Original Article

Pre-emptive multimodal analgesic regimen reduces post-operative epidural demand boluses in traumatic shaft of femur fracture - A randomised controlled trial

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ABSTRACT

Background and Aims: The efficacy of preemptive multimodal analgesia in post-traumatic patients has not been elucidated. Our aim was to evaluate the efficacy of preemptive MMA regimen in reducing the epidural demand boluses in the first 48 hours following the traumatic shaft of femur fractures. **Methods:** Patients scheduled for traumatic femur fracture surgery were randomised (n = 135) into two groups in this double blind, placebo controlled trial. Patients received either (Preemptive multimodal group) intravenous acetaminophen 1 gm, diclofenac 75 mg, morphine 3 mg, 75 mg Pregabalin (per oral) or a placebo 30 minutes pre-operatively. Intra-operatively, all patients were managed with spinal and epidural anaesthesia. Post-operatively, patients received patient-controlled epidural analgesia (PCEA) programmed to deliver a bolus of 5 ml of 0.2% Ropivacaine with 2 μg/ml of Fentanyl with lockout interval time of 15 min. Primary outcome was number of PCEA boluses received post-operatively over 48 h. Secondary outcomes measures were time to receive first epidural bolus, postoperative VAS scores and episodes of post-operative nausea, vomiting and sedation. Total number of PCEA bolus doses over 48 hours and VAS scores were analysed using Mann-Whitney test. **Results:** Significant reduction in median number of demand boluses were observed in preemptive multimodal group (3 [2-4]) compared to placebo group (5 [4-7]); P = 0.00. Time to first rescue epidural bolus was significantly greater in preemptive multimodal group than placebo group. **Conclusion:** The use of preemptive MMA regimen reduced the requirement of demand epidural bolus doses.

Key words: Femur fracture, patient controlled epidural analgesia, pre-emptive analgesia, trauma

INTRODUCTION

Management of acute postoperative pain carries utmost importance as poorly treated pain can activate cascade of events leading to nausea, vomiting, ileus, delayed feeding and immobilisation thus increasing postoperative morbidity and mortality.[1] Multimodal analgesia (MMA) targets multiple nociceptive pathways (both central and peripheral) through several mechanisms resulting in additive or synergistic effects of analgesic medications.[2,3] Although the value of MMA in the treatment of postoperative pain was established 20 years ago,[4] it is quite well re-established in clinical practice in the recent years.[5] The term MMA describes the administration of pharmacological medications of different classes, employing various analgesic agents

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and techniques, thus providing greater pain relief with lower dose of medications and less side effects compared to monomodal therapy.[6] There is a high quality evidence for the efficacy of MMA in treating both acute and chronic pain.[7] However, the efficacy of MMA on peri-operative pain management as reviewed by many authors is limited to common surgical procedures performed under general anaesthesia like colorectal surgery, hernia surgery, non-cosmetic breast surgery, cholecystectomy, spine surgery, total hip and knee arthroplasty, cardiothoracic and laparoscopic procedures.[8]

Literature is scarce with regards to effect of preemptive MMA on requirement of epidural demand boluses in traumatic patients posted for fixation of shaft of femur fractures. So, we tried to see the efficacy of MMA in subset of traumatic fracture femur patients. In the present double blind placebo controlled study, we hypothesised that preemptive MMA regimen will reduce acute post-operative pain by decreasing the demand boluses of patient controlled epidural analgesia (PCEA) over 48 hours.

METHODS

This randomised double blind placebo controlled study was carried out in the trauma operating room of a tertiary care hospital from march 2016 to April 2017. The study was approved by the Institutional Ethics Committee (INT/IEC/2016/883 dated 10/02/2016) and registered prospectively with the Clinical Trials Registry of India (CTRI/2016/02/006692). The study adhered to the principles of the 2013 Declaration of Helsinki. Written informed consent was obtained from all patients who were enrolled into the study. Patients scheduled for intramedullary nailing of traumatic shaft of femur fracture, aged between 18-60 years, American Society of Anesthesiologists (ASA) physical status I/II and planned for spinal epidural (two puncture technique) procedure were enrolled into the study. Patients with associated head injury, blunt trauma abdomen, blunt trauma chest, pathological fractures, rheumatoid arthritis, psychiatric disorder, diabetes with impaired renal function, morbid obesity, history of anti- coagulants or antiplatelets as well as those with inability to use patient-controlled epidural analgesia (PCEA) were excluded.

