23.33%) | 1 (3.33%) | 30 |
| 3 | 22 (80%) | 8 (20%) | | 30 |

Table no 6 shows that 21 patients in group 1, 20 patients in group 2 and 22 patients in group 3 showed complete motor block. 9 patients in group 1 , 9 patients in group 2 and 8 patients in group 3 showed almost complete block.1 patient in group 2 showed partial motor block.

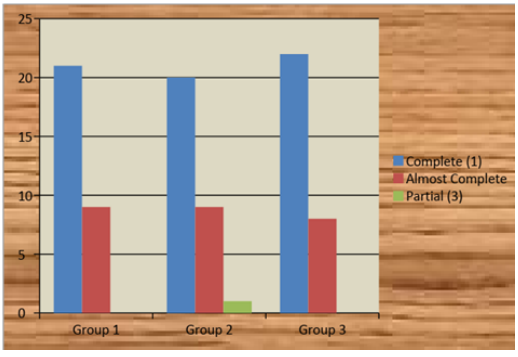


*Table 7 Duration of Analgesia ; Mean + S.D. (Minutes)*

| | Group 1 | Group 2 | Group 3 |
|---|---|---|---|
| Mean ± SD | 207.33 ± 26.12 | 369.66 ± 46.49 | 392.33 ± 46.95 |

Table no 7 shows the duration of analgesia. The mean duration of analgesia was 392± 46.95 minutes in clonidine group and 369.66± 46.49 minutes compared to 207.33± 26.12 minutes in bupivacaine group. There was a significant difference in total duration of analgesia in between group 1 and 2 (p 0.001) and group 1 and 3 ($p < 0.001$). There was no significant difference in total duration of analgesia in between group 2 and 3($p > 0.05$).

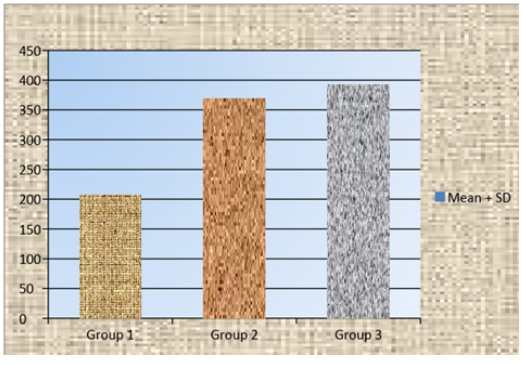


*Table 8 Intraoperative Side Effects*

| S.No. | Side Effects | Group 1 | Group 2 | Group 3 |
|---|---|---|---|---|
| 1. | Nausea | 2 (6.66%) | 7 (23.33%) | 1 (3.33%) |
| 2. | Hypotension | 3 (10%) | 2 (6.66%) | 4 (13.33%) |
| 3. | Bradycardia | 3 (10%) | 1 (3.33%) | 2 (6.66%) |
| 4. | Pruritus | 0 | 4 (13.33%) | 0 |
| 5. | Respiratory Depression | 0 | 0 | 0 |

*Table 9 Post Operative Side Effects*

| S.No. | Side Effects | Group 1 | Group 2 | Group 3 |
|---|---|---|---|---|
| 1. | Nausea | 2 | 5 | 0 |
| 2. | Hypotension | 0 | 0 | 1 |
| 3. | Bradycardia | 0 | 0 | 0 |
| 4. | Pruritus | 0 | 4 | 0 |
| 5. | Respiratory Depression | 0 | 0 | 0 |

**DISCUSSION** The use of augmentation strategies (Neuraxial Opioids or Non- opioids) in epidural analgesia is widespread and increasing for the management of intra operative and post operative pain. The improved postoperative analgesia with epidural blockade may reduce the incidence of cardiac and pulmonary morbidity and mortality in patients undergoing major abdominal surgeries.

The routine use of regional anaesthesia for lower abdominal and lower limb surgeries is associated with a short duration of analgesia post operatively which can be extended by intramuscular analgesics via epidural catheter once patient experiences pain and demand for its relief. This causes intermittent and relatively ineffective analgesia, demands more patient care and provides least patient satisfaction. This problem is circumvented by giving analgesics prior to occurrence of pain. The pre-emptive mixing of analgesics with local anaesthetics for epidural anaesthesia provides a better alternative.

In clinical practice, neuraxial opioids , especially fentanyl is widely used for the prospective pain relief. They have advantages, compared with local anaesthetics, of potent and long-lasting analgesia accompanied by a reduce incidence of nervous system depression without motor effects of hypotension.

