

Clinical Study

A prospective randomized study to analyze the efficacy of balanced pre-emptive analgesia in spine surgery

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Abstract

BACKGROUND CONTEXT: Surgical procedures involving the spine are known to cause moderate to severe postoperative pain. Inadequate management of acute pain in the postoperative period results in higher morbidity, and consequently may lead to chronic pain caused by central sensitization. The role of pre-emptive analgesia (PA) and intraoperative analgesia in management of postoperative pain has gained precedence over recent years. Pathophysiology of postoperative pain in spine surgery is unique, as it is a combination of nociceptive, inflammatory, and neuronal stimuli. Blockage of all three stimuli in the perioperative period by pre-emptively administering a combination of paracetamol (P), ketorolac (K), and pregabalin (PR) might help in adequate management and alleviation of acute postoperative pain.

PURPOSE: To evaluate the analgesic effect of a combination of P, K, and PR as pre-emptive multimodal analgesia, aimed to block or reduce acute postoperative pain after spine surgery.

STUDY DESIGN: A prospective, randomized, controlled, and double-blinded clinical trial.

PATIENT SAMPLE: After Institutional Review Board approval, 100 consecutive patients requiring single- or double level spinal fusion procedures were randomized into two groups—PA and control (C).

METHODS: The PA group received P, K, and PR 4 hours before surgery, as PA. Both groups underwent identical anesthetic and postoperative pain management protocol.

OUTCOME MEASURES: Demographic and surgical data, 4 hourly postoperative pain levels—Numeric Pain Rating scale (NRS), Ambulatory NRS scores; level of consciousness—Ramsay sedation scale, total amount of opioids consumed (TOC) through patient-controlled analgesia; functional levels—Oswestry Disability Index (ODI), surgical satisfaction index—North American Spine Society (NASS) satisfaction scale, duration of hospital stay, and all complications were recorded and analyzed. A research grant of 6,032 USD was obtained from AO Spine toward this work. There is no conflict to disclose.

RESULTS: Both the groups had identical demographic backgrounds and surgical profiles. The average NRS score within the first 48-hour period in the PA group (2.7 ± 0.79) was significantly less than the C group (3.4 ± 0.98) and the differences were more in the first 12 hours following surgery. Similarly, Ambulatory NRS scores were significantly low in the PA group during the first and second postoperative days. The PA group individuals were found to be more physically motivated, as 95.7% were able to ambulate 50 m on the first postoperative day compared with 30% in the C group. The PA group had significantly low TOC (3.02 ± 2.29 mg) in comparison to the C group

FDA device/drug status: combination of paracetamol (P), ketorolac (K), and pregabalin (PR).

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(4.94±3.08 mg). The duration of hospital stay was 4.17±1.02 and 4.84±1.62 days in the PA and C groups (p=.017), respectively. No major complications occurred in either groups and were found to be similar in percentage between both the groups, except for nausea and vomiting which were more in C group. Dry mouth was the most common side effect noted irrespective of the groups. All patients had significant improvement in ODI with better results in PA group at first month follow up. The PA group (97.90%) was extremely satisfied compared with C group (72%, p=.002) according to NASS scale.

CONCLUSIONS: Postoperative pain management in spine surgery is maximized if perioperative painful stimuli can be inhibited, which requires adequate blood levels of analgesic, anti-inflammatory, and neuropathic drugs intraoperatively. The employed strategy of preoperative administration of balanced analgesia with a combination of P, K, and PR, each having different mechanisms of action, resulted in lesser pain intensity, allowed better ambulation tolerance, improved functional outcomes and has also reduced the requirement of opioids and duration of hospital stay with no additional complications. Thus, this balanced analgesia administered preoperatively would address the complicated postsurgical pain. © 2018 Elsevier Inc. All rights reserved.

Keywords: Pre-emptive analgesia; Preventive analgesia; Functional outcome; Postoperative pain; Lumbar fusion; Oswestry disability index score; Numeric Pain Rating scale; Central sensitization; Peripheral sensitization; Opioid usage

Introduction

The global increase in incidence of low back pain has resulted in an increase in number of spine surgeries being performed worldwide. The current focus of all surgeons is toward risk stratification and achievement of better functional outcomes in standard spine procedures by improving patient satisfaction. It has been noted that the quality of surgical procedure alone does not contribute to satisfactory results [1]. Postoperative experience plays a vital role in recovery of a patient [2]. Inadequate postoperative pain management following spine surgery can result in medical complications such as deep vein thrombosis, pulmonary embolism, myocardial infarction, and poor wound healing, thereby contributing to patient dissatisfaction and poor functional outcomes. Adequate postoperative pain management allows early ambulation, reduces hospital length of stay, and improves quality of life [3].

