Epidural Naloxone Attenuates Fentanyl Induced PONV in Patients Undergoing Lower Limb Orthopaedic Surgeries. A Prospective Randomized Double-Blind Comparative Study

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Abstract
Background and aim: Epidural administration of opioids with local anaesthetics is a popular choice for perioperative pain relief. But opioid induced side effects limit their use for postoperative analgesia. Hence, this study was designed to evaluate the effectiveness of epidural naloxone, an opioid receptor antagonist, in reducing PONV in patients receiving epidural fentanyl. Methods: After obtaining the Institutional Ethics Committee approval and written informed consent, 46 patients, between 18–80 years, of either sex, with ASA physical status 1-3, undergoing lower limb orthopaedic surgeries were enlisted for this prospective, randomized, double blind comparative study. Subjects were allocated to one of the two groups and received epidurally, either fentanyl with bupivacaine (Group C, n = 23) or fentanyl with bupivacaine and naloxone 2 mcg (Group N, n = 25), for reducing postoperative pain. PONV score and Wong Bakers Scale (WBS) for pain score were recorded at 6, 12 and 18hrs, postoperatively. Results: All patients were comparable with respect to age, gender, ASA PS, height, body weight as well as duration of surgery. A statistically significant decrease in PONV score was observed in Group N at 6 and 12 hours, postoperatively. The patients who required rescue antiemetic were also significantly lower in Group N at 6 and 12 hours. The mean WBS score for pain also showed significant reduction in Group N at 6 hours, postoperatively. Conclusion: Concomitant use of low dose epidural naloxone and fentanyl is effective in attenuating PONV, besides enhancing analgesia in the early postoperative period.

Keywords: Naloxone • Fentanyl • PONV • Epidural • Wong Bakers Scale

INTRODUCTION
The practice of anaesthesiology has now become remarkably safe with rare occurrences of mortality and morbidity. Hence, those less severe adverse events of anaesthesia are gaining more significance recently. Postoperative nausea and vomiting (PONV) is still the most troublesome sequelae encountered in the recovery room, inspite of new advances in its prevention and treatment. Even though a minor complication, it not only causes significant agony and annoyance to the patient, but it also results in profound patient dissatisfaction with the overall quality of anaesthesia. Besides, the recent heightened interest in ambulatory procedures has shifted the focus more on PONV, as its incidence may prolong discharge or cause undesirable hospital stay. Lower limb orthopaedic procedures are commonly associated with severe postoperative pain, therefore adequate alleviation of pain is essential during this period. An infusion of a local anaesthetic–narcotic mixture given epidurally, is a commonly used method for analgesia after lower limb orthopaedic surgeries, and previously, epidural morphine was widely used. However, it had been associated with a higher incidence of PONV, pruritus and respiratory depression. Fentanyl, a highly lipophilic synthetic opioid, is used instead of morphine, as it causes a lesser incidence of delayed respiratory depression due to its rapid absorption and clearance from CSF. However, PONV still remains high even in those patients administered with epidural fentanyl. Numerous studies in the past had reported the efficacy of small doses of opioid antagonist naloxone, administered intravenously or epidurally, for the maintenance of analgesia with marked reduction in morphine, buprenorphine and sufentanil associated PONV. But no similar studies on epidural fentanyl have been found till date. Hence, this study was formulated to assess the effectiveness of epidural naloxone in attenuating PONV in patients receiving epidural fentanyl for pain relief after lower limb orthopaedic procedures.
MATERIALS AND METHODS

After procuring Institutional Ethics Committee approval and written informed consent, 46 patients, between 18–80 years, of either sex, with ASA physical status 1–3, undergoing lower limb orthopaedic surgeries were enrolled in this prospective, randomized double blind comparative study. Patients with allergy to study drugs, contraindications to neuraxial anaesthesia, chronic opioid use, severe myocardial, renal, or hepatic impairment, psychiatric illness or nausea and vomiting during the operation were exempted from our study. A preanaesthetic examination was conducted on the preoperative day and a written file with all the details regarding the anaesthesia technique to be performed was provided to all the enlisted patients, before taking consent. On arrival at the operating room on the day of surgery, all standard monitors were connected and baseline Heart Rate (HR), SpO2, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Mean arterial Blood Pressure (MABP) of all patients were recorded. Premedications with midazolam 0.5–1 mg intravenously (IV) and ondansetron 50 mcg/kg IV were given to all patients.