Clonidine administered spinally or epidurally has potent antinocic eptive action through an $\alpha_2$- receptor- mediated mechanism in the dorsal horn of the spinal cord. Clonidine has been used as an adjuvant in regional anaesthesia in various settings, including post operative epidural analgesia. Clonidine has been shown to improve analgesia when added to an epidural infusion of morphine after major abdominal surgery.

This randomized comparative interventional study included 90 patients (age 35-55 years) who underwent elective total abdominal hysterectomy with or without bilateral salpingo-oophorectomy under epidural block. The patient selected in the present study belonged to ASA grade -1 and 2.

In our study mean time of onset of analgesia in clonidine group was 11.90± 1.45 minutes which was same (11.83±1.51 minutes) as in fentanyl group ($P > 0.05$). These values were significantly different from the bupivacaine group in which onset time of analgesia was 15.97 minutes (P,0.001).

Our results were consistent with previous studies on neuraxial clonidine analgesia. Rockemann MG et al (1995)[11] reported in their comparative study of epidural clonidine and morphine in post surgical patients of pancreatectomy that clonidine groups had a rapid onset of analgesic action with a significant reduction of pain scores occurring within 30 minutes compared to morphine groups.

Clonidine enhances sensory blockade from epidural or peripheral nerve block injection of local anesthetics. Clonidine blocks conduction of C and A delta fibers ( Butterworth JF at al 1993) [12].

In our study , mean time of onset of motor block was shorter in clonidine (13.63± 1.49 minutes) group compared to fentanyl group (15.96± 1.65minutes) and bupivacaine group (16.93± 2.08 minutes) which was significantly less ($p < 0.001$) from the bupivacaine group.

Our observations were in accordance with those of Gaumann DM et al [13] who reported clonidine enhances both sensory and motor blockade from epidural or peripheral nerve block injection of local anaesthetics. Clonidine enhances motor blockade from epidural or peripheral nerve block injection of local anesthetics.It increases potassium conductance ( Rodrigo A et al 1985) [14] in isolated neurons in vitro and intensifies conduction block of local anaesthetics.

Rucci et al (1985)[9] noted that as the dose of narcotic (fentanyl) was increased in the extradural space, the anaesthetic solution lost its ability to block the motor fibres. The degree of motor blockade was less intense and incomplete $S_1$ blockade (root jumping) was more frequent with mixture containing increasing doses of fentanyl.

The mean duration of analgesia was 392± 46.95 minutes in clonidine group and 369.66± 46.49 minutes compared to 207.33± 26.12 minutes in bupivacaine group.There was a significant difference in total duration of analgesia in between group 1 and 2 (p 0.001) and group 1 and 3 ($p < 0.001$). There was no significant difference in total duration of analgesia in between group 2 and 3($p > 0.05$).

Our results were consistent with previous comparative studies on neuraxial clonidine performed by Motsch J et al [15], Mogensen T et al. [16] Prolongation of the duration of action of local anesthetics by epidural clonidine may result from local vasoconstriction and altered local anesthetic disposition or form a direct analgesic effect on $\alpha_2$-adrenocepters in the substantia gelatinosa of the spinal cord.

Alpha$_2$ –adrenergic agoinsts could reduce pain by action at all 3 sites: reduction in peripheral norepinpherine release by stimulation of prejunctional inhibitory alpha $_2$-adrenoceptors, inhibition of noxial neural transmission in the dorsal horn by both pre- and postsynaptic mechanisms, and direct inhibition of spinal preganglionic sympathetic neurons.

Our study showed a significantly higher incidence of nausea and vomiting in fentanyl group ( 23.33%) compared to bupivacaine group ( 6.66%) and clonidine group ( 3.33%) during intra-operative period. In postoperative period 5 patients in fentanyl group complained of nausea and vomiting. This may be attributed to the supraspinal mechanism of emetic effect of epidural opioid while clonidine exhibits anti- emetic properties.Our study was consistent with previous studies performed by Constant I et al [17].

Our study showed that pruritus was present only in patients of fentanyl group , in 4 patients during surgery and in 4 patients after surgery (26.66%) compared to bupivacaine (0%) group or clonidine (0%) group. Our study was consistent with previous studies performed by Constant I et al [17].

Our study showed that the degree of sedation was more in clonidine treated patients than the patients in the bupivacaine group .

## CONCLUSION

Our results show that epidural clonidine has the same safety and analgesic efficacy as epidural fentanyl when combined with a local anaesthetic. It also showed that it is possible to significantly reduce the incidence of side effects (like nausea, vomiting, pruritus) caused by epidural fentanyl by replacing fentanyl with clonidine.

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