Postoperative pain in spine surgery is usually rated as moderate to severe [4]. The intensity of pain is proportional to the number of segments and invasiveness of the procedure rather than the level of spine involved [5]. Opioids, considered to be gold standard analgesics, are highly effective in controlling postoperative pain but are associated with dose-dependent side effects such as nausea, vomiting, respiratory depression, feelings of apathy, and orthostatic hypotension [6]. Caused by these deleterious effects, opioids are best avoided as standalone drugs. Postoperative multimodal analgesic approaches with opioids, nonsteroidal anti-inflammatory drug (NSAIDs), paracetamol (P), local infiltrations, epidural injections, patient-controlled analgesia (PCA), and other adjuvants have been used in varying combinations. Such an approach not only reduces the dosage of drugs required but also exhibits synergistic actions among the drugs used [7]. Pre-emptive analgesia (PA), administered before the start of the procedure, and its rationale of prevention of central sensitization by blocking incisional and

inflammatory stimuli, is widely accepted [8]. A multitude of drugs have been administered in spine surgery and varied results have been reported.

None of the studies has aimed at inhibiting all the possible pathways of pain secondary to nociceptive, inflammatory, and neuropathic stimuli pre-emptively in spine surgery. The blockage of all three stimuli in the perioperative period by administering a combination of P, ketorolac (K), and pregabalin (PR) pre-emptively might aid in efficient management of acute postoperative pain. The purpose of this study was to analyze the efficacy of such a combination.

Materials and methods

After Institutional Review Board approval, 132 consecutive patients who required elective single- or double level spinal fusion procedures were screened and later randomized using online software (www.randomizer.org) into two groups: pre-emptive analgesia (PA) and control (C) between October 2016 and July 2017. Inclusion criteria were individuals with 30–70 years of age weighing between 50 and 90 kg. Exclusion criteria included individuals with American Society of Anesthesiologists (ASA) category ≥3, preoperative administration of analgesics 24 hours before surgery, adjacent segment disease requiring surgeries, inflammatory or infective etiology, and foreign nationals. The Consolidated Standards of Reporting Trials guidelines for reporting randomized trials (<http://www.consort-statement.org/>) were used to represent the allocation details of the study (Fig. 1).

Both groups received 40 mg of esomeprazole and 30 mg of domperidone as preanaesthetic medication 8 hours before surgery, whereas the PA group alone received three drugs (P, K, and PR) 4 hours before surgery, orally with sips of water, as PA. The dosages of pre-emptive drugs

were 1 g of P, 20 mg of K, and 75 mg of PR. It was administered by an independent anesthetic nurse who was not involved in monitoring or follow-up of the individuals. Standard monitoring devices were used. Both groups underwent identical anesthetic protocol, induction by Fentanyl 2 µg/kg and Propofol 2 mg/kg, and tracheal intubation was facilitated by administering Rocuronium 0.8 mg/kg. In addition 1 g P infusion and 8 mg Dexamethasone IV were administered after skin incisions on patients of both the groups. Patients' lungs were ventilated with a tidal volume of 7–9 mL/kg, I:E ratio of 1:2 at a respiratory rate of 8–12 breaths/min in 50% oxygen and N2O to maintain normocarbia (aPco2=30–40 mm Hg) throughout the surgery. Anesthesia was maintained with continuous inhalational agent Sevoflurane (1 MAC) and top up doses of Rocuronium at 0.1 mg/kg were used.

Postoperatively, a uniform pain management regime was executed with P infusion of 1 g sixth hourly, IV K 30 mg eighth hourly, PR capsule 75 mg once a day with the first dose administered 12 hours after surgery, and a transdermal

patch of buprenorphine 10 mg. All patients were provided with a CADD-Legacy 6300 PCA ambulatory infusion pump for a period of 48 hours and were educated on how to use it. The medication cassette reservoir was loaded with 100 mL pump comprising of morphine, prepared by diluting 20 mg in 100 mL distilled water to constitute 0.2 mg/mL. The PCA pump was preset to be used only on demand providing 1 mg/5 mL every time the patient pressed the associated button. Lockout period of 30 minutes was set and no bolus or baseline infusions were used, allowing for easy measurement of amount of opioids used as rescue analgesic by the patient through PCA. Sedation in the form of 1 mg Butorphanol was provided on the night of surgical procedure.

