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ORIGINAL RESEARCH

# Preemptive analgesia after lumbar spine surgery by pregabalin and celecoxib: a prospective study

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**Objective:** To evaluate the preemptive analgesic effect of combination pregabalin with celecoxib for lumbar spine surgery.

**Methods:** A prospective, randomized study was conducted among 60 lumbar spine surgery patients and divided into two groups. Postoperative pain relief was achieved with intravenous patient-controlled analgesia with morphine. The preemptive analgesia group received oral pregabalin (150 mg) and celecoxib (200 mg) 2 hrs before surgery, and the control group received a placebo. Pain was assessed by visual analogue scale (VAS). Side effects and morphine consumption were monitored until 48 hrs after surgery.

**Results:** VAS score at rest and during movement was statistically significantly lower in the preemptive analgesia group at most time points ($p<0.05$). Morphine consumption was significantly lower in the preemptive analgesia group compared with control group in the 24 first hours (29.03±4.38 mg vs 24.43±4.94) and 48 hrs (52.23±9.57 mg vs 44.20±10.21 mg), $p<0.05$. Hemodynamics, respiratory rate, and $SpO_2$ were similar for both groups. The sedation score was only statistically significant at H8 time point. The incidence of nausea/vomiting in the preemptive group did not statistically differ from the control group.

**Conclusion:** Preoperative administration of pregabalin combined with celecoxib had a good preemptive analgesia effect and reduced intravenous morphine consumption after lumbar spine surgery. Side effects were mild and transient.

**Keywords:** preemptive analgesia, pregabalin, celecoxib, lumbar spine surgery

## Introduction

Postoperative pain management is an ongoing challenge and involves risk of side effects and complications during recovery, especially for major surgeries or patients with co-existing diseases. A survey by Apfelbaum, J.L showed that 80% patients (n=250) experienced postoperative pain and that 86% of them had moderate, severe, or extreme pain.[1] Lumbar spine fusion surgeries result in significant pain after surgery due to a long skin incision, trauma from tissue retractors used to expand the surgical space, surgical implants, and long operative time. After spine surgery from 6 weeks to 6 months, Coronado et al, found that 12.9% of the patients continued to experience persistent back pain, 24.2% had pain that interfered with sleep or other activities, and 46.8% suffered from disability. This study also showed that good perioperative pain control reduces the rate of chronic pain after spine surgery.[2]

Multimodal analgesia with various pharmacologic agents was effective in providing adequate pain management, as well as improving functional outcome, early ambulation, early discharge, and reducing the incidence of chronic pain.[3,4] It is a

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key contributor to enhance recovery pathways.[5] Reducing postoperative pain improves the quality of life and satisfaction of patients.[6]

Preemptive analgesia with pregabalin 150–300 mg orally perioperatively has been shown to reduce pain intensity and narcotic consumption after spinal surgery.[7] The preemptive effect of combination pregabalin and celecoxib in spine fusion surgeries still needs further study. Our study aimed to evaluate the preemptive analgesic effect of combination pregabalin with celecoxib for lumbar spine surgery.

# Methods

## Materials and methods

This study was a prospective, randomized study to evaluate the efficacy of a preemptive analgesia for postoperative pain management.

Consolidated Standards of Reporting Trials (CONSORT) guidelines for reporting randomized trials (http://www.consort-statement.org/) were provided as a CONSORT flow diagram (Figure 1).

The study was carried out on elective spine fusion surgery patients in American Society of Anesthesiologists (ASA) physical status I–III from March to September 2017. The procedure and analgesic methods were explained to all patients, and informed consent was obtained before surgery and enrollment in this study. Exclusion criteria were: 1) history of lumbar spine surgery, 2) recent local anesthesia, 3) prior use of pregabalin or celecoxib, 4) allergy or other contraindication to pregabalin or celecoxib, 5) a comorbid alcohol, opioid, or other substance abuse disorder, 6) failure to adhere to the postoperative follow-up protocol, and 7) major surgical complications.

Patients enrolled study before surgery and were randomly divided into two groups by computer-based method. The preemptive analgesia group received 150 mg of pregabalin and 200 mg of celecoxib orally 2 hrs before induction with 30 mL of water, while the control group received placebo with the same amount of water.

