Comparative study of outcome in epidural bupivacaine with buprenorphine and bupivacaine with fentanyl in lower limb surgeries

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Abstract

Pain is a complex subjective experience which has been proved difficult to measure in reproducible way. It is found that operative pain is more severe after surgery and thereafter gradually diminishes over next 24 hours. Providing effective analgesia for patients undergoing major surgery is a daily challenge for most anesthetists. The treatment of acute postoperative pain is a major health care issue. Epidural anesthesia /analgesia is one of the best accepted techniques for lower limb surgeries as it provides good sensory and motor block, decreases adverse physiologic responses to surgery such as autonomic hyperactivity, cardiovascular stress, tissue breakdown, increased metabolic rate, pulmonary dysfunction, and immune system dysfunction. Intraoperatively, sensory and motor blockade, quality and duration of Postoperative analgesia, hemodynamic and respiratory parameters, side effects like nausea, vomiting, respiratory depression, urinary retention. In this observational study an effort was made to study the peri operative analgesic efficacy of Inj. buprenorphine and Inj. fentanyl with 0.5 % Bupivacaine epidurally for lower limb surgeries. There were no significant hemodynamic and respiratory side effects in either of the groups. The postoperative analgesia was definitely of a longer duration with the Buprenorphine group. So it is concluded that epidural Buprenorphine is better in providing prolonged satisfactory postoperative analgesia as compared to Inj. Fentanyl. Regarding the side effects, the incidence of nausea and vomiting was more in buprenorphine as compared to fentanyl group, which could be easily treated with antiemetic’s like Ondansetron. Both buprenorphine and fentanyl along with bupivacaine 0.5% can be given epidurally as a single shot injection for perioperative analgesia obviating the need for epidural catheter.

Keywords: Analgesia, bupivacaine, fentanyl, buprenorphine

Introduction

The word pain is derived from the Greek term poine (“penalty”) [1]. Pain is not just a sensory modality but is an experience. The international Association for the study of pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. The father of the field of pain management as we know today is John. Bonica. He founded the international association for study of pain in 1974. Other than psychological trauma, pain is shown to affect the physiology of almost all the system including respiratory, cardiovascular and metabolic, thereby increasing the morbidity [2].

Regional anesthesia has lots of advantages as compared to GA for lower limb surgeries. The advantages are [3]

1. Awake patient
2. Poly pharmacy avoided
3. No airway manipulation
4. Good motor and sensory blockade
5. Early food intake by the patient
6. Less incidence of post-operative nausea and vomiting
7. Prolonged postoperative analgesia
8. Ideal operating conditions can be met
9. Reduce incidence of hypercoagulability
10. Decreases the incidence of myocardial infraction and postoperative pulmonary complication.
Epidural Anesthesia is becoming one of the most useful and versatile procedures in modern anesthesiology. It is unique in that it can be placed at virtually any level of the spine, allowing more flexibility in its application to clinical practice. It is more versatile than spinal anesthesia, giving the clinician the opportunity to provide anesthesia and analgesia, as well as treatment of chronic disease syndromes. It can be used to supplement GA, decreasing the need for deep levels of GA, therefore providing a more hemodynamically stable operative course. It provides better postoperative pain control and more rapid recovery from surgery. When combined with spinal anesthesia in a technique called a CSE, or combined spinal epidural, benefits of both techniques can be combined and shortcomings of each, avoided. Hence EA is the most preferred anesthetic technique for lower limb surgeries these days. The knowledge of specific opiate receptors in the substantia gelatinosa of the posterior horn of spinal cord resulted in wide spread use of epidural opiates in the treatment of acute and chronic pain (Pert and Snyder 1973). Though morphine has already established its role in epidural administration for pain relief, its side effects like respiratory depression, nausea, vomiting, urinary retention etc., have lead the physician to search for a better drug for epidural employment. Bupivacaine is a widely used drug in epidural anesthesia; it was first synthesized by Ekenstam in 1956 but was introduced in clinical practice by Telivuo and Widman 1963. It is a type of amide group of local anesthetics and is characterized as pipiiloxyldide as the molecule possesses an asymmetric carbon atom. Buprenorphine is a thebaine derivative, it is 33 times more potent than morphine, and it is a mu-receptor partial agonist and antagonist. It is effective in relieving moderate to severe pain. When placed in epidural space the high lipid solubility and affinity for opioid receptors limits the cephalad spread. Fentanyl is a phenylpiperidine-derivative synthetic opioid agonist. It is 75 to 125 times more potent than morphine.