Two independent anesthetic physician assistants unaware of the randomization, monitored and recorded fourth hourly, the Numeric Pain Intensity (NRS) scores, levels of consciousness—Ramsay sedation scale, total amount of opioids consumed (TOC) through PCA, and all complications. All patients were encouraged to ambulate

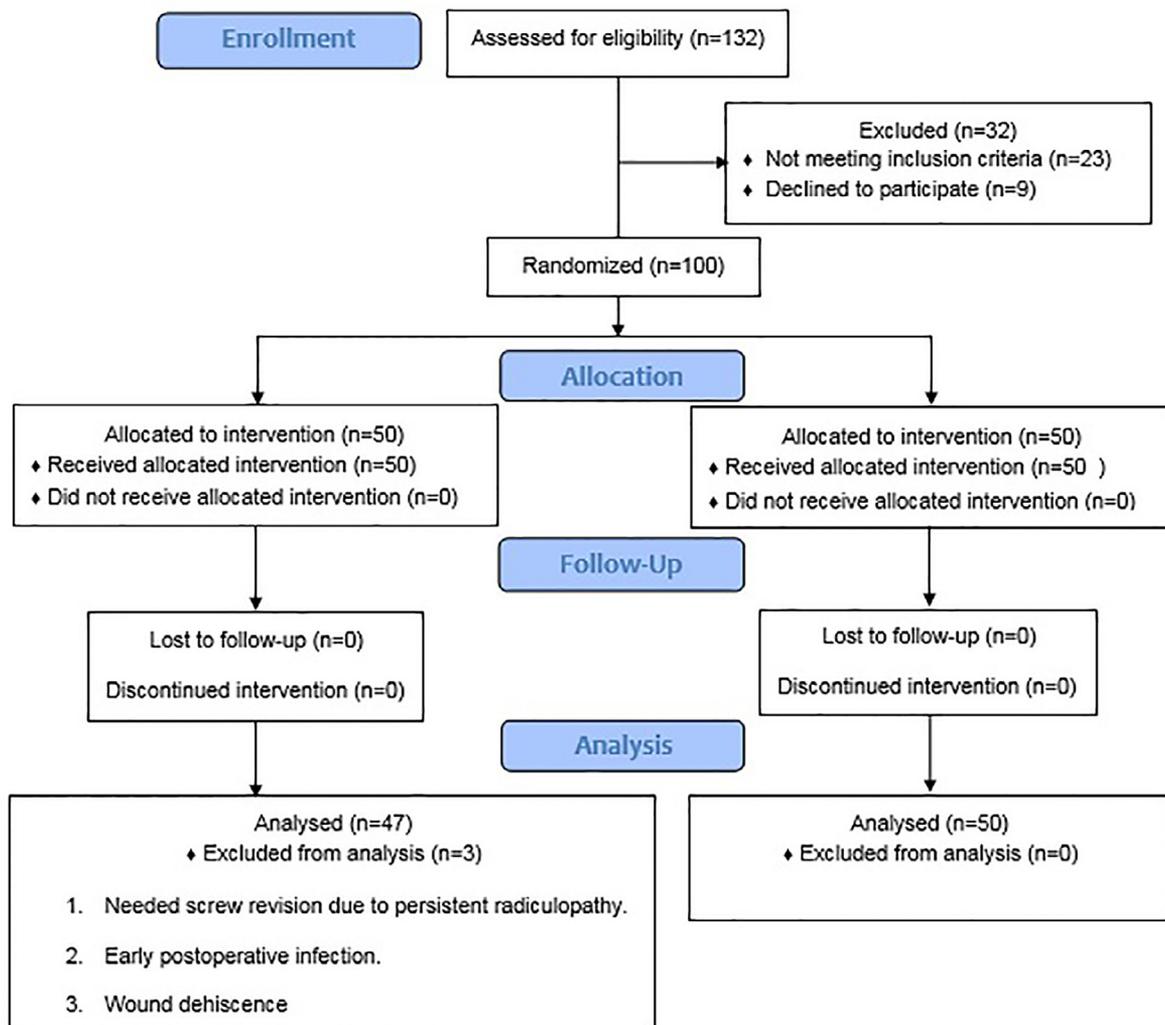


Fig. 1. Study allocation flow diagram.

on the day of surgery by turning over on bed, and walk on first postoperative day. Ambulatory NRS was noted by a physiotherapist who was blinded to the details of the study. Demographic and surgical data, functional levels—Oswestry Disability Index (ODI), surgical satisfaction index—North American Spine Society (NASS) satisfaction scale, duration of hospital stay were documented by a clinical physician assistant. The principal investigator who was aware of the allocation was not involved in monitoring or recording of the outcomes until the data collection was completed.

Statistical analysis

Based on other similar studies, preliminary study statistics, and to satisfy the central limit theorem by, considering a mean difference of at least 1, standard deviation of 1.2, power of 0.95, and alpha 0.05, along with 30% possible drop out cases, 50 cases were randomly assigned to each of the study groups (PA and C). Several variables, mainly postoperative pain on the NRS, were assessed and statistically analyzed and compared. Continuous variables were analyzed using Student's *t* test and categorical variables were analyzed using either the chi square test or Fisher's exact test. Some variables such as NRS and PCA were observed at different time points and thus were compared using repeated measures ANOVA followed by *t* test at individual time points. Significance was set at $p \leq .05$.

