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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 earlypostoperative 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.[1]Eventhough 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.[2]Besides, the recent heightened interest in ambulatory procedures has shifted the focus more on PONV, as its incidence may prolong discharge[3]or cause undesirable hospital stay.[4]Lower limb orthopaedic procedures are commonly associated with severe postoperative pain, therefore adequate alleviation of pain is essential during this period.[5,6]An infusion of a local anaesthetic–narcotic mixture given epidurally, is a commonly used method for analgesia after lower limb orthopaedic surgeries,[7]and previously, epidural morphine was widely used.[8]However, it had been associated with a higher incidence of PONV, pruritus and respiratory depression.[9,10]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.[11]However, PONV still remains high even in those patients administered with epidural fentanyl.[12] 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.[13–16]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.

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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 pre-operative 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 intravenous (IV) and ondansetron 50 mcg/kg IV were given to all patients.

All patients were positioned in left lateral decubitus position for combined spinalepidural anaesthesia and local anaesthesia was given in the skin at L2-L3 space, following which a Tuohy needle of 18gauge was introduced via midline approach. Epidural space wasidentified using a loss of resistance technique and epidural catheter was introduced. Later, with a 25gauge 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 with the modified Bromage scale:[17]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 was 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, 12and18hours 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).[18]

Sample size was calculated from the study,[16]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).

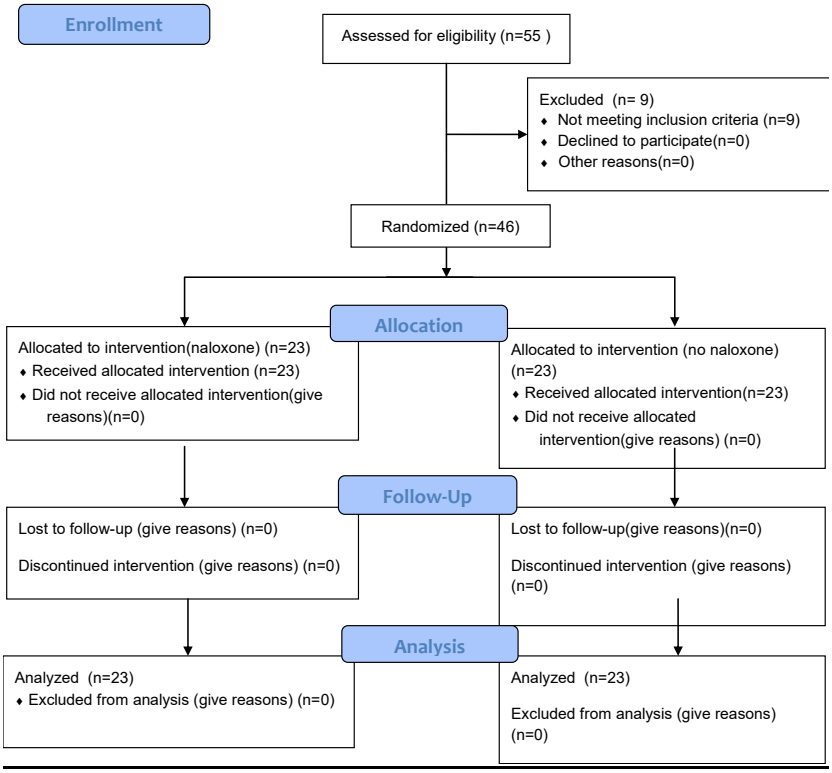

Figure 1. Consort flow diagram significant

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

0		PONV Scores			P value	WBS PAIN Scores				P value
		1	2		0	1	2	3		
6 HRS	GROUP N	21	2	0	0.011*	18	5	0	0	0.007*
	GROUP C	12	8	3		9	14	0	0	
12 HRS	GROUP N	18	3	2	0.026*	5	15	3	0	0.403
	GROUP C	9	9	5		2	16	5	0	
18 HRS	GROUP N	17	3	3	0.060	3	10	9	1	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, post operatively(Table 2). The mean pain score in Group N was also significantly lower at 6thhour 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 %.[14]Hence, avoidance of PONV was always a higher priority among patients,[19] 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.[13–16]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.

