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A comparative study of epidural fentanyl and clonidine as an adjunct to bupivacaine in patients undergoing abdominal hysterectomy

Dr. K Rajarajeswaran, Dr. S Sivakumar

Assistant Professor, Department of Anesthesia and Critical Care, Madha Medical College Hospital and Research Institute, Chennai.

Abstract

Aim and background: Epidural techniques are widely used for operative anaesthesia, postoperative pain control, with less physiological disturbances and side effects than spinal anaesthesia. Aim of this study is to compare epidural bupivacaine alone, with clonidine-bupivacaine and fentanyl-bupivacaine combination in patients undergoing abdominal hysterectomy in terms of duration of analgesia, the hemodynamic effects, side effects, onset of sensory and motor blockade.

Methods and Materials: Ninety ASA I and II, female patients between 35-55 years, were randomly selected into three groups (Group I bupivacaine alone, group II bupivacaine with fentanyl and group III bupivacaine with clonidine in epidural). The onset of analgesia, onset of motor block, duration of analgesia and degree of sedation were noted in each group after performing epidural anesthesia.

Results: The mean time of onset of analgesia were 15.97 ± 1.99 min, 11.83 ± 1.51 min, 11.90 ± 1.45 min in group I, II, III respectively. The mean time for total duration of analgesia were 207.33 ± 26.12 min, 369.66 ± 46.49 and 392.33 ± 46.95 in group I, II and III respectively.

Conclusion: Our study show 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 with the same safety and analgesic efficacy as epidural fentanyl when combined with a local anesthetic.

Keywords: Epidual anesthesia, Clonidine, Fentanyl, Motor blockade, Duration of analgesia

1. 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 [1]. The relief of peri-operative pain is a subject which has been receiving an increasing amount of attention in the past few years. Severe post-operative pain has a well-known morbidity and causes distress to patients. The transmission of nociceptive stimuli from the periphery to the CNS results in neuro-endocrine stress response resulting in increased sympathetic tone, increased catecholamine levels and catabolic hormone Secretion [2]. Besides causing emotional stress, pain may lead to increased incidence of postoperative complications like reduced pulmonary compliance, muscle splinting, inability to breathe deeply, atelectasis, tachycardia, increased cardiac work, myocardial ischaemia, deep vein thrombosis, ileus, nausea, vomiting, insomnia etc [3]. Therefore anaesthesiologists have been in constant search for newer improved techniques for peri-operative pain relief over past decade. Regional anaesthesia is highly effective both for surgical procedure and postoperative pain management [3, 4]. It has lower adverse effects and sequelae than general anaesthesia, in addition promotes economy of time and money, improves quality of life. Epidural blockade induces less physiological disturbances than 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 [5]. Bupivacaine, synthesized by Ekenstam and his colleagues in 1957, is at present acknowledged as one of the most suitable agent for epidural use in postoperative pain and for pain relief in labour. It is three to four times more potent and possessed longer duration of action than lignocaine. Local anesthetics provide good analgesia for surgical and immediate post-operative period but duration is limited so for postoperative analgesia it has to be continued repeatedly by continuous epidural or spinal, at the cost of motor paralysis or reflex suppression which are not beneficial in post-operative period. The first report of use of narcotics injected into the extradural space came from Jerusalem by Behar, *et al.* in 1979. Epidural opioid analgesia is an effective and common method to control postoperative pain (Rawal *et al*. 1987). Many opioids have been used for post-operative analgesia via intrathecal or epidural route. 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. It has been commonly used as an adjuvant for post-operative analgesia. It has advantages over morphine because of its rapid onset of action (Leighton *et al*. 1989) and superior intraoperative conditions (Connely *et al*. 1994). The duration of postoperative analgesia is prolonged with the use of fentanyl than with spinal local anesthetics alone (Dahlgren *et*