Results

One hundred thirty-two consecutive patients enrolled for lumbar fusion surgery were screened and 23 patients were excluded. Further, nine patients declined to participate in the study. Surgery was performed successfully in the remaining 100 patients who were randomized and all the data were available for analysis. Three patients were excluded from the study because of persistent radiculopathy requiring screw revision, early postoperative infection, and wound dehiscence. Both groups had similar demographic and surgical characteristics (Table 1). The average 48-hour NRS score in PA group (2.7 ± 0.79) was lesser than C group (3.4 ± 0.98 ; $p < .001$). Among the fourth hourly NRS scores statistically significant difference were noted at four time points during the first 48 hours after surgery (Fig. 2). The two spikes noted at 28 and 36 hours in both the groups were probably caused by ambulation. Ambulatory pain scores were noted separately by an independent physiotherapist blinded to randomization and was found to be significantly lower in PA group (Fig. 3). The ambulatory NRS scores were (4.5 ± 0.97) and (2.5 ± 0.62) in the PA group on first and second postoperative days which were significantly less compared with (5.4 ± 1.41) and (3.5 ± 0.85 ; $p < .001$) in the C group. The ambulatory status of PA group on the first postoperative day was better as 95.7% in PA group was able to ambulate 50 m, when compared with only 30% in the C group ($p < .001$).

Table 1
Distribution characteristics of the two study groups

Variables	Pre-emptive analgesia (PA) N=47	Control (C) N=50	p value
Gender	N, F=37, M=10	N, F=37, M=13	.585
Age	49.7±12.33 years	51.6±9.46 years	.403
BMI	26.4±4.61	25.8±3.48	.448
NRS-Pre op	2.64±0.87	2.86±1.44	.359
Blood loss	350.8±157.6 mL	313.2±153.7 mL	.237
1 level fusion	35 (74.5%)	39 (78%)	.683
2 level fusion	12 (25.5%)	11 (22%)	
Duration of surgery	112.98±21.59 min	106.90±17.78 min	.135

N, number, F, females, M, males, BMI, body mass index, NRS-pre op, preoperative numerical pain rating scale score. Values are expressed as mean ± standard deviation.

Opioids were available only on demand in the form of PCA as rescue analgesics. Total consumption was 3.02 ± 2.29 mg in PA group versus 4.94 ± 3.08 mg in the C group ($p = .001$) over 48 hours, (Table 2) and this difference was found to be statistically significant at different time points up to 16 hours (Fig. 4). No additional analgesics were administered apart from the pretailored pain management regime opted for both the groups. According to the Ramsay sedation scale, level 1 indicates agitated or anxious state and level 2 indicates tranquil state, and increasing levels suggest of progressively sedated states. The percentage of patients who were labeled 1 was more in C group compared with PA group indirectly suggesting higher intensity of pain which the patient was suffering from (Fig. 5). No major complications occurred and the noted complications were found to be similar between both the groups except nausea and vomiting which were more in C group. Dry mouth was the most common side effect noted irrespective of the groups (Table 3). According to the NASS satisfaction scale, level 1—the treatment met patients' expectations, level 2—did not improve as expected, yet would undergo the same procedure for the same outcome, level 3—did not improve as expected, and would not undergo the same procedure for the same outcome, and level 4—the same or worse after the procedure. All patients had significant improvement in ODI with significantly better results in PA group (30.8 ± 6) compared with (34.8 ± 6.3) at first month of follow-up ($p = .002$). Pre-emptive analgesia group (97.9 %) compared with C group (72%, $p = .002$) was extremely satisfactory according to NASS scale.

Discussion

Postsurgical pain in spine surgery is complex such that it may originate from skin, muscle, vertebra, intervertebral disc, facet joints, or neural tissue [9]. Since it is a combination of nociceptive, inflammatory, and neuronal stimuli, opioids, which are considered to be the gold standard agent for acute pain, alone may not be sufficient to control pain after spine surgery. Moreover, they are effective in

