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ORIGINAL RESEARCH

Preventive Epidural Analgesia in Bilateral Single-Stage Knee Arthroplasty: A Randomized Controlled Trial

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ABSTRACT

Introduction: Although controversial, preemptive analgesia has shown some promise in preventing altered pain perception and reducing pain amplification after surgery. Hence, it has the potential to be more effective than a similar analgesic regimen started after surgery with an appropriate combination of patient category and analgesic modality. Hence, the present study was undertaken to evaluate the effect of preventive epidural analgesia in reducing pain severity and duration after bilateral single-stage knee arthroplasty.

Methods: Fifty patients, 18–70 years, with American Society of Anesthesiologists physical status class I & II posted for bilateral single-stage knee replacement under regional anesthesia were randomly allocated into preventive versus postoperative epidural analgesia group to compare severity of post-operative pain, analgesic consumption, day of mobilization, C-reactive protein (CRP) levels, and hospital stay.

Results: The pain score after surgery [2.0 (1.5, 2.0); 3.0 (1.5, 3.0), $p = 0.005$] and day of mobilization [(2. 92 ± 0. 28; 3. 31 ± 0. 48; p value 0.02)] were significantly lesser in the preventive epidural group. However, there was no difference in the hospital stay (9.92 ± 3.71 and 9.00 ± 2.12, $p = 0.95$) and analgesic consumption (65.38 ± 37.55 and 73.08 ± 43.85, $p = 0.30$). The preventive group had a larger drop in CRP and experienced a lesser number of days with pain after surgery as compared to the controls [(64.29 ± 21.29); (142.37 ± 80.04), $p = 0.0001$]. Six patients in the preemptive group (24%) and 13 of the control group (24 vs. 56.5%; $p = 0.02$) had chronic postsurgical pain.

Conclusions: Preventive epidural analgesia reduces the severity and number of chronic pain days after bilateral single-stage knee replacement.

Trial Registration: The study was registered in the Indian national registry (CTRI/2017/03/008240 on 28/03/2017).

Keywords: Analgesia; Arthroplasty; Chronic pain; Epidural; Knee; Replacement

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Key Summary Points

Why carry out this study?

To reduce chronic pain after bilateral arthroplasty by providing preemptive epidural analgesia.

The study evaluated whether preemptive epidural analgesia could be proven to provide preventive analgesia in bilateral knee replacement surgery, which is never studied.

What was learned from the study?

Preemptive epidural analgesia is preventive to some extent in knee arthroplasty.

Preemptive epidural analgesia reduces the severity and chronic pain after knee arthroplasty.

INTRODUCTION

Pain relief is an indispensable component of perioperative management. Even after persistent developments, pain management is still inadequate and often patients experience the worst pain of their lives after surgery. This results in prolonged hospital stays and worsens the overall outcome [1].

Although controversial, pre-emptive analgesia has shown some promise in preventing altered pain perception and pain amplification after surgery. Therefore, it has the potential to be more effective than a similar analgesic regimen initiated just after surgery. Epidural analgesic technique is one of the multimodal regimens for postoperative pain management in bilateral single-stage knee arthroplasty in some centers.

It has been raised that an appropriate combination of patient group and pain management modality might be the perfect answer to re-establish preemptive analgesia as preventive analgesia.

Hence, the present study was undertaken with an attempt to start epidural analgesia preemptively and evaluate its effect on postoperative analgesic requirements, pain scores, inflammatory biomarkers, hospital length of stay, and development of chronic pain in patients undergoing bilateral single-stage knee arthroplasty.

METHODS

We carried out a hospital-based randomized trial in the operation theatre of our institute. Ethical approval for this study (T/IM-F/Ansth/15/08) was provided by the institute ethics committee (All India Institute of Medical Science, Sijua, Bhubaneswar, India). This study conformed to the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights, and Springer's policy concerning informed consent has been followed and was received from all participants. All patients aged 18 to 70 years with American Society of Anesthesiologists physical status class I & II posted for bilateral single-stage knee replacement under regional anesthesia were recruited in the study. Written informed consent was obtained from each participant. They were explained regarding 0–10 numeric pain rating scale where 0 means no pain and 10 means worst pain imaginable.