All patients had an intravenous line inserted in the operating theatre and their vital signs monitored closely with a Nihon Kohden monitor. Induction of general anesthesia was achieved with propofol 2 mg/kg, rocuronium 1 mg/kg, and fentanyl 2 mcg/kg. Anesthesia was maintained with sevoflurane 2–4% and fentanyl

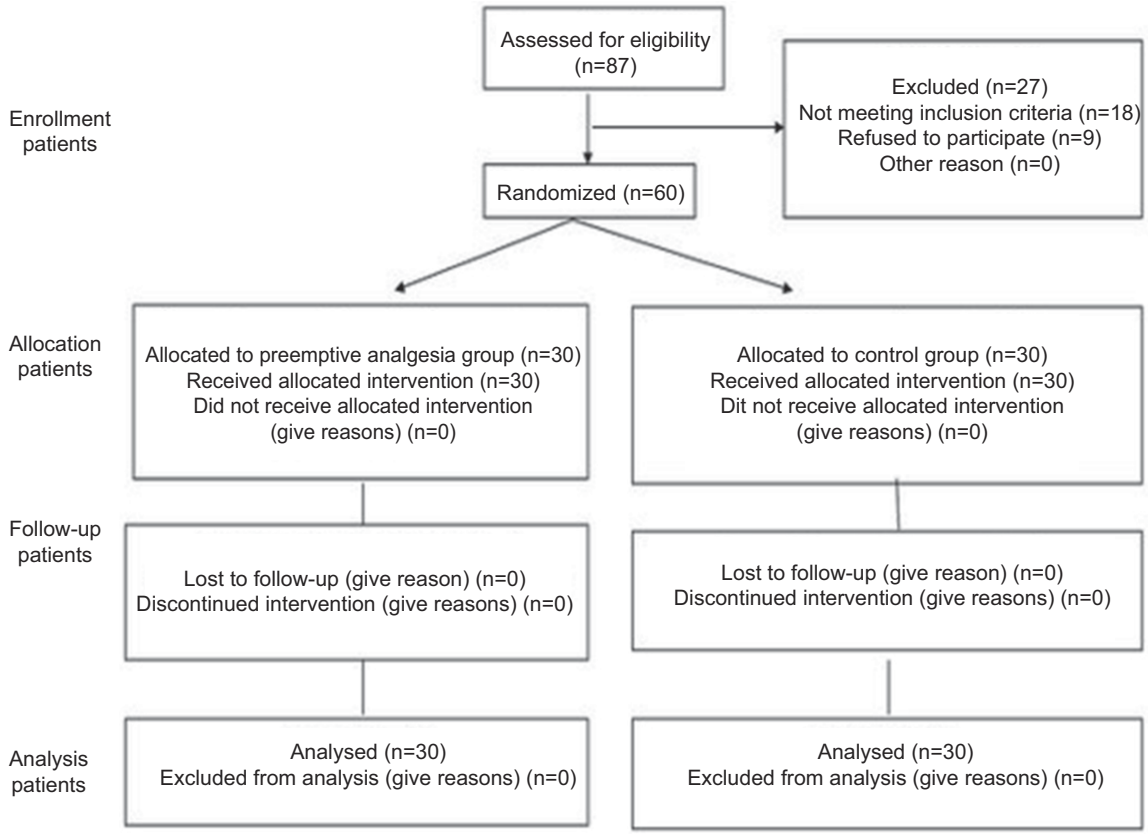


**Figure 1** CONSORT study participant flow diagram.

2 mcg/kg/hr. Surgery was performed in the prone position. Anesthetic agents were stopped at the end of surgery, and patients were returned to the supine position before reversing rocuronium with 0.03 mg/kg neostigmine and 0.02 mg/kg atropine.

All patients were extubated in the operating room before transferring to post-anesthesia care unit (PACU) with standard monitoring. In the PACU, postoperative pain was assessed by a visual analogue scale (VAS) of 0–10 (0: no pain, 1–3: mild pain, 4–6: moderate pain, 7–9: severe pain, 10: miserable pain). When VAS score over 4, patients were given morphine 2 mg every 3 mins until VAS score was lower than 4. At this time, intravenous patient-controlled analgesia (PCA) program was started with bolus dose 1 mg, lockout interval 10 mins, and a cumulative dose limited to 8 mg per 4 hrs. Rescue analgesia with fentanyl 0.5 mcg/kg was provided if a patient had three consecutive successful PCA attempts, but VAS score was still over 4.

VAS score was assessed at rest and during movement of lower legs. Postoperative pain scores, morphine consumption, and side effects were recorded until 48 hrs after surgery. Assessments were performed preoperatively and at 0.25, 0.5, 1, 4, 8, 16, 24, 36, and 48 hrs postoperatively (abbreviated to H0, H0.25, H0.5, H1, H4, H8, H16, H24, H36, and H48).

We used SPSS software (version 20.0, IBM, USA) to perform statistical analysis. Data were analyzed and results expressed by standard methods (mean ± standard deviation). Comparative data between two groups were analyzed by Student's *t*-test (to compare mean differences in patient demographics, VAS, morphine consumption, sedation score) and Chi-square (to evaluate the difference in nonunion rates). *p*-value <0.05 was considered as significant.