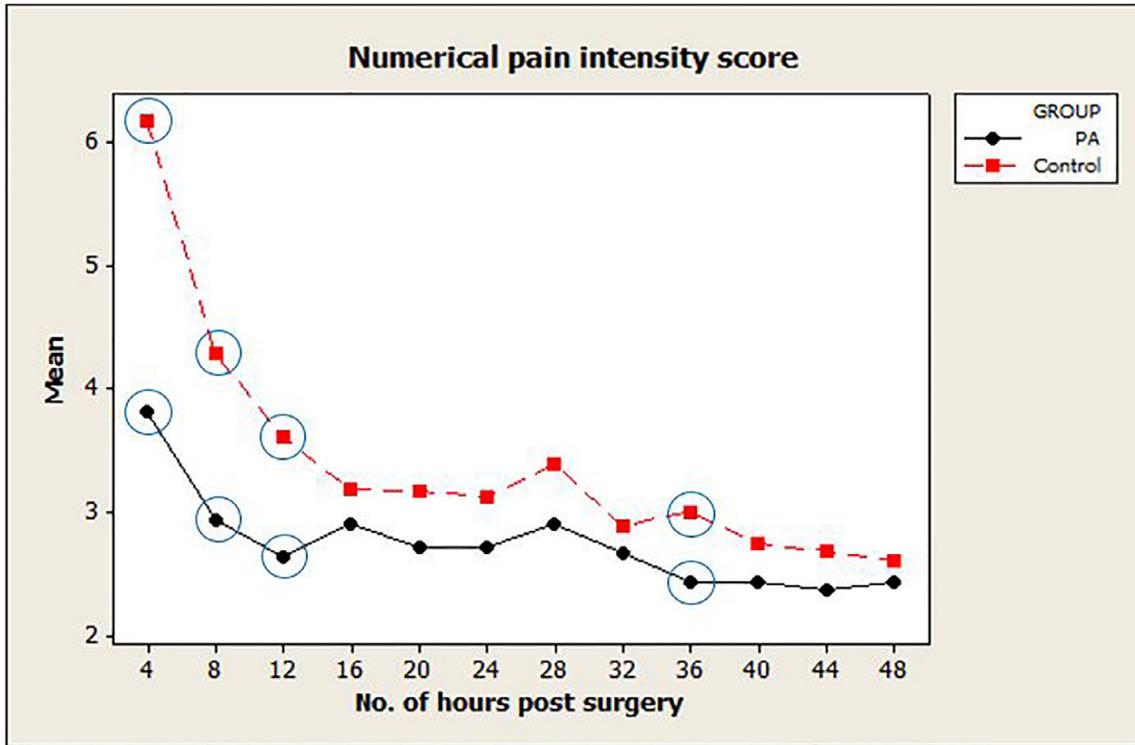


Fig. 2. Average NRS scores of the two study groups at various time points after surgery. Blue-circled points indicate statistically significant differences between the groups at that particular time point. NRS, Numeric Pain Rating scale.

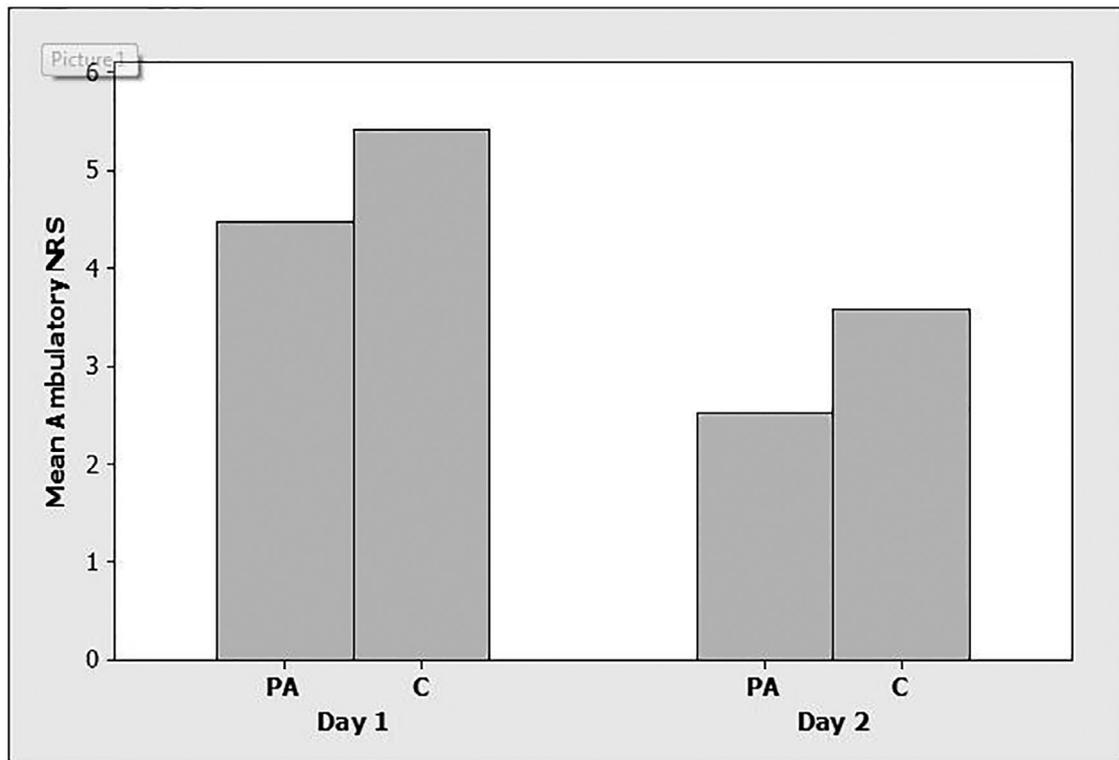


Fig. 3. Average NRS scores after ambulation on days 1 and 2 following surgery was significantly lower in PA group. NRS, Numeric Pain Rating scale; PA, pre-emptive analgesia.