al. 1997). The benefits also include hemodynamic stability with use of smaller doses of spinal anaesthetics (Kang *et al*. 1998) and less troublesome side effects than morphine (Hamber and Viscomi 1999). Use of epidural fentanyl with epidural bupivacaine provides quicker onset and spread of anaesthesia, and prolonged analgesia but is associated with side effects notably nausea, vomiting, pruritus, urinary retention, respiratory depression (Ghos AA *et al*. 2000). Because of some side effects like sedation, hypotension, respiratory depression, pruritus, nausea-vomiting and convulsions, there is a constant search about the drug which provides or prolongs the analgesia duration in postoperative period with minimal side effects. Clonidine is a partial alpha-2 adrenergic agonist that has a variety of different actions including antihypertensive effects as well as ability to potentiate the effects of local anaesthetics [11]. 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). The primary goal of this study was to determine whether the combination of epidural bupivacaine and clonidine has better analgesic efficacy than combination of epidural bupivacaine and Fentanyl, during intraoperative and postoperative period in patients undergoing elective hysterectomy surgery and also to study whether the epidural clonidine decreases the incidence of side effects compared with epidural Fentanyl.

2. Materials and Methods

After getting approval from the ethical committee and informed written consent from the patients, Ninety patients of ASA grade I and grade II were randomly selected. 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.

Study Design: Prospective, randomized, double blind, controlled comparative study.

Exclusion criteria: Any deformity or local sepsis in spinal or lumber region, Severe hypovolemia, increased intracranial pressure, major pre-existing neurological, cardiovascular, metabolic, respiratory or renal disease, history of hypertension, diabetes mellitus, respiratory disease, epilepsy, cardiac disease, spinal disorders, any absolute or relative contraindication to study drug, bleeding or coagulation abnormalities.

Each group consisted of 30 patients.

1. **Bupivacaine group (Group 1):** (Control group): Patients received 23 ml of 0.5% plain bupivacaine (115mg) with 2ml of normal saline.

2. **Fentanyl group (Group 2):** Patients received 23ml of 0.5 % plain bupivacaine (115mg) with 1.5ml (75µg) of fentanyl + 0.5 ml of normal saline.

3. **Clonidine group (Group 3):** Patients received 23ml of 0.5% plain bupivacaine (115mg) with 0.5ml (75µgm) of clonidine + 1.5ml of normal saline.

The total injected volume in the epidural space was 25 ml in all three groups. Premedication done with 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, Using all aseptic technique, at Lumbar space between L2 –L3 vertebrae, Lumbar epidural puncture was performed with 18 G Tuohy needle. 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. Following parameters were monitored: Pulse rate (PR), Noninvasive blood pressure (BP), Respiratory rate (RR), and SpO2. The above mentioned parameters 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. Side effects: hypotension, bradycardia, respiratory depression, nausea and vomiting were noted. In postoperative period PR, BP, RR, SpO2, degree of sedation, grade of analgesia and motor blockade were noted at 30 minutes interval for the total duration of complete analgesia.

Duration of analgesia was observed and recorded following pain scoring system – Visual analogue score (VAS). The VAS consisted of a 10cm horizontal paper strip with two endpoints labeled “No Pain” and “Worst pain ever”. Duration of effective analgesia was measured as time from onset of analgesia to the patient’s first request for analgesic (or VAS score $\geq$3) either in the recovery room or the ward, and was recorded in regular intervals. 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. Side effects i.e. nausea, vomiting, hypotension, bradycardia, respiratory depression, pruritus were noted. Degree of sedation done with scoring scale 1-5: 1 Awake and fully alert. 2 Awake but drowsy. 3 Sleeping but easily arousable. 4 Sleeping but difficult arouse. 5 Unresponsive to verbal or tactile command. Intensity of Motor block, Modified Bromage score (Breen TW 1993): Score Criteria 1 Complete block (unable to move feet or knees), 2 Almost complete block (able to move feet only), 3 Partial block (just able to move knees), 4 Detectable weakness of hip flexion while supine (full flexion of knees), 5 No detectable weakness of hip flexion while supine. 6 Able to perform partial knee bend. Patient Satisfaction: Good - Patient very happy with technique opted for the same in future if needed. Fair - Patient satisfied but not very curious about the technique. Poor - Patient not at all happy with the technique.