Patients with uncontrolled systemic illness, those with contraindication to regional anesthesia, difficulty in epidural placement, and those who refused to participate were all excluded from the study.

After obtaining consent, all of the patients received epidural catheters at third and fourth lumbar intervertebral space in sitting position in the minor theatre in the ward area with 4 cm of the catheter inside the space with bevel of the Tuohy needle faced upwards. After that, patients were randomized into two groups using a computer-generated random number table. Patients in the preemptive group received a minimum preoperative epidural infusion of bupivacaine 0.125% at a rate of 0.1 ml/kg/h and

titrated to a pain score of 3 or less in those with higher pain scores. The infusion ran until the patient entered the operation theatre. The replacement surgery was conducted under subarachnoid block administered in the operation theater one space below the epidural insertion with a 26G Quincke's spinal needle with 0.5% bupivacaine heavy and 25 mcg of fentanyl in both the groups. At the end of surgery, patients in both of the groups were shifted to an intensive care unit and epidural infusion of bupivacaine 0.125% along with fentanyl 2 mcg/ml was initiated in all patients irrespective of group allocation and level of blockade. The infusion was titrated to achieve a pain score of 3 or less with hemodynamic monitoring. To achieve better pain relief, all patients received injection paracetamol 1 g intravenous every 8 h as a component of multimodal regimen. Assessment of pain was done at 4-h intervals preoperatively and at every 1 h for the first 4 h, then every 4 h for 24 h after surgery. Two blood samples were drawn from each patient for the estimation of C-reactive protein (CRP); the first sample was drawn in the preoperative area just before entering the theatre and the second sample at 6 h after surgery in the intensive care unit.

In addition, hemodynamic parameters, age, weight, height, duration of surgery, total consumption of bupivacaine, any side effects, day of mobilization with support, total length of hospital stay, and chronic postsurgical pain defined as pain persisting for more than 3 months with a pain score of 3 or more were also recorded by a senior registrar not involved in the study. Hospital stay was defined as the day of epidural insertion to the day of hospital discharge.

Sample Size Calculation

To achieve a mean pain score difference of 2 with a standard deviation of 2.3 at 24 h after surgery, as obtained from a previous similar study and an allocation ratio of 1 between control and experimental subjects, we required to study 22 experimental and 22 control subjects to be able to reject the null hypothesis with a power of 80% and type I error of 5%. We took 25 subjects in each group to a total of 50 [2].

Statistical Analysis

The full analysis included two groups of patients that received either preventive epidural analgesia (study group) or received it only after surgery (control group). Descriptive statistics were computed for each treatment group; data were expressed as mean ± SD or median (interquartile range) as deemed fit according to the distribution. Hypothesis tests were done two-sided using the 0.05 significance level. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS 21.0) software.

RESULTS

A total 50 patients were recruited (Fig. 1). We found no difference in the baseline characteristics, vital and other parameters like duration of surgery, or blood loss among the two groups (Table 1). Hypertension was the most common comorbid illness followed by hypothyroidism and diabetes mellitus (Fig. 2). The pain score at