Table 2
Statistical comparison (student’s *t* test) of various outcome variables (continuous)

Variables	Pre-emptive analgesia (PA) N=47	Control (C) N=50	p value	
NRS before surgery	2.64±0.87	2.86±1.44	.359	
NRS 48 h average postsurgery	2.74±0.79	3.40±0.98	<.001	
Ambulatory NRS Day 1	4.47±0.97	5.42±1.42	<.001	
Ambulatory NRS Day 2	2.51±0.62	3.58±0.86	<.001	
PCA total	3.02±2.29 mg	4.94±3.08 mg	.001	
ODI before surgery	73.62±7.97	69.5±12.09	.05	
ODI first month	30.89±6.04	34.88±6.33	.002	
ODI third month	11.49±6.37	12.36±7.38	.535	
No. of complications	1.79±1.08	2.4±1.71	.037	
Duration of hospital stay	4.17±1.03 days	4.84±1.62 days	.017	
NASS	Level 1	46 (97.9%)	36 (72%)	0.002 (chi-square)
	Level 2	1 (2.1%)	13 (26%)	
	Level 3	0 (0%)	1 (2%)	

Statistically significant p values are highlighted in bold.

managing rest pain (tonic) rather than ambulatory pain (phasic) [10]. Multimodal analgesia has synergistic effects and helps in reducing individual doses of the drugs, thus reducing the dose-dependent toxic effects, which is usually given as a combination of opioids, NSAIDs, and other adjuvants. In addition to the adverse clinical effects, undermanaged acute pain might result in chronic postsurgical pain believed to occur in 10%–50% of individuals caused by intense tissue trauma during the surgery inciting an inflammatory process or neuronal stimuli from peripheral nerve damage. This results in the release of algogenic substances from peripheral nerve endings and other tissues mounting to peripheral sensitization of nociceptors ending up in

hyperalgesia and allodynia (central sensitization) [11]. The administration of analgesics well after the impact of incisional and intraoperative tissue trauma would not be of benefit in preventing central sensitization [12].

The concept of PA uses antinociceptive techniques before injury. A number of studies involving different agents have been performed to assess its efficacy in reducing central sensitization in comparison to analgesics administered postoperatively. Yukawa et al., in their randomized prospective study in lumbar fusion surgeries, analyzed the efficacy of three pre-emptive analgesics combined with local anesthesia: continuous subcutaneous morphine, continuous epidural morphine, and diclofenac sodium [13].

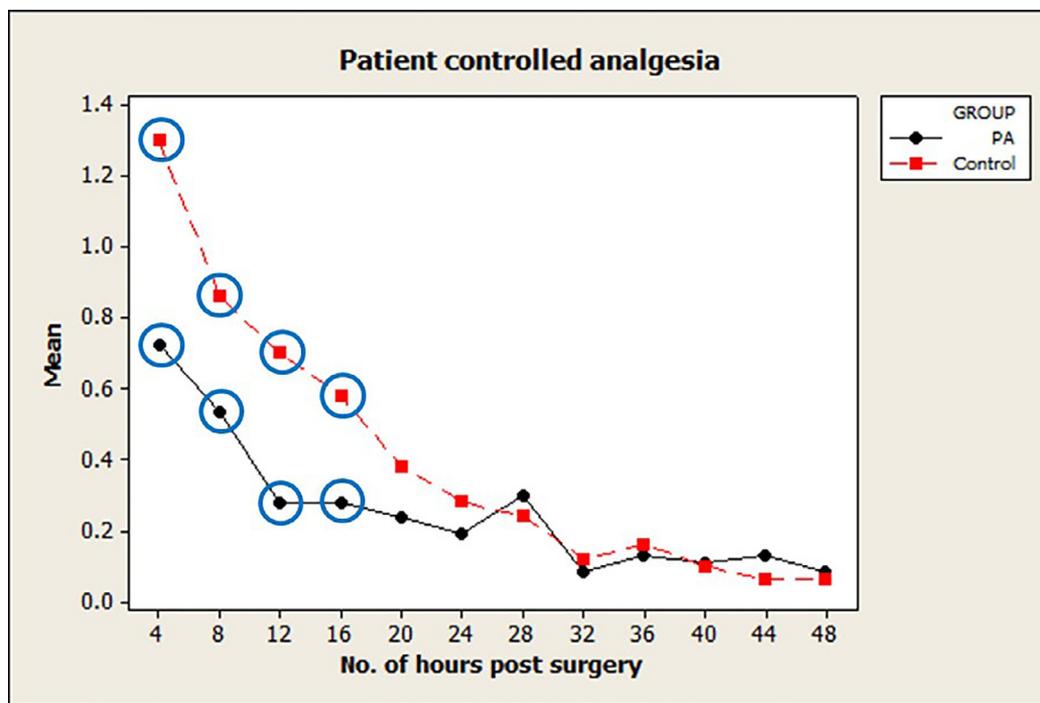


Fig. 4. Average PCA used at various time points after surgery. Blue-circled points indicate statistically significant differences between the groups at that particular time point. PCA, patient-controlled analgesia.