3. Results

Categorical data i.e. ASA grade, type of surgery and the incidence of adverse events (hypotension, bradycardia,

respiratory depression, nausea, pruritus) are presented as numbers (percent) and were compared among groups using Chi square test. P value <0.05 was considered statistically significant. Groups were compared for demographic data (age, weight), duration of surgery, total duration of motor block and analgesia by analysis of variance (ANOVA) and t-test [table 1]. Probability was considered to be significant if less than 0.05. Data is represented as mean and standard deviation.

In groupI, the time of onset of analgesia was between 12-14 minutes in 26.66% of the patients and 15-17 minutes in 43.33% of the patients. 30% of the patients had time of onset of analgesia between 18-20 minutes. The mean time of onset of analgesia was 15.97 ± 1.99 minutes [table 2]. In group II, the time of onset of analgesia was between 9-11 minutes in 43.33% of the patients and 12-14 minutes in 56.66% of the patients. The mean time of onset of analgesia was 11.83 ± 1.51 minutes. In group III, the time of onset of analgesia was between 9-11 minutes in 36.66% of the patients and 12-14 minutes in 63.33% of the patients. The mean time of onset of analgesia was 11.90 ± 1.45 minutes [table 2]. In group I, the time of onset of motor block was between 14-16 minutes in 26.66% of the cases and 17-19 minutes in 43.33% of the cases. 30% of the cases had time of onset of motor block between 20-22 minutes. The mean time of onset of motor block was 16.93 ± 2.08 minutes. In group II, the time of onset of motor block was between 11 – 13 minutes in 10% of the cases and 14-16 minutes in next 50% of the cases. 40% patients had time of onset of motor block between 17 – 19 minutes. The mean time of onset of motor block was 15.96 ± 1.65 minutes. In group III, the time of onset of motor block was between 11-13 minutes in 60% of the cases and 14-16 minutes in 33.33% of the cases. 6.66% of the patients had time of onset of motor block between 17 – 19 minutes. The mean time of onset of motor block was 13.63 ± 1.49 minutes. In group I, the total duration of analgesia was between 180 – 240 minutes in 96.66% of the cases and 241 – 300 minutes in 3.33% of the cases. The mean time for total duration of analgesia was 207.33 ± 26.12 minutes. In group II, the total duration of analgesia was between 241 – 300 minutes in 16.66% of the cases and 301 – 360 minutes in 26.66% of the cases. 56.66% of the patients had analgesia lasting between 361 - 420 minutes. The mean time for total duration of analgesia was 369.66 ± 46.49 minutes. In group III, the total duration of analgesia was between 301 – 360 minutes in 40% of the cases. 46.66% of the patients had analgesia lasting between 361 – 420 minutes. 10% of the patients had analgesia lasting between 421 – 480 minutes. 3.33% of the patients had analgesia lasting between 481 – 540 minutes. The mean time for total duration of analgesia was 392.33 ± 61.47 minutes [table 2]. In all the three groups insignificant difference in systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate occurred in intra operative period from the pre-operative values(P values >0.05) [table 3]. In group 2; 77% patients were awake and alert (Grade 1), 33% patients were awake and drowsy (Grade 2). In group 3; 66.66% patients were awake and alert (Grade 1), 30% patients showed mild sedation (Grade 2) while 3.33% patients showed deep sedation (sleeping but easily arousable) (Grade 3).The main side effects during intraoperative and post-operative period in fentanyl group are pruritus and nausea, other side effects like hypotension and bradycardia shows no significant correlation with the addition of fentanyl or clonidine [table 4].