All enrolled patients were explained to report their post-operative pain intensity on a Visual Analogue Scale (VAS) of 0-10 cm where 0 = no pain and 10 = worst possible pain. All patients were instructed to push the button of the PCEA pump each time they felt VAS pain score >3.

Randomisation was performed using a computer-generated randomisation program (http://www.randomiser.org). Concealment of randomisation was performed by sequentially numbered sealed opaque envelopes that were handed over to anaesthetic nurse in charge of preoperative holding area of patients. One hour prior to scheduled surgery, anaesthetist (JK) picked up a sealed envelope according to serial number labeled on the envelope and administered drugs according to the group regimen. This anaesthetist was not involved in further management and follow up of the patient. Anaesthetists who followed up the patients intra-operatively and postoperatively were blinded to the allocation of groups. Pre-emptive multimodal group received intravenous (i.v) acetaminophen 1 gm, iv diclofenac 75 mg diluted in 10 ml, i.v morphine 3 mg, and 75 mg pregabalin per orally 30 minutes pre-operatively. Placebo group received intravenous saline in 100 ml vial, one bolus of 2 ml normal saline, one bolus of 10 ml normal saline and a placebo pill in preoperative period for the purpose of blinding.

Standard ASA monitoring including electrocardiography, non-invasive blood pressure and pulse oximetry was applied to all patients in the operating room. Intravenous access was secured using an 18 G cannula and co-loading was done with 500 ml Ringer lactate solution. Under all aseptic precautions, in sitting position, at L3/L4 level, using an epidural catheter set (Perifix®, B Braun Ltd, Australia), epidural space was identified with the help of Pencan® 18 G Tuohy epidural needle with loss of resistance to saline technique and a multiorifice epidural catheter (Peridural®) was threaded 3-5 cms cephalad into the epidural space. Subsequently, dural puncture was performed by inserting a 26 G pencil point non-cutting needle. After free flow of cerebrospinal fluid was obtained, patient received spinal drug of 3 ml 0.5% hyperbaric bupivacaine. Once the sensory dermatomal block of T10 was attained, patient was positioned for surgery. Intra-operatively, epidural anaesthesia for all patients were managed according to departmental protocol i.e., once the spinal sensory level receded below T10, epidural anaesthesia was initiated with 6 to 10 ml bolus of 0.5% bupivacaine titrated to T10 sensory level. If required, patients were sedated with titrated bolus doses of midazolam. All patients

received supplemental oxygen through venturi mask. Hypotension was managed with either i.v boluses of 200 to 300 ml normal saline or i.v mephentermine 3-6 mg bolus doses or both at the discretion of anaesthetist.

On arrival to the post-anaesthesia recovery unit, patients were connected to a Patient-controlled epidural analgesia (PCEA) pump (Graseby™ 2000, Smith Medical, Minnesota, USA). The PCEA pump was programmed to deliver a bolus of 5 ml of 0.2% ropivacaine with 2 μg/ml of fentanyl with a lockout interval time of 15 min. The total number of PCEA boluses received by the patients over 48 hours were recorded. The time to receive first epidural bolus i.e. from the arrival of patient in PACU to the time at which patient operated the push button of PCEA pump for the first time was noted. VAS scores were recorded immediately on shifting to recovery and then at 30 min, 1 h, 2 h, 4 h, 8 h, 12 h, 24 h and 48 h. Even after two PCEA boluses, if the patient complained of pain, diclofenac 75 mg was given as rescue analgesia if VAS is between 3 to 6 and both morphine 6 mg and diclofenac 75 mg were given if VAS ≥6. Any episodes of nausea and vomiting were recorded and patients were given 4 mg of ondansetron. Any episodes of respiratory depression, apnoea, hypoventilation, desaturation were noted. Primary objective of the study was to compare the number of PCEA boluses received post-operatively over 48 hours. Secondary objectives were time to receive first epidural bolus, number of times rescue analgesic received over 24 hours, postoperative VAS scores at 30 min, 1 h, 2 h, 4 h, 8 h, 12 h, 24 h and 48 h intervals, and any episodes of post- operative nausea, vomiting and sedation.