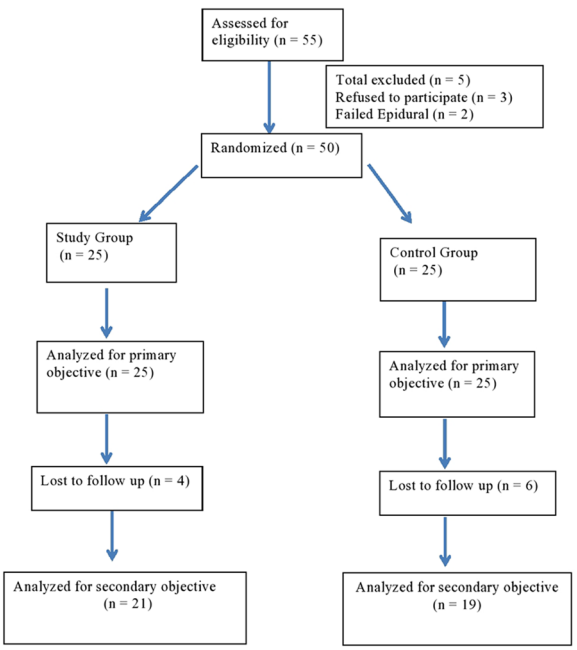

Fig. 1 Consort study flow diagram

Table 1 Clinical characteristics of patients in the preventive and control group

	Preventive group (n = 25)	Control group (n = 25)	P value
Age in years	58.46 ± 5.97	58.38 ± 5.57	0.91
Sex (M:F)	8:17	9:16	
ASA Score (I:II)	4:21	6:19	
Heart rate	83.83 ± 6.02	82.84 ± 4.64	0.98
Blood pressure	90.65 ± 6.70	88.56 ± 6.69	0.26
Duration in minutes	106.15 ± 16.60	101.92 ± 16.27	0.82
Preoperative pain score**	5.0 (3.5, 6.0)	4.00 (2.5, 5.5)	0.46
Pain at 24 h postoperative	2.0 (1.5, 2.0)	3.0 (1.5, 3.0)	0.005*
24 h bupivacaine consumption	65.38 ± 37.55	73.08 ± 43.85	0.30
Drop in CRP (Preop–Postop)	7.64 (10.10, 1.95)	1.12 (3.91, 0.18)	0.04*
Blood loss (ml)	540.38 ± 232.34	564.23 ± 204.08	0.95
Day of mobilization	2.92 ± 0.28	3.31 ± 0.48	0.02*
Days of hospital stay	9.92 ± 3.71	9.00 ± 2.12	0.95
Days of pain after surgery***	64.29 ± 21.29	142.37 ± 80.04	0.0001*

ASA American Society of Anesthesiologists

**Numeric pain rating scale is expressed as median (interquartile range)

***No. of patients assessed at follow-up: (21 in the study group and 19 in the control group)

24 h after surgery [2.0 (1.5, 2.0); 3.0 (1.5, 3.0), p = 0.005] and time to start of mobilization in days [(2.92 ± 0.28; 3.31 ± 0.48; p value 0.02)] were significantly lesser in the preemptive group as compared to the patients in the control group. However, we did not observe any reduction in the number of hospital days (9.92 ± 3.71 and 9.00 ± 2.12, p = 0.95) and amount of postoperative analgesics (65.38 ± 37.55 and 73.08 ± 43.85, p = 0.30) used. In addition, we found the preemptive group patients to experience a lesser number of days of pain after surgery as compared to the group of patients who did not receive preemptive epidural analgesia [(64.29 ± 21.29); (142.37 ± 80.04), p = 0.0001} (Table 1). Six patients in the preemptive group (24%) and 13 of the control group (24% and 56.5%; p = 0.02) had chronic postsurgical pain. None of the patients required any epidural top up during the surgery.

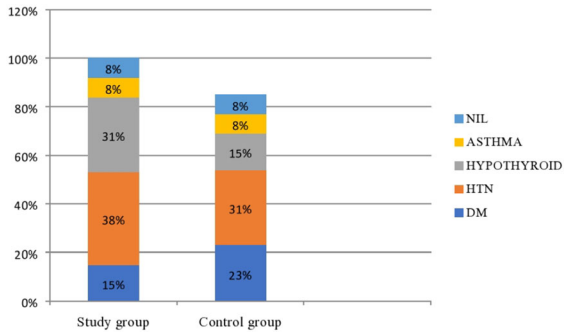

Fig. 2 Distribution of comorbidity among the groups

DISCUSSION

We observed that preemptive epidural analgesia promoted early mobilization, reduced postoperative pain score and days of chronic pain after surgery, and contributed to a significant drop in CRP levels as compared to the conventional treatment group. There was no difference seen with regards to the days of hospitalization and amount of bupivacaine consumed in the postoperative period.

Preemptive analgesia has been defined in the literature variably. One of the definitions is: analgesics given before surgical incision whereas another considers analgesics given before incision to prevent development of sensitization secondary to surgical incision [3]. The third and the most accepted definition states

"administration of analgesics before surgical incision with an adequate duration to prevent development of sensitization secondary to both surgical incision and the postoperative inflammation" [4]. Varied definitions lead to varied outcomes and bring in controversies. Hence, preemptive analgesia is not routine in many centers even though the concept never really died since its inception.