Table 1: Patient Characterstics and Baseline Clinical Variables; Mean ± S.D.

variables	Group I	Group II	Group III
Age (years)	42.40 ± 4.74	41.70 ± 5.17	42.00 ± 5.34
Baseline PR	76.67 ± 6.92	78.57 ± 7.15	76.30 ± 7.37
Baseline Systolic BP	122.13 ± 7.79	120.80 ± 6.72	122.27 ± 8.13
Baseline Diastolic BP	77.53 ± 7.38	75.73 ± 5.98	76.93 ± 4.83
Respiratory rate	17.93 ± 1.44	18.17 ± 1.39	17.70 ± 1.68
Weight (kg)	57.33 ± 3.32	56.57 ± 3.77	57.23 ± 3.31

Table 2: Onset, Duartion of Analgesia and Motor Blockade MEAN ± S.D. (Minutes)

Variables	Group I	Group Ii	Group Iii
Onset of analgesia	15.97 ± 1.99	11.83 ± 1.51	11.90 ± 1.45
Onset of motor blockade	16.93 ± 2.08	15.96 ± 1.65	15.96 ± 1.65
Duration of analgesia	207.33 ± 26.12	369.66 ± 46.49	392.33 ± 46.95

Table 3: Intraoperative Pulse Rate, Blood Pressure and Respiratory rate; MEAN ± S.D.

Group	Pulse Rate	Systolic BP	Diastolic BP	Respiratory Rate
Group 1	72.87 ± 5.24	117.67 ± 4.95	75.20 ± 4.71	17.63 ± 1.32
Group 2	72.40 ± 5.39	118.53 ± 7.53	73.87 ± 5.12	17 ± 1.14
Group 3	70.23 ± 5.25	116.67 ± 6.18	73.07 ± 4.78	17.36 ± 1.38

Table 4: Intraoperative and Postoperative Side Effects

S. No.	Side Effects	Group 1		Group 2		Group 3	
		intraop	postop	intraop	postop	intraop	postop
1	Nausea	2 (6.66%)	2	7(23.33%)	5	1 (1.33%)	0
2	Hypotension	3 (10%)	0	2 (6.66%)	0	4 (3.33%)	1
3	Bradycardia	3 (10%)	0	1 (1.33%)	0	2 (6.66%)	0
4	Pruritus	0	0	4 (3.33%)	4	0	0
5	Respiratory Depression	0	0	0	0	0	0

4. 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 [1]. In clinical practice, neuraxial opioids, especially fentanyl is widely used for the postoperative pain relief [1]. They have advantages, compared with local anaesthetics, of potent and long-lasting analgesia accompanied by a reduced incidence of central nervous system depression without motor effects or hypotension. However, such use is limited by adverse effects which mainly depend on the dose of opioids. In the last decade, several experimental and clinical studies have demonstrated that clonidine administered spinally or epidurally has potent antinociceptive action through an α2- receptor- mediated mechanism in the dorsal horn of the spinal cord [2]. 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 [3].

Pre-operative pulse rate and systolic and diastolic blood pressure were almost equal in all the groups. The mean change in pulse rate and blood pressure in intra-operative and postoperative values from preoperative values was not significantly different in the three groups. Similar findings were observed by Klimscha W *et al.* (1995). Slight more reduction in clonidine group (Group 3) was observed compared to bupivacaine group (Group 1) and fentanyl group (Group 2) which was statistically not significant. Similar findings were observed by Klimscha W *et al.* (1995) and Rockemann MG *et al.* (1995) who observed insignificant reduction in blood pressure after low dose epidural clonidine. Clonidine can decrease blood pressure by inhibiting preganglionic sympathetic neural activity in the spinal cord. Clonidine can also decrease blood pressure by action in the brain stem, which could be reached after neuraxial administration by systemic redistribution or cephalad spread in cerebrospinal fluid. This may be explained by clonidine's pharmacology and mechanism of action. Epidural injection of local anaesthetic decrease mean arterial pressure and sympathetic outflow, presumably by blocking axonal transmission along spinal roots and nerves. Therefore, the spinal preganglionic sympathetic cellular inhibition by clonidine would be hidden by dense axonal blockade by local anaesthetic. Another reason of haemodynamic stability in our study may be the use of a smaller dose of epidural clonidine compared to previous studies in which a comparatively larger dose was used. Rockemann *et al.* (1995) also reported that no reduction of haemodynamic parameters was observed when half the clonidine dose was used in the clonidine 4µg/ kg-morphine 2mg combination. After epidural block, during intra-operative and postoperative period, there was no statistically significant change observed in respiratory rate in the three groups. The results are consistent with those of Bailey PL *et al.* (1991) and Marruecos L *et al.* (1988).