The study was approved by the Ethics Committee of 103 Military Hospital. The study was in line with the Declaration of Helsinki. Written informed consent has been provided to all participants after a thorough explanation of the purpose of this study.

# Results

## Patient characteristics

Table 1 shows the characteristics of the 60 patients completing the study. There were no differences in demographic characteristics, surgical duration, extubation time, or first analgesic requirement time.

## Morphine consumption

Table 2 shows the average morphine consumption at each of the postoperative time, beginning with the initial morphine titration prior to initiation of PCA.

Total 48-hr cumulative morphine consumption was different between the two groups.

## VAS scores

VAS score at rest was shown in Table 3 and Figure 2. At rest, the preemptive analgesia group had statistically significantly lower VAS at time points (H4, H8, H16, H24, H36, H48) than the control group.

VAS score at lower legs movement was shown in Table 4 and Figure 3. With movement, the preemptive analgesia group had statistically significantly lower VAS at time points (H0.5, H1, H4, H8, H16, H24, H36, H48) than the control group.

## Side effects

Hemodynamics, respiratory rate, and $SpO_2$ did not differ among the two treatment groups during the postoperative period (Table 5).

The level of sedation during the postoperative period was only statistically significant at H8 (Table 6).

**Table 1** Patients demographic and clinical data

| | Preemptive analgesia group (n=30) | Control group (n=30) | *P*-value |
|---|---|---|---|
| Age (years) | 44.93±10.26 | 48.23±11.88 | 0.254 |
| Gender (male/female) | 3/2 | 2/3 | |
| Height (cm) | 161.30±6.74 | 158.33±7.15 | 0.103 |
| Weight (kg) | 56.67±5.76 | 54.87±6.51 | 0.261 |
| Duration of surgery (mins) | 128.33±20.52 | 128.17±21.52 | 0.976 |
| Extubation time (minutes after completion of surgery) | 16.70±2.40 | 16.77±2.93 | 0.919 |
| First analgesic requirement time (minutes after extubation) | 25.67±8.73 | 27.73±8.40 | 0.355 |

**Notes:** Results: mean ± SD; analysis by Student's *t*-test.

**Table 2** Postoperative morphine consumption

| | Preemptive analgesia group (n=30) | Control group (n=30) | *P*-value |
|---|---|---|---|
| Morphine titration (mg) | 3.07±1.14 | 4.50±1.50 | 0.0001* |
| First 24 hrs | 24.43±4.94 | 29.03±4.38 | 0.0003* |
| Next 24 hrs | 20.77±4.56 | 23.83±4.739 | 0.0134* |
| 48 hrs | 44.20±10.21 | 52.23±9.57 | 0.0026* |

**Notes:** Results: mean ± SD; *$p<0.05$ analysis by Student's *t*-test.

**Table 3** VAS score at rest

| Time points | Preemptive analgesia group (n=30) | Control group (n=30) | *P*-value |
|---|---|---|---|
| H0 | 5.43±0.68 | 5.67±0.61 | 0.155 |
| H0.25 | 3.17±0.53 | 3.27±0.64 | 0.512 |
| H0.5 | 2.87±0.63 | 2.90±0.76 | 0.868 |
| H1 | 2.67±0.48 | 2.80±0.55 | 0.333 |
| H4 | 5.23±0.77 | 5.70±0.47 | 0.006* |
| H8 | 5.33±0.55 | 6.00±0.95 | 0.001* |
| H16 | 4.87±0.73 | 5.53±0.86 | 0.002* |
| H24 | 4.63±0.62 | 5.43±0.89 | 0.0002* |
| H36 | 4.27±0.69 | 4.77±1.10 | 0.039* |
| H48 | 4.33±0.96 | 4.90±0.86 | 0.018* |

**Notes:** Results: mean ± SD; *$p<0.05$ analysis by Student's *t*-test.

The incidence of nausea/vomiting in the preemptive group was not statistically different than the control group (1 vs 1).

## Discussion

This study revealed that the combination of pregabalin and celecoxib is effective adjuncts to pain management after lumbar spine fusion surgery. This combination produced a significant reduction in pain scores at rest and with legs movement, and reduced morphine consumption during the first 48 postoperative hours.