In the absence of literature regarding the effect of preemptive MMA on requirement of PCEA boluses, we conducted a pilot study with 30 patients who underwent nailing of traumatic fracture shaft of femur under CSE. The median [IQR] number of PCEA boluses needed over 48 hours were 5[4-7] SD. To detect a clinically relevant difference of reduction in total number PCEA boluses by 20% from placebo group at an alpha (a) of 5% and a power of 80%, we needed 61 patients in each group. 135 patients were enrolled taking into consideration possible drop outs.

Data are presented as mean with SD or median with interquartile range or number (proportion) as appropriate. The Kolmogorov–Smirnov test was used to test for normality. Age, duration of surgery, time to receive first epidural bolus (h) were analysed with unpaired samples *t*-test. The total number of PCEA boluses over 48 hours and VAS scores were analysed using Mann-Whitney U test. Categorical data like sex of patient, number of patients who had nausea and vomiting were analysed using Chi-square test. *P* value of less than 0.05 was considered statistically significant. Calculations were performed using SPSS 21.0 for Windows (SPSS, Chicago, Illinois, USA).

RESULTS

Out of the 186 patients who were assessed for eligibility, 135 patients were randomly allocated into one of the two groups. Data was analysed for 126 patients as shown in Figure 1 Consort diagram. Demographic data was comparable in both the groups [Table 1].

Significant reduction of median [IQR] number of PCEA was observed in preemptive multimodal group (3 [2-4]) compared to placebo group (5 [4-7]); $P = <0.001$. Time to first rescue epidural bolus was also significantly greater in preemptive multimodal group than in placebo group, [4.75 ± 3.098 h vs 3.80 ± 1.939 h] $P = 0.04$. None of the patients in both the groups required intravenous morphine post-operatively (i.e. VAS ≥6). The median VAS scores between both the groups did not differ significantly. The median [IQR] number of times diclofenac was administered as rescue analgesic was lower in preemptive analgesic group 0[0-0] compared to placebo group[1[0-1].

No complications like sedation, dizziness, and somnolence were reported by any patients in preemptive multimodal group. Incidence of post-operative nausea vomiting did not differ significantly in both the groups. (Preemptive multimodal group $n = 8$ (12%) placebo group $n = 6$ (9%) $P = 0.58$. None of the patients had episodes of respiratory depression, apnoea, hypoventilation or desaturation post-operatively.

DISCUSSION

The results of our study show that administration of preemptive MMA regimen reduced the number of PCEA boluses post-operatively in the first 48 hours in

Table 1: Patient Demographics

	Preemptive multimodal group	Placebo group
Age (yrs)	30.7±10.9	33.9±14.3
Gender ratio (M:F)	87:13	80:20
Duration of surgery (h)	5.4±1.7	4.9±1.6