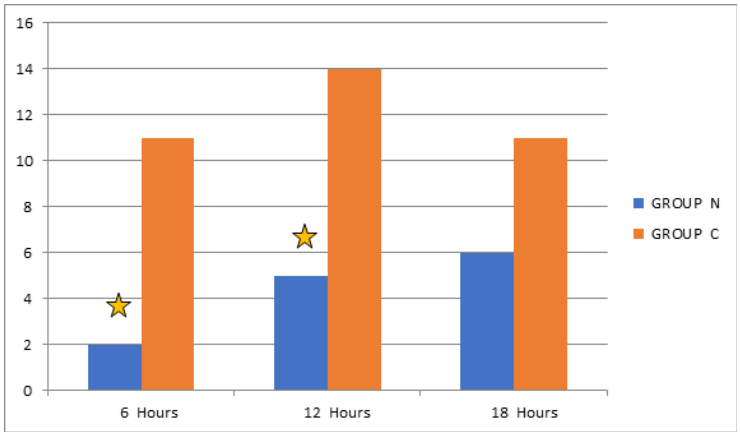

Figure 2. Rescue antiemetic consumption. Number of patients on Y axis, Time in hours on X axis. *P < 0.05 in between group comparison considered statistically significant

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)

[12]On comparing with hydrophilic morphine, a significantly lower PONV was observed with epidural fentanyl,[20] but fentanyl showed a similar degree of incidence in PONV when compared with another lipophilic opioid, sufentanil. [21]The increase in PONV seen with epidural morphine may be due to its longer duration of action, as it remains in the CSF and spinal tissues for an increased period, while opioids thatare more lipid soluble are rapidly absorbed from the epidural space.Eventhough the exact mechanism of opioid induced PONV is not fully known, a possible mechanism may be due to the stimulation on the chemoreceptor trigger zone by the mu-opioid receptor, resulting in vomiting.Hence, opioid receptor antagonist, naloxone may play a vital role in attenuating PONV.

In our study,statistically significant lower mean PONV scores were observed in naloxone group at 6th and 12th hours post operatively.The rescue antiemetic consumption was also predominantly lesser in naloxone group during the early postoperative period.These results were similar to the findings obtained byChoi et al.[14] and Kim et al.[16]Choi et al., in his study,concluded that epidurally administered naloxone significantly decreased morphine-induced side effects such as pruritis and nausea in a dose dependent fashion without affecting analgesia.[14]While, Kim et al. evaluated the effect of epidural naloxone in decreasing PONV in patients receiving epidural sufentanil for postoperative analgesia and found out that concomitant epidural infusion of sufentanil and low dose naloxone not only reduced PONV but also enhanced the analgesic effect of sufentanil.[16] Similarly, during this study, a statistically significant reduction in pain scores were noticed in naloxone group, especially in the early postoperative period. The mean pain scores were significantly lower at 6th hour, post operatively.These findings also support the evidence from some previous studies.[14–16]The potential explanation for these effects observed with low doses of naloxone may be due to: a) low-dose naloxone enhancing the release of endogenous opioid peptides, as it blocks presynaptic auto inhibition of enkephalin release,[22] and b) Gs protein-coupled excitatory opioid receptors causing hyperalgesia often noticed with opioid administration, is directly and competitively antagonized by low-dose naloxone, while not attenuating analgesia mediated by the inhibitory Gi/Go-coupled opioid receptors.[23]There were a few limitations in our study.The dose used for naloxone, fentanyl and bupivacaine was not weight-based but was in agreement with other previous studies on opioids and local anaesthetics.Also, we did not take into consideration the agents used for premedication and intraoperative sedation,which might have had an impact on the incidence of PONV.The postoperative monitoring was not extended beyond 24 hours in the PACU. Further studies are advocated in these areas.

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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