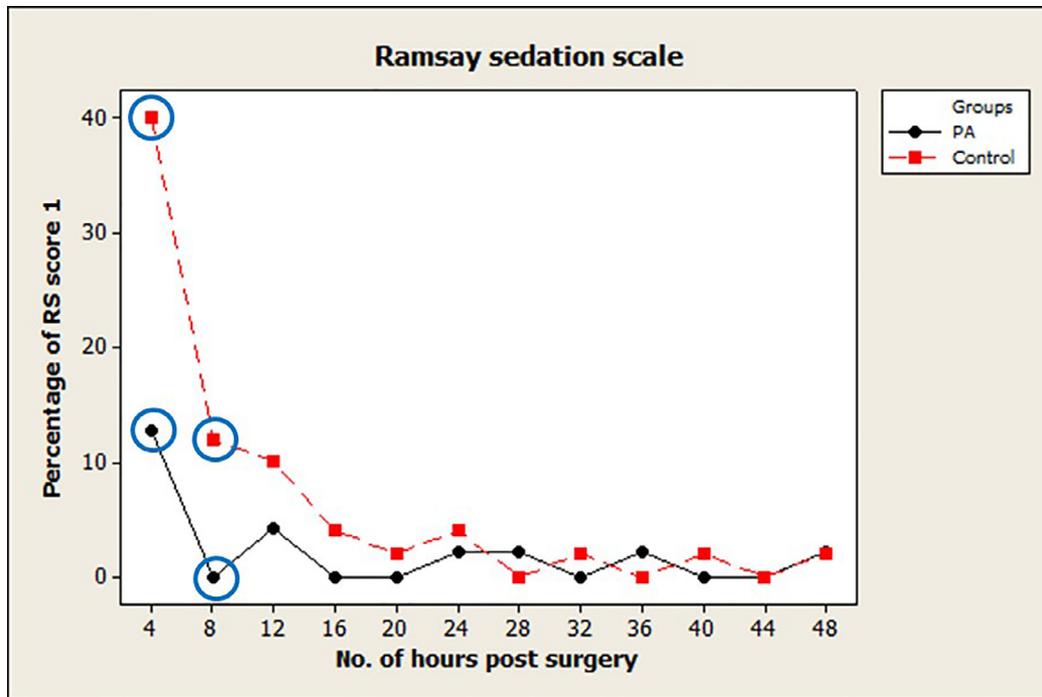


Fig. 5. Percentage of subjects who had level 1 meaning agitated state on Ramsay Sedation Scale (RSS) at various time points after surgery among the two study groups. Blue-circled points indicate statistically significant differences between the groups at that particular time point.

They concluded that only diclofenac sodium had a positive effect, but it lasted only for a short period. Similarly Sekar et al. demonstrated that a single caudal epidural injection of bupivacaine and tramadol before incision is effective as PA in lumbosacral spine surgeries [14]. Reynolds et al. found that adding continuous infusion of local anesthetics to a postoperative pain management protocol reduced opioid usage in lumbar fusion surgeries [15].

The common drawback of all these trials was that they used invasive procedures and required careful monitoring. Most of the recent studies in spine surgery have been around the usage of oral drugs pre-emptively, especially GABA analogues as standalone agents [16–18]. Perioperative pain is a combination of “primary hyperalgesia” (to peripheral sensitization of nociceptors) and “secondary hyperalgesia” (central sensitization). Since GABA analogues such as PR and gabapentin have an effect only on the latter, varied results were reported in these studies. Reuben et al. used a combination of

NSAIDs and PR and noted improvement in rest and ambulatory pain scores [19]. However, most of these studies did not have identical postoperative analgesic regimes and employed various agents as rescue drugs and some of them used bolus opioid dosing or baseline infusions, which may affect the measurement of pain scores accurately. In addition, none of the studies had aimed at inhibiting all the possible pathways of pain secondary to nociceptive, inflammatory, and neuro-pathic stimuli pre-emptively in spine surgery. This prospective double-blinded randomized clinical trial was aimed at assessing the analgesic efficacy of a combination of P 1 g, PR 75 mg, and K 20 mg as PA in spine surgery as compared with multimodal analgesia alone.