All patients were positioned in left lateral decubitus position for combined spinal epidural anaesthesia and local anaesthesia was given in the skin at L2-L3 space, following which a Tuohy needle of 18 gauge was introduced via midline approach. Epidural space was identified using a loss of resistance technique and epidural catheter was introduced. Later, with a 25 gauge Quincke needle, lumbar puncture was done at L3-L4 space. After confirming the subarachnoid space by free flow of CSF, spinal anaesthesia was given using 3ml of 0.5% heavy bupivacaine. Electrocardiogram (ECG), HR and SpO2 was monitored continuously and blood pressure was recorded non-invasively every 5 min till end of the procedure. Onset of analgesia and level of sensory block was also noted. The sensory block level was assessed at the maximal level of cold sensation at the midclavicular line using an alcohol swab bilaterally. The intensity of motor block was evaluated of cold sensation at the midclavicular line using an alcohol swab bilaterally. The intensity of motor block was evaluated using the modified Bromage scale: 0 = no motor block, 1 = inability to raise the extended leg, but able to move knees and feet, 2 = inability to raise extended leg and move knee, but able to move feet, 3 = complete motor block of lower limb.

In post anaesthesia care unit (PACU), sensory block level and level of cold sensation were checked every 15 min and when there was regression of sensory level below T10 dermatome, epidural analgesia was administered. Using a computer-generated randomization list, the enrolled 46 patients were assigned into two groups of 23 each using opaque, sealed and serially numbered envelopes. For epidural analgesia, Group C: received 5 ml of bupivacaine 0.125% with fentanyl 50 mcg.

Group N: received 5 ml of bupivacaine 0.125% with fentanyl 50 mcg and naloxone 2mcg. Epidural bolus was repeated at 6, 12 and 18 hours following surgery. PONV and WBS pain scores were monitored by the staff nurse in PACU, who was unaware of the patient group allocation. Patients were also blinded as both the preparations were colourless.

PONV and pain intensity was recorded at 6, 12 and 18 hours, post operatively. PONV was evaluated using a PONV score: 0= no nausea or vomiting, 1= nausea only, 2= vomiting once, 3=vomiting more than once. Rescue antiemetic ondansetron 4 mg IV was given to all patients with PONV score ≥ 1. Pain intensity was assessed using Wongbakers FACES pain scale (WBS). Sample size was calculated from the study, with a power of 80% and a significance level of 5% and the minimum sample size needed was calculated to be 23 for each group. The statistical calculations were performed using the software SPSS (Statistical Presentation System Software, SPSS Inc.) version 15.0. Categorical data was represented in the form of frequencies and proportions. Continuous data was represented as mean and standard deviation. Chi square test or Fisher exact t-test was used as test of significance for qualitative data. Independent t test or Mann Whitney U test was used as test of significance to identify the mean difference between two quantitative variables. Repeated measure ANOVA was used as test of significance to assess the pain score. Level of significance was set at 0.05.

RESULTS

We screened 55 patients for this prospective, parallel-group, double blind, randomized comparative study. Nine patients were exempted from our study for not satisfying the inclusion criteria; four patients had significant myocardial impairment, three patients had contraindication for administering central neuraxial blockade, two patients were not willing for spinal anaesthesia. Finally, a total of 46 patients were enlisted, randomized and assigned into two groups of 23 each. All the patients of both groups finished the study and were followed up and evaluated (Figure 1). Both groups were comparable with respect to the distribution of age, gender, ASA PS, body weight, height and BMI. No statistically significant difference was noted in maximum sensory level achieved as well as duration of surgery (Table 1).

PONV scores of Group N were significantly lower when compared to Group C at 6 and 12 hours, post operatively (Table 2). A statistically significant decrease in mean PONV score was also observed in Group N at 6 and 12 hours (Table 3). The rescue antiemetic consumption was also significantly lesser in Group N at 6 and 12 hours in the post-operative period (Figure 2).
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Figure 1. Consort flow diagram

Table 1. Patient characteristics

| Group          | N (23) | Group C (23) | P value |
|----------------|--------|--------------|---------|
| AGE            | 48.91 (18.9) | 56.22 (17.2) | 0.179   |
| SEX (M/F)      | 14 / 9 | 10 / 13      | 0.238   |
| ASA STATUS (1/2/3) | 14 / 9 / 0 | 13 / 8 / 2 | 0.351   |
| HEIGHT (M)     | 164.04 (6.89) | 162.09 (7.077) | 0.348   |
| WEIGHT (KG)    | 65.87 (7.7) | 64.22 (6.8) | 0.446   |
| BMI (KG/M2)    | 23.34 (1.6) | 24.4 (1.6) | 0.900   |
| PREV HISTORY OF PONV | 5 | 4 | 0.738   |
| MAXIMAL SENSORY BLOCK | T6 (T6-T8) | T6 (T6-T8) | -       |
| DURATION OF SURGERY | 10.74 (18.15) | 110.83 (27.8) | 0.631   |