**Aims & objectives**

**Following points will be considered for the comparison**

1. Onset of action.
2. Sensory analgesia.
3. Degree of motor blockade.
4. Duration of sensory analgesia.
5. Hemodynamic and respiratory changes.
6. Adverse Effects, if any.

**Material & methods**

This study is a prospective case control study, conducted After obtaining Ethical committee clearance and written informed consent from the patients, a total of 60 patients of either sex, aged between 20-60 years, belonging to ASA Grade I & II scheduled for elective lower limb surgeries were randomly selected.

**Inclusion criteria**

- Patients aged between 20-60 years.
- Patients of either sex.
- Patients with ASA Grade I & II.
- All Patients selected for elective lower limb surgeries.

**Exclusion criteria**

- Pregnant women.
- Patients with H/o Cardio-Respiratory, Hepatic and Renal disorders.
- Patients allergic to study drugs.
- Patients with H/o convulsions & neurological deficits.
- Patients with Spinal deformities & Psychiatric disorders.
- Patients not willing for regional anesthesia.
- Patients with contra-indications for epidural anesthesia.

60 Patients posted for elective lower limb surgeries were randomly selected for the study. All patients underwent thorough pre-anesthetic evaluation a day before surgery and were explained in detail regarding the anesthetic procedure. Routine investigations were done. Drugs used were explained to the patients and also educated about Verbal numerical scale for assessment of pain. Written informed consent was obtained. All patients received Tab. Alprazolam 0.25 mg orally on the previous night of surgery as pre-medication. Patients were advised nil orally for a period of 6 hours prior to surgery. On the day of surgery patients were shifted to operating room, connected to multipara monitor and baseline heart rate, non-invasive blood pressure (systolic & diastolic) and Spo2 was recorded. After insertion of 18G IV cannula, patients were preloaded with ringer lactate 500ml over 30 minutes. The anesthesia machine, circuits, emergency resuscitation trolley and airway equipment’s were kept ready. Patient in sitting position, L2-L3 interspace was identified. Under strict aseptic precautions, after injecting local anesthetic solution, epidural space was identified using 18G Tuohy’s needle by loss of resistance technique to air, epidural catheter was inserted 3cm inside epidural space and secured in place, continuous monitoring was done.

**Patients were divided into two groups**

| Group A   | Buprenorphine with Bupivacaine group - 0.5% Bupivacaine 15ml (75mg) with 0.5ml (150 ug) Buprenorphine (preservative free) with 0.5ml sterile normal saline made to a total of 16ml. |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Group B   | Fentanyl with Bupivacaine group - 0.5% Bupivacaine 15ml (75mg) with 1ml (50ug) Fentanyl (preservative free).                                                                                     |

**Intra operative**

Assessment of sensory and motor blockade were done at the end of each minute with the patient in supine position after completion of the injection of 16 ml of the study drug, the time at which epidural injection of the study drug completed was considered as zero (t=0). The onset time and the time for maximum motor and sensory block and the maximum level of sensory and motor block were recorded. Sensory blockade was assessed using a short beveled 22-gauge needle and was tested in the mid clavicular line on the chest, trunk and lower limbs on either side. Motor blockade in the lower limbs was assessed using modified Bromage scale.

0. no motor blockades
1. Inability to raise extended leg (just able to move knee)
2. Inability to flex the knee (able to move the foot)
3. Inability to flex ankle joint (unable to move knee or foot).
Vital parameters such as the heart rate, blood pressure, respiratory rate, and oxygen saturation were continuously monitored for every 5 min for first 15 min and every 15 min throughout surgery during intraoperative period and every half an hour in the post-operative period for 2 hours. Intraoperatively and postoperatively complications, like nausea, vomiting, bradycardia, hypotension, respiratory depression and pruritus noted, treated and tabulated. Hypotension is defined as reduction of systolic blood pressure more than 30% from basal systolic blood pressure or SBP less than 90 mmHg and is treated with increased rate of intravenous fluids and if needed injection mephenteramine 3 mg (I.V) given in increments. Bradycardia (<60 beats/min) was treated with injection Atropine 0.6 mg (IV).

Surgery was allowed to commence when adequate sensory blockade (T10) level is achieved for lower limb surgery.

Post-Operative
Following observations were made post-operatively:

1. Duration of post-operative analgesia.
2. Quality of post-operative analgesia (VNS).
3. Hemodynamic monitoring (NIBP & HR).
4. The need for rescue analgesic supplementation.
5. Episodes of postoperative side effects such as hypotension (>30% of baseline or <90 SBP), bradycardia (>20% of base line or <50 BPM), desaturation (SpO2 <90%) and respiratory depression (<10 breaths per minute), pruritis, nausea vomiting, urinary retention noted and treated.

The results of the study were statistically analyzed between the two groups.

Results
A total of 60 patients of either sex were selected for the study and divided into group A and B by computer generated randomization. Statistical data was analysed using SPSS Software, Graph Pad software and statistical calculators.

### Table 1: Demographic Data Analysis

|            | Group-A (Mean ± S.D.) | Group-B (Mean ± S.D.) |
|------------|-----------------------|-----------------------|
| Age in years | 43.9 ±8.28            | 41.76 ± 8.90          |
| Weight in kgs | 58.73 ± 9.01          | 61 ± 11.34            |
| Height in cms | 162.96 ± 6.38         | 164.76 ± 7.43         |
| Male: Female | 18:12                 | 21:9                  |
| ASA I:II    | 19:11                 | 22:8                  |

### Table 2: Onset of Analgesia

| Dermatome Level | Group A (in min ) | SD | Group B (in min ) | SD | t value | p value | Significance |
|-----------------|-------------------|----|-------------------|----|---------|---------|-------------|
| T12             | 7.4               | 2.02 | 6.7               | 2.11 | 1.18    | 0.240   | NS          |
| T10             | 10.4              | 1.8  | 10.3              | 2.04 | 0.198   | 0.843   | NS          |
| T8              | 14.03             | 1.4  | 13.8              | 2.07 | 0.389   | 0.698   | NS          |
| T6              | 17.14             | 1.9  | 17.46             | 2.78 | 0.343   | 0.737   | NS          |

NS - Not significant

It was observed that onset of analgesia in Group- A (0.5% bupivacaine + 150mcg buprenorphine). When compared to Group-B (0.5% bupivacaine + 50 mcg fentanyl) was statistically insignificant (P>0.05) at all levels of T12, T10, T8, T6. This shows that there was no difference in the onset of action.

### Table 3: Bromage Scale

| Bromage Scale | Group A (In Min) | SD | Group B (In Min) | SD | T- Value | P Value | Significance |
|---------------|------------------|----|------------------|----|----------|---------|-------------|
| 0             | 6.53             | 2.3 | 6.63             | 1.93 | 0.16     | 0.873   | NS          |
| 1             | 9.6              | 2.23| 10.63            | 2.23 | 1.73     | 0.088   | NS          |
| 2             | 13.46            | 2.28| 14.5             | 2.44 | 1.69     | 0.096   | NS          |
| 3             | 18.06            | 2.47| 18.36            | 2.63 | 0.45     | 0.651   | NS          |

NS - Not significant

The mean time to achieve complete motor blockade was 18.06 min in group A and 18.36 in group B which was statically insignificant in both the groups.
By applying students unpaired t test, difference between mean heart rate was found to be insignificant ($p > 0.05$) at all-time intervals.

By applying students unpaired t test, difference between mean arterial pressure was found to be insignificant ($p > 0.05$) at all-time intervals.
Fig 3: Variation in respiratory rate per minute within each group and in between the groups

By applying students unpaired t test, difference between respiratory rate was found to be insignificant (p > 0.05) at all-time intervals.

Fig 4: VNS Score

Pain score (VNS) was compared between the two groups at different time interval for the first 7 hrs. It was found that difference in mean VNS scores were statistically significant between two groups after 1 hr interval. This was due to considerably low VNS scores in group A as compared to group B.

9 patients out of 30 i.e 30% in group A had nausea as compared to 3 out of 30 patients i.e 10% in group B.
3 patients out of 30 i.e 10% in group A had vomiting as compared to group B in which none had vomiting.
5 patients had Pruritis in Group B and none in Group A.
In both Groups none patient had Urinary Retention and Hypotension.

By applying chi-square test p value (p > 0.05). No significant statistical difference exists between side effect among two groups.

**Discussion**

Pain is a more terrible lord of mankind than death itself. Pain is a complex subjective experience, which has proved difficult to measure in reproducible way \(^4\). Pain perception can be sensory discriminative aspect that describes the
location and quality of the stimulus called fast pain and motivational affective portion that leads to aversive aspect of pain, also known as slow pain. Satisfactory pain relief has always been a difficult problem in clinical practice [5]. It is found that operative pain is more severe after surgery and thereafter gradually diminishes over the next 24 hours. Existence of pain has been a constant stimulus to the discovery of both drugs and procedures for relief of pain [6]. Traditionally epidural bupivacaine was used for post-operative analgesia. The epidural bupivacaine 0.5% causes motor, sensory and sympathetic blockade, 0.25% causes sensory and autonomic blockade and 0.125% causes autonomic blockade only Epidural and intrathecal opioids are today being used for intraoperative and postoperative analgesia. Epidural administration of various analgesics gained increasing popularity following the discovery of opioid receptors in the spinal cord capable of producing potent analgesia as reported by Taksh and Rudy in 1976. It is now clear that epidural administration of opioids is superior to traditional intravenous and intramuscular injections of opioids.

The hypothesis that was made before the study was, the treatment of acute postoperative pain is a major health care issue. The use of epidural analgesia for pain relief was revolutionized by use of epidural opioids after discovery of opioid receptors in the dorsal horn of the spinal cord, combinations of opioids and local anesthetics have been administered epidurally in an attempt to optimize analgesia and minimize total drug doses. Advantages of lower administered drug doses include lower incidences of adverse effects and a decreased rate of opioid tolerance development. Various studies are conducted on buprenorphine and fentanyl in combination with bupivacaine, and showed that both opioids have good analgesic potency and lesser side effects profile, but buprenorphine has longer duration of analgesia compared to fentanyl, due to its high affinity for spinal receptors & smaller doses produced a high concentration of the drug at spinal receptors [5, 8]. The volume of 0.5% bupivacaine used in our hospital routinely for lower limb orthopedic surgeries under epidural anaesthesia is 15 ml after using 3 ml of 2% xylocaine with adrenaline, the total dose being 18 ml. This is calculated as 1 ml/segment upto 150 cms of height, and adding 0.1ml / segment for every 5 cms of increasing height. Mamtha Agarval et al, in their study (1998) on postoperative analgesic efficacy of extradural buprenorphine, received 4 mcg/kg of buprenorphine dissolved in 10 ml of normal saline. The maximum pain relief and longest duration were observed with buprenorphine [9]. Bharagara et al, [10] did a study, where first group received 20 ml of lignocaine with 1 in 200,000 adrenalinics, the second group received the same solution with morphine 7.5 mg while third group received 0.3 mg buprenorphine added in the lignocaine solution in place of morphine, were assessed for 48 hours. They concluded that overall pain relief and duration was better in buprenorphine group. In 1982 Ichiishi N et al. studied effects of epidural buprenorphine on post-operative respiratory function using respiratory inductive plethysmography in two groups of patients [(1) 0.1 mg (2) 0.2 mg] after upper abdominal surgery. They observed there was decreased respiratory rate and increased tidal volume; however, there was no severe respiratory depression [11]. Keeping above studies in mind we chose 3 mcg/kg of buprenorphine and fixed the dose as 150mcg for our study Zenz M, Pipenbrocks S, did a double-blind comparison of epidural buprenorphine and epidural morphine for postoperative pain relief. Morphine 4 mg and buprenorphine 0.15 mg were given through epidural route. Buprenorphine produced analgesia with short latency 6.8 min. This is close to our observation of 7.4 min [12]. High lipid solubility and high potency may explain the faster onset of pain relief in buprenorphine group. Suraj Dhale, Vaishali Shelgaonkar, in 2000 studied different doses of epidural fentanyl (25mcg, 50mcg, 75mcg) with 0.5% bupivacaine for perioperative analgesia found that 50mcg had a quicker onset of analgesia within 9.53 min which is close to our observation [13]. Boas RA et al. in their study on clinical actions of fentanyl and buprenorphine, the significance of receptor binding. Receptor binding assays were undertaken in an attempt to elucidate the opioid binding characteristics of fentanyl and buprenorphine, and to investigate some of the differences between them. Buprenorphine showed slow receptor association (30 min), but with high affinity to multiple sites from which dissociation was very slow (T 1/2 = 166 min) and incomplete (50% binding after 1 h). This contrasted with the receptor binding of fentanyl, which achieved rapid equilibrium (within 10 min) and dissociated equally rapidly (T 1/2 = 6.8 min) and completely (100% by 1 h). And concluded that competitive displacement showed buprenorphine displacement of fentanyl binding was concentration and time dependent over ranges encountered in clinical use, but buprenorphine binding was displaced with only very high concentrations of other opioids [14].

Duration of analgesia is taken from the time of injection till the patient complains of pain at the site of surgery. Time at which, patients complained of pain more than 5 and above on the verbal numerical scale was noted. That point was taken as the end of fair analgesia and at that point, top up doses were given based on requirement. In our study mean duration of analgesia in group A was 767.3 min which was significantly longer compared to group B of mean duration of analgesia was 454 min. Y. Bhargav, in 1994 studied the postoperative pain relief between epidural morphine and of buprenorphine with 20ml lignocaine with 1 in 2,00,00 adrenaline. He found that duration of analgesia was around 22-24 hours in buprenorphine group which is very significantly longer than our group.10 Grace Maria George, in 2014 compared extradural anesthesia using 0.75% ropivacaine, 0.75% ropivacaine with fentanyl, and 0.75% ropivacaine with buprenorphine for cesarean section from a rural teaching hospital in India and found that ropivacaine 0.75%, ropivacaine 0.75% with fentanyl 50 mcg, or buprenorphine 300 mcg provided safe anesthesia when given extramurally for cesarean section. Addition of both fentanyl and buprenorphine to ropivacaine hastened the onset of sensory block, while addition of buprenorphine provided prolonged excellent postoperative analgesia.15 Arun Kumar Gupta, in 2015 compared Epidural fentanyl and buprenorphine for post-operative analgesia in lower abdominal and lower limb surgeries and found that the onset of analgesia was earlier with fentanyl group. The duration of analgesia was 30 hours with buprenorphine group and 6 hours with fentanyl group. Fentanyl causes pruritis, headache and drowsiness but other systemic side effects like nausea, vomiting, and urinary retention are more common with epidural buprenorphine [16]. Thomas H, Asskali F, Vettermann J in 1996 did a study on
addition of fentanyl to bupivacaine for peridural analgesia in cesarean section with 8 ml of 0.5% bupivacaine (+) 0.1 mg fentanyl (Group A) / 8 ml 0.5% bupivacaine +2 ml saline (Group B) through the epidural catheter and observed that mean postoperative duration of analgesia was significantly longer in the Group A (382 min) in fentanyl group [17]. Suraj Dhale, Vaishali Shelgaonkar in 2000 studied different doses of epidural fentanyl (25mcg, 50mcg, 75mcg) with 0.5% bupivacaine for perioperative analgesia found that 50mcg had mean duration of analgesia 256.66 + 6.17 min. In our study mean duration of action was 454 min [13]. Higher lipophilicity of fentanyl offers a number of advantages over morphine for epidural analgesia including shorter duration of action, lower incidence of side effects, and reduced risk of respiratory depression.

In our study mean base line respiratory rate in Group A fell from 16.17/min to around 13.73 in 45min gradually picking up by 90 min and remained to 15.97/min. In Group B mean basal respiratory rate which was 16.07/min fell to 14.03 at 45min, picked up to 15.70/min at 90 min which is again comparable without any significant difference (graph 11). Following below studies correlates with our observation. In 1981, Zenz M, Pipenbrook S, Hubner S, Glocke M, did a double-blind comparison of epidural buprenorphine and epidural morphine in post-operative pain. Morphine 5 mg and buprenorphine 0.15 mg given by epidural route were compared, in fifty patients, recovering from abdominal surgery. They observed there was decreased respiratory rate and increased tidal volume; however, there was no severe respiratory depression [12].

In the other study, Ichiishi N., Hiraishi T. et al. (1992) studied effects of epidural buprenorphine on post-operative respiratory function were studied using respiratory inductive plethysmography in two groups of patients [(1) 0.1 mg (2) 0.2 mg] after upper abdominal surgery. Buprenorphine 0.1 mg group showed decreased respiratory rate and increased tidal volume. Decrease in the respiratory rate and tidal volume were seen in buprenorphine 0.2 mg group and continued for 3-4 hrs after epidural administration. However, there was no severe respiratory depression in either group. They found that 0.2 mg of epidural buprenorphine may give a satisfactory post-operative pain relief and less respiratory depression and respiratory inductive plethysmography is a useful method for the measurement of post-operative respiratory function [23]. In our study Group B, 5 patients (16.66%) developed pruritus compared to none in Group A. Studies done by SA Lytle et al. [18] correlates with our study.

Summary

Epidural anaesthesia /analgesia is one of the best accepted technique for lower limb surgeries as it provides good sensory and motor block, decreases stress response, retaining spontaneous respiration, hemodynamic stability and indwelling catheter facilitates further administration of analgesic doses for postoperative analgesia. In this study the efficacy of 0.5% bupivacaine 15ml (75mg) with 0.5ml (150 ug) buprenorphine (preservative free) with 0.5ml normal saline made to a total of 16ml and 0.5% bupivacaine 15ml(75mg) with 1ml(50ug) fentanyl (preservative free), were compared in providing adequate intraoperative and postoperative analgesia. Onset of sensory block was 7.4 min in group A and 6.7 min in group B which is statically insignificant. Mean time to achieve motor blockade was same in both groups. Both the groups maintained hemodynamic stability which was statistically significant, there was no significant changes with respiratory parameters in either of the groups both intra and postoperative period. Duration of analgesia was significantly longer in Group A (767.3 min) compared to Group B (454 min) with significant P value (< 0.05). Incidence of nausea and vomiting was more in Group A (40 %) compared to Group B (10 %). 16.66 % of patients in group B developed pruritus which was mild in nature and did not require any interventions. None of the patients in group A developed pruritus.

With the above observations it can be concluded that both inj. buprenorphine 150 mcg and Inj. fentanyl 50 mcg given epidurally with Inj. bupivacaine 0.5% as a single shot provided excellent operative conditions and satisfactory postoperative analgesia in both the groups. However, the duration of postoperative analgesia was much longer in the buprenorphine group than fentanyl group, with side effects like nausea and vomiting is more as compared to fentanyl group. Hence both the drugs, buprenorphine and fentanyl were effective for postoperative analgesia and as the duration of analgesia was more than 454 minutes, the procedure can either be done as a single shot injection, thus obviating the need for an epidural catheter whenever not available. The method is economical, safe, convenient and acceptable and also poly pharmacy is avoided.

Conclusion

In this comparative observational study, an effort was made to study the peri operative analgesic efficacy of Inj. buprenorphine and Inj. fentanyl with 0.5 % bupivacaine epidurally for lower limb surgeries. There were no significant hemodynamic and respiratory side effects in either of the groups. The postoperative analgesia was definitely of a longer duration with the buprenorphine group. So, it is concluded that epidural buprenorphine is better in providing prolonged satisfactory postoperative analgesia as compared to Inj. fentanyl. Regarding the side effects, the incidence of nausea and vomiting was more in buprenorphine as compared to fentanyl group, which is easily treated with antiemetic’s like Ondansetron. Both buprenorphine and fentanyl along with bupivacaine 0.5% can be given epidurally as a single shot injection for perioperative analgesia obviating the need for epidural catheter.

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