Rationale behind the selection of analgesic regime

Ketorolac is an efficient NSAID available both in oral and parenteral preparations including IV form, with linear pharmacokinetics. The only concern is its potential negative effects on spinal fusion rates. However, a meta-analysis in 2016 showed that administering K for ≤ 2 days or at dosages less than 120 mg/day does not affect fusion rates. We had opted safe limits of 20 mg orally before surgery and 30 mg IV every 8 hours after surgery for 48 hours [20]. NSAIDs block secretion of prostaglandins, thus reducing the inflammatory process and the hypersensitivity state.

Pregabalin blocks $\alpha_2\delta$ subunit of voltage-dependent calcium channels, which gets upregulated after surgical trauma, thus aiding in preventing central sensitization. Caused by its dose-independent absorption property, superior efficacy compared with Gabapentin, and linear

Table 3

Statistical comparison (chi-square test) of complications (categorical) between the two study groups

Complications	Pre-emptive analgesia (PA) N=47	Control (C) N=50	p value
Nausea	6 (12.8%)	16 (32%)	.024
Vomiting	5 (10.6%)	9 (18%)	.303
Dry mouth	38 (80.9%)	38 (76%)	.562
Difficulty in urination	18 (38.3%)	18 (36%)	.815
Constipation	10 (21.3%)	11 (22%)	.082

Statistically significant p values are highlighted in bold.

pharmacokinetic profile, a dose of 75 mg of PR was used [21]. In addition, administration of NSAIDs and GABA analogues is believed to have a synergistic action [22]. Paracetamol is a selective cyclooxygenase-2 inhibitor that exerts analgesic effect through activation of descending serotonergic pathways. Moreover, the inhibition of cyclooxygenase-3 in brain and the spinal cord has been described recently and is believed to be responsible, especially for its effects on pain relief [23]. Its pre-emptive effects have already been proved in various surgeries [24–26]. Caused by its safety and efficacy, a dose of 1 g was used. We hypothesized that, a combination of these drugs, which acts on peripheral tissues, central nervous system (CNS), and neural sites, would be able to block all possible stimuli, which lead to peripheral and central sensitization providing a balanced analgesia, and possibly be useful as an effective pre-emptive analgesic combination.

This combination reduced the postoperative pain scores in the intervention group as evident by the mean 48-hour pain scores. The subanalysis of 4 hourly intervals revealed better pain management with statistical significance during the first 12 hours following surgery. In addition, PA also allowed early ambulation as 95.7% in PA group was able to ambulate 50 m, when compared with only 30% in the C group on the first postoperative day. Also, collateral evidence of better pain management in the PA group was obtained from the fact that it resulted in lesser opioid consumption which was statistically significant up to 16 hours. The effective pain management in the PA group over C group correlates with the better functional scores of ODI, as significantly better results were noted in the PA group (30.8 ± 6) compared with (34.8 ± 6.3) at first month of follow-up ($p = .002$). In addition, the patients' satisfaction of surgical outcome measured by the NASS scale were better in PA group with 97.9% being extremely satisfactory compared with only 72% in the C group ($p = .002$). Most importantly, no additional side effects or complications were observed caused by this combination. Though we have assessed the efficacy of PA in this study, we have also used a good intraoperative and postoperative multimodal analgesic regime, which does play a vital role. Apart from the incisional and surgical stimuli, postoperative inflammation and ectopic neural activity after the surgery also plays an unequivocal stint in triggering acute pain and central sensitization. Preincisional administration of analgesics alone will not solve this complex inflammatory and pain cascade. Thus, the term preventive analgesia with extended duration of all perioperative measures taken, including PA, to reduce postoperative pain and chronic postsurgical pain, would be more appropriate than PA alone to manage postoperative pain.

The main strength of this study was that it was a prospective, randomized, double-blinded clinical trial in two groups with similar demographic and operative profiles. Strict adherence to pain management protocols with no deviations allowed us to quantitate pain in a foolproof manner. The PCA pump was used only in “on demand” mode

which enabled the accurate quantification of opioid usage. The selection of analgesic agents in the regime was based on sound knowledge of pharmacokinetic profile of the drugs, their action mechanism and molecular basis of central sensitization. Our study population was divided into two groups, one received a combination of orals drugs (P, K, and PR) and the other was C group. The efficacy of this three-drug combination alone was investigated. However, the efficacy of these drugs both individually, or in various two drug combinations, as pre-emptive analgesic agents were not analyzed and remains unknown. A larger study population would be required if the synergistic effect of the drugs in different combinations need to be assessed. Though this combination of drugs has been effective in reducing postoperative pain and did not involve any additional complications, the safety and cost effectiveness need to be analyzed in a separate study involving larger number of patients.

Conclusions

Our strategy of preoperative administration of balanced analgesia with the combination of P, K, and PR, each having different mechanisms of action resulted in less pain intensity, allowed better ambulation tolerance, improved functional outcomes, reduced requirement of opioids, and shorter duration of hospital stay without additional complications. Thus, this balanced analgesia, administered preoperatively, is proposed to address the complicated postsurgical pain after spine procedures.

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