Most of the published research on preemptive analgesia reflects animal study findings in the laboratory, where the tested intensity and duration of painful stimulus is minimal and guided. In contrast, the surgical stimulus is varied and intense. Hence, analgesic modalities with limited efficacy and coverage might fall far from showing any positive outcome. The concept of preemptive is being preventive and shall be effective only when it completely inhibits and keeps preventing both inflammatory and nociceptive inputs throughout its perioperative period [5].

There are two types of pain often seen after surgery: the first is physiological, and usually short-lasting, whereas the second type is pathological, and stays relatively longer. Classically, perioperative analgesia caters to the physiological postoperative pain, whereas preventive analgesia is meant for the pathological variety. This second pathological variety is of high intensity and is often triggered by trivial stimuli. Fundamentally, there are two ways by which one can prevent the development of pain hypersensitivity and pathological pain; either by inhibiting the glutamate receptors or by blocking the afferent signals that maintain the process of sensitization—hence, medications like NMDA antagonists, which may not have an appropriate utility for the physiological pain post-surgery but have a greater role in the prevention of hypersensitivity and development of chronic postsurgical pain. Similarly, epidural analgesia, due to its universally accepted role, is expected to cover for not only the perioperative analgesia but also reduce the intensity and development of chronic pain by blocking the conduction of afferent signals [4, 6].

Hence, as far as preemptive is concerned, it was suggested that appropriate definition, patient selection, and a combination of analgesic modalities might result in a favorable outcome [4].

Therefore, we chose to evaluate epidural analgesia in bilateral knee replacement patients. These are the group of individuals who suffer from pain even in the preoperative period. Additionally, they are to undergo bilateral single-stage surgery, which is expected to result in extensive tissue injury and inflammation [7].

A study by Adams et al. compared three-in-one block, epidural analgesia and intravenous patient-controlled analgesia in patients undergoing knee replacement. Although adequate pain relief was obtained in all, epidural anesthesia was found to be superior in reducing the sympathoadrenergic stress response. Therefore they recommended epidural analgesia technique for high-risk patients with diabetes, hypertension, and coronary artery disease [8]. Here it makes sense because with increasing life expectancy, a rise in both comorbid conditions and the need for knee arthroplasty are expected to rise. Therefore, rather than decreasing, we see there may be an enhanced necessity for epidural analgesia [9]. Additionally, prevention of hypercoagulability is one of the non-analgesic utilities of epidural technique without affecting the physiological coagulation process. This further adds to the benefits of epidural over other analgesic modalities [10].

Although a period of phasing out of epidural due to availability of other techniques for pain relief was there, to date epidural analgesia it still used due to its excellent effectiveness and reduced side effect profile with different combinations [9].

Preemptive and multimodal are the two primary ways of approach towards better pain control in knee arthroplasty patients [1]. Different modalities like opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), pregabalin, and regional techniques have been utilized preemptively to reduce postoperative pain and analgesic requirements [11]. Studies evaluating the effect of preemptive epidural analgesic technique are limited. Klasen et al. compared the effect of preemptive epidural analgesia on postoperative pain and analgesic consumption in patients posted for elective hip replacement surgery [12]. They observed a similar pain score

in both of the groups but a reduction in local anesthetics consumption in the preemptive group. In contrast, another study by Kilickan et al. did not find any reduction in analgesic consumption after epidural morphine compared to intravenous use [13]. Another study evaluated the efficacy of ropivacaine administered as a single preemptive epidural injection in patients undergoing lumbosacral spine surgery. They concluded it to be a safe and effective approach reducing the intraoperative opioid requirement, providing better postoperative pain relief, and facilitating early mobilization, which is very similar to our results [14].

In the present study, we observed better pain scores 24 h after surgery in the preemptive group without much reduction in analgesic consumption. The outcome of preemptive analgesia depends on selection of patient groups, modalities, and duration of analgesic; therefore results vary between studies. In the future, studies must address all the above factors. Additionally, a meager reduction in analgesic consumption should not be the only criteria for outcome evaluation; rather, better pain control without side effects is the goal. Therefore, we chose to run the preemptive epidural analgesia for up to 48 h after surgery.

Therefore, the evidence regarding the utility of preemptive epidural analgesia in different types of surgery is inconclusive. This further necessitates the need for further study on the subject to establish the utility of the concept.