Results are expressed as ratio or mean and standard deviation

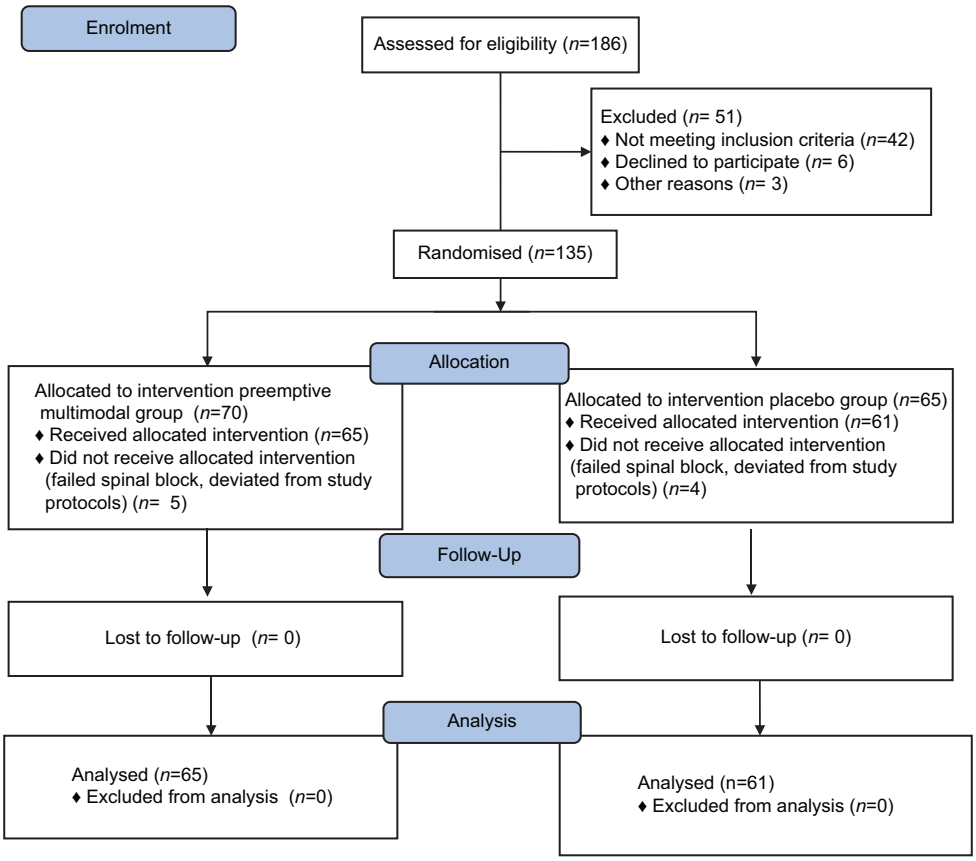

Figure 1: CONSORT flow diagram showing recruitment of patients

trauma patients undergoing nailing of fracture shaft of femur. We demonstrated that use of preemptive MMA allowed us to achieve improved post-operative pain control with consumption of lower doses of local anaesthetic and without the adverse effects associated with use of intravenous opioids.

Use of MMA involves the administration of pharmacological medications of different classes, employing various analgesic agents and techniques, thus providing greater pain relief with lower dose of medications and less side effects compared to mono-modal therapy. Typical MMA regimen starts in the preoperative period, continues through the intra-operative period and preferably, there should be a continuation of the regional analgesic technique (with a local anaesthetic-based solution) in the post-operative period. Various regimens of MMA including preemptive analgesics have been introduced.[9] Common medications include NSAIDs, COX-2 inhibitor, ketamine, local anaesthetics and alpha2-agonist. The preemptive MMA regimen followed in our study has been studied in previous studies in other surgical patients.[8,10,11]

Multimodal analgesic regimens and techniques consisting of non-opioid agents might be effective in today's opioid epidemic. Also, it is well-proven fact that epidural analgesia provides better post-operative analgesia compared to PCA opioids which are associated with unwanted side effects like ventilatory depression, sedation, drowsiness, pruritis, nausea, vomiting, urinary retention and constipation.[12] Enhanced recovery after surgery (ERAS) pathway further emphasises the need of multimodal pain management to avoid aforementioned side effects. None of the patients required opioids in preemptive multimodal group.

We used intermittent epidural boluses (IEB) as primary postoperative rescue analgesic as current evidence suggests that intermittent epidural boluses provide more effective analgesia that continuous infusion.[13] The mechanism suggested for superior analgesia with intermittent boluses is greater spread of drug in epidural space, thereby providing better sensory blockade compared to continuous epidural infusion. These clinical observations are consistent with the finding that equal distribution is due to large volumes of drug as experimented in cadavers,[14]

and observations of greater dye solution spread in semi-absorbent paper with boluses compared to continuously infused solution, despite the same hourly volume being administered.[15] We did not come across any incidence of hypotension or muscle weakness with use of epidural boluses with 0.2% ropivacaine with 2 μg/ml of fentanyl.

Incidence of postoperative nausea, vomiting which usually used to be high in POD 1 was less in both the groups because pain scores were <6 due to effective PCEA management which avoided the post-operative morphine consumption as rescue treatment.

Our study has few limitations. In both the groups, we had a low rate of PCEA bolus use (and very low post-operative pain scores). In that case, although the results are statistically significant, clinical relevance is doubtful. We did not measure patient satisfaction. Also, we did not record if any analgesic drugs administered to patients before arrival to pre-operating room. The concept of preemptive analgesia is to administer medications before pain stimulus or before the process of central sensitisation. In traumatic patients, where pain stimulus and the process of central sensitisation to pain is the preceding event, the concept of preemptive analgesia is questionable. Post-operative ambulation and rehabilitation was not evaluated since patients were not mobilised after surgery. Further, impact of the technique on length of hospital stay in trauma patients was not seen.

CONCLUSION

To conclude, preemptive MMA regimen reduces the number of PCEA demand boluses post-operatively in the first 48 hours in trauma patients undergoing nailing of fracture shaft of femur

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Conflicts of interest
There are no conflicts of interest.

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