Severe pain after spine surgery occurrs in 20–40% and last 3–4 days, increasing the risk of opioid-related respiratory depression, impairing neurological function. Delayed ambulation increases the risk of venous thrombosis. Inadequate postoperative pain management is not only associated with a greater incidence of complications as well as a lengthened hospital stay, but also increases the risk that persistent chronic pain will develop. Thus, it is of great concern for patients, surgeons, and anesthesiologists, and really benefits from a multidisciplinary approach.[4,8,9] Many preoperative, intraoperative, and postoperative analgesia regimens have been proposed in order to achieve adequate pain management after spine surgery. In 2016, the American Pain Society made the recommendation that multimodal therapies be initiated in the preoperative period.[10]

There is a lack of evidence regarding optimal postoperative pain management after neurosurgery.[11] Effective multimodal methods for spine surgery may

The preemptive analgesia group (blue line) had statistically significant lower VAS at time point (H4, H8, H16, H24, H36, H48) than the control group (red line). *P* values are shown in Table 3.

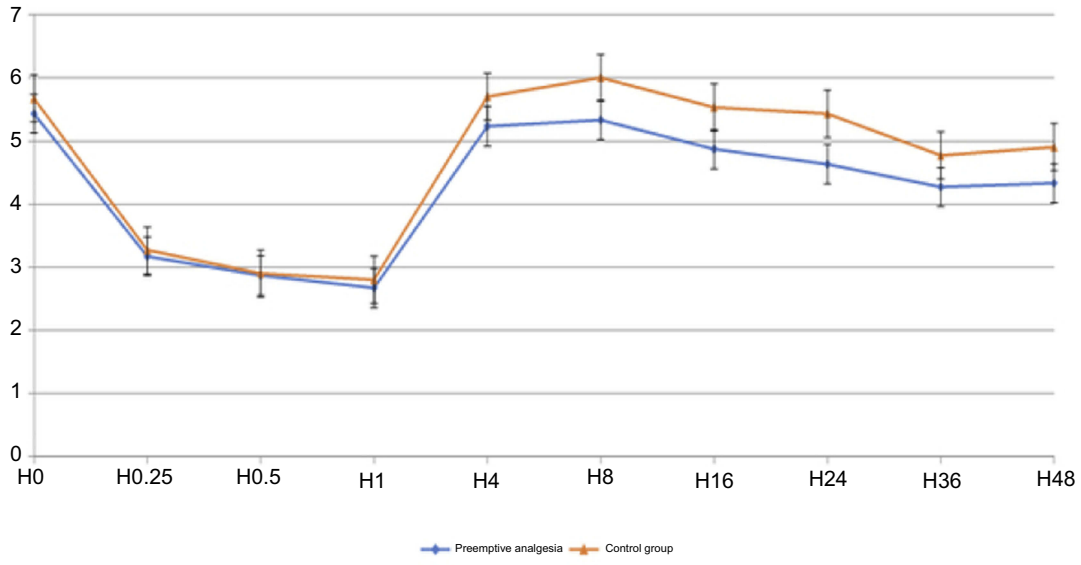


**Figure 2** VAS score at rest.

**Table 4** VAS score during lower legs movement

| Group / time | Preemptive analgesia group (n=30) | Control group (n=30) | *P*-value |
|---|---|---|---|
| H0 | 6.12±0.53 | 6.21±0.63 | 0.551 |
| H0.25 | 4.33±0.54 | 4.64±0.66 | 0.051 |
| H0.5 | 4.22±0.58 | 5.57±0.57 | <0.0001* |
| H1 | 4.17±0.45 | 5.46±0.52 | <0.0001* |
| H4 | 4.26±0.71 | 5.72±0.64 | <0.0001* |
| H8 | 3.93±0.62 | 5.67±0.53 | <0.0001* |
| H16 | 3.86±0.83 | 5.54±0.72 | <0.0001* |
| H24 | 4.04±0.67 | 5.42±0.66 | <0.0001* |
| H36 | 4.29±0.68 | 4.71±0.67 | 0.019* |
| H48 | 4.32±0.82 | 4.94±0.84 | 0.005* |

**Notes:** Results: mean ± SD; *$p$<0.05 analysis by Student's $t$-test.

include the use of preemptive analgesia with non-steroidal anti-inflammatory drugs (NSAIDs), gabapentinoids (gabapentin and pregabalin), acetaminophen, and local anesthesia.[12] Preemptive analgesia may improve patient satisfaction and quality of life by reducing postoperative pain narcotic consumption.[6,7,13] Preemptive analgesia is a term that refers to treatment that starts before surgery, and is intended to prevent central sensitization caused by surgical incisional injury and other inflammatory responses to surgery.[14] It has previously been found to be safe and effective after lumbar fusion surgery.[15] In addition to the oral medications used in our study, a single caudal epidural injection or parenterally administered medications may also be effective.[16]

Preoperative use of gabapentinoids (pregabalin, gabapentin) showed a reduction in postoperative pain and total morphine consumption following spine surgery.[17] After spine surgery, postoperative pain management with pregabalin was considered equivalent to gabapentin. Khurana, G. et al, showed that preoperative pregabalin administration is associated with less pain intensity and improved