C-Reactive Protein Levels and Implications

Osteoarthritis is a degenerative disease with variable rates of inflammation requiring knee replacement [15]. Being a marker of systemic inflammation, high-sensitivity CRP levels in serum are associated with both pain and progression in patients with knee osteoarthritis [16].

C-reactive protein is an acute-phase reactant synthesized by the liver to activate the classical complement pathway. The serum values vary widely with inflammation and infection but the factors associated with these variations are quite unknown. Serum levels of CRP vary in the preoperative period to postoperative period. Serum levels of CRP usually peak on the second postoperative day and fall gradually by the fifth to seventh day after knee replacement surgery [17].

We evaluated the levels of CRP after surgery as compared to the preoperative levels in all patients. Surprisingly, we observed a drop in CRP in the postoperative period in both the groups rather than a rise, but the drop was comparatively larger in the preemptive group, which probably reflects the effect of epidural analgesia on systemic and local inflammation and differential rise in the levels of CRP in the postoperative period. Similar to our findings, Chloropoulou et al. did a similar study in knee arthroplasty patients and concluded a similar reduction in inflammatory response after epidural analgesia in knee arthroplasty patients [18]. We understand that any reduction in inflammation leads to a reduction in pain intensity after surgery reflected by a smaller rise in CRP levels after preemptive epidural analgesia as compared to the other group.

Chronic Postsurgical Pain

Noxious stimulus is usually followed by two different and distinct phases of pain response; the initial phase is brief, sharp, and well localized, whereas the second phase is often dull, diffuse, and prolonged. This second phase of nociception results from a process called sensitization, and this is the target of preemptive analgesia. Prevention of this second phase inhibits the development of chronic pain after surgery [19].

The term chronic postsurgical pain refers to one of the commonest complications after surgery, which is defined as postoperative pain that persists for more than 3 to 6 months. Being chronic in nature, it disrupts one's personal and social life along with psychological alterations. Further, literature states that the incidence of chronic pain after knee replacement is 19–43% [20]. Therefore, prevention of development of chronic pain after surgery, especially in knee arthroplasty patients, is immensely important

and justified. Multimodal analgesia has been found to be of essence here. In our study, we observed that the initiation of epidural analgesia in the preoperative period along with multimodal analgesic regimen immediately after surgery resulted in a reduction in the number of pain days after surgery as compared to the control group.

Initial studies by different researchers like Woolf and Chong established the beneficial role of starting an anti-nociceptive therapy before surgery rather than in the postoperative period [21], but not all studies had consistent results. Therefore, it was suggested to choose an appropriate multimodal regimen with adequate duration encompassing the preoperative to postoperative period. Our study results not only corroborate with these concepts but also reinstate the notion of preventive analgesia in reducing the incidence of chronic postsurgical pain.

Limitations

A small sample size, lack of blinding due to the inherent nature of epidural analgesia, and limited combinations of epidural analgesic regimen are the limitations of this study.

CONCLUSIONS

Preemptive epidural analgesia was found to reduce the severity of pain and inflammation after bilateral single-stage knee replacement surgery, resulting in a reduced development of chronic pain after surgery but failed to produce any reduction in the immediate analgesic consumption and hospital stay.

The major and long-term goal of pre-emptive analgesia is prevention of the development of central and peripheral sensitization and development of chronic pain, hence called preventive analgesia. Studies with an aim of mere reduction in some milligrams or micrograms of an analgesic in the postoperative period just by administering a specified dosage of an analgesic pre-emptively, is probably not the concept and does not lead us anywhere scientifically. Therefore, it is prudent to suggest here that all future studies must evaluate the preventive effects of pre-emptive analgesic modalities on the basis of both clinical and molecular evidence of inhibition of sensitization or development of chronic pain. Additionally, the analgesic modality for preventive evaluation must be chosen with due consideration towards analgesic efficacy, mechanism, and duration of action.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Compliance with Ethics Guidelines. Ethical approval for this study (T/IM-F/Ansth/15/08) was provided by the institute ethics committee (All India Institute of Medical Science, Sijua, Bhubaneswar, India). This study conformed to the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights, and Springer's policy concerning informed consent has been followed and was received from all participants.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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