Mean time of onset of analgesia in clonidine group was 11.90 minutes which was same (11.83 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). Mean time of onset of motor block was shorter in clonidine (13.63 minutes) group compared to fentanyl group (15.86 minutes) and bupivacaine group (16.93 minutes) which was significantly less (P<0.001) from the bupivacaine group (16.93 minutes). Clonidine is rapidly and extensively absorbed into the spinal CSF compartment after epidural administration, with concentrations peaking 30-60 min after injection. This coincides closely with attainment of near-maximal analgesia. The mean duration of analgesia was 427 minutes in Clonidine group (Group 3) and 369 minutes in Fentanyl group (Group 2) compared to 207 minutes in Bupivacaine group (Group 1). There was a significant difference in total duration of analgesia in between group 1and 2 (P<0.001) and group 1and 3 (P<0.001). There was no significant difference in total duration of analgesia in between group 2 and 3 (P>0.05). These results are consistent with previous comparative studies on neuraxial clonidine performed by Motsch J *et al.* (1990), Mogensen T *et al.* (1992), Bouguet D *et al* (1994), Klimscha W *et al* (1995), Constant I *et al.* Motsch J *et al.* (1990) and Mogensen T *et al.* (1992). Prolongation of the duration of action of local anesthetics by epidural clonidine may result from local vasoconstriction and altered local anesthetic disposition from a direct analgesic effect on α2-adrenoceptors in the substantia gelatinosa of the spinal cord. Alpha2 -adrenergic agonists could reduce pain by actions at all three sites: reduction in peripheral norepinephrine release by stimulation of prejunctional inhibitory alpha 2 -adrenoceptors, inhibition of noxious neural transmission in the dorsal horn by both pre- and postsynaptic mechanisms, and direct inhibition of spinal preganglionic sympathetic neurons.

Our study demonstrated an increased 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. The emetic effect of epidural opioid is well known and involves supraspinal mechanisms, while clonidine exhibits antiemetic properties when administered by the oral (Mikawa K *et al.*1995) or intravenous route (Saumpelmann R *et al.*1996; Oddby-Muhrbeck E *et al.* 2002). In group 1 all the patients were awake and alert. In group 2; 77% patients were awake and alert, 33% patients were awake and drowsy. In group 3; 66.66% patients were awake and alert, 30% patients showed mild sedation while 3.33% patients showed deep sedation (sleeping but easily arousable). In general, the clonidine treated patients were more sedated than the patients in the control (bupivacaine) group. But all patients were easily arousable, all maintained a respiratory rate greater than 14. Sedation commonly accompanies the use of clonidine for regional anesthesia, consistent with the known sedative/anesthetic-sparing properties of alpha2 -adrenergic agonists by actions in the locus coeruleus (Maze M *et al.* 1991).

The results of our study demonstrated that it is possible to decrease the unwanted side effects of epidural fentanyl by replacing it with epidural clonidine. The analgesic effects of the bupivacaine-clonidine combination (Group 3) were equivalent / better to those of the bupivacaine-fentanyl combination (Group 2). This may be an argument for the use of clonidine rather than fentanyl as an additive to local anaesthetics when prolongation of anaesthesia is required.

5. Conclusion

To conclude, our results show 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. Also, epidural clonidine has the same safety and analgesic efficacy as epidural fentanyl when combined with a local anesthetic.

6. References

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