Data expressed as Mean (standard deviation) or Number

Table 2. Comparison of PONV and WBS pain scores between groups

| Time  | PONV Scores | WBS PAIN Scores | P value |
|-------|-------------|-----------------|---------|
|       | 1 | 2 | 3 | 1 | 2 | 3 |         |
| 6 HRS | Group N | 21 | 2 | 0 | 18 | 5 | 0 | 0.011* | 0.007** |
|       | Group C | 12 | 8 | 3 | 9  | 14 | 0 | 0       |
| 12 HRS| Group N | 18 | 3 | 2 | 5  | 15 | 3 | 0       | 0.026* | 0.403 |
|       | Group C | 9  | 9 | 5 | 2  | 16 | 5 | 0       |
| 18 HRS| Group N | 17 | 3 | 3 | 3  | 10 | 9 | 1       | 0.060 | 0.991 |
|       | Group C | 12 | 10| 1 | 3  | 9  | 10| 1       |

*significant at the 0.05 level
WBS pain scores showed a statistically significant reduction in Group N at 6 hours, postoperatively (Table 2). The mean pain score in Group N was also significantly lower at 6th hour in the postoperative period when compared to Group C (Table 4).

**DISCUSSION**

Concomitant epidural administration of local anaesthetic with opioids is a popular choice in perioperative analgesia due to its synergistic effect. However, opioid induced side-effects such as nausea and vomiting, pruritus, respiratory depression and urinary retention can cause severe distress and dissatisfaction to the patients regarding the overall surgical and anaesthesia experience. This may limit the use of opioids for postoperative pain relief. PONV, in particular, is of a major concern with the use of neuraxial opioids, as it is considered as the most undesirable and troublesome complication, with incidence as high as 20–30%. Hence, avoidance of PONV was always a higher priority among patients, sometimes even more than postoperative pain. The commonly seen risk factors for PONV are age, female gender, non-smoking status, history of PONV or motion sickness, post-operative opioid use and extended duration of anaesthesia. In our study, both groups were comparable with respect to age, gender, ASA PS as well as BMI. No significant difference was noticed either in maximum sensory level achieved or duration of surgery, among the groups.

There had been many studies in the past, aimed at investigating or reducing the side effects of neuraxially administered lipophilic as well as hydrophilic opioids. Among them, trials on epidural naloxone and its effects in decreasing the side effects of epidural opioids are very few. And, no studies had been conducted so far investigating the effects of epidural naloxone on lipophilic opioid fentanyl, which also significantly increases PONV with epidural administration.

![Figure 2. Rescue antiemetic consumption. Number of patients on Y axis, Time in hours on X axis. *P < 0.05 in between group comparison considered statistically significant](image)

**Table 3:** Comparison of Mean PONV score at 6, 12 and 18 hrs between Group N and Group C

|            | GROUP N       | GROUP C       | P VALUE  |
|------------|---------------|---------------|----------|
| 6 hrs      | 0.09 (0.288)  | 0.61 (0.722)  | 0.002*   |
| 12 hrs     | 0.30 (0.635)  | 0.83 (0.778)  | 0.017*   |
| 18 hrs     | 0.39 (0.722)  | 0.52 (0.593)  | 0.507    |

*significant at the 0.05 level. **Data expressed as Mean (standard deviation)

**Table 4:** Comparison of Mean pain score at 6, 12 and 18 hrs between Group N and Group C

|            | GROUP N       | GROUP C       | P value |
|------------|---------------|---------------|---------|
| 6 HOURS    | 0.22 (0.422)  | 0.61 (0.499)  | 0.006*  |
| 12 HOURS   | 0.91 (0.596)  | 1.13 (0.548)  | 0.205   |
| 18 HOURS   | 1.35 (0.775)  | 1.39 (0.783)  | 0.851   |

*significant at the 0.05 level. **Data expressed as Mean (standard deviation)
CONCLUSION

A low dose epidural naloxone significantly attenuates PONV induced by epidural fentanyl, besides enhancing the analgesic effect during the early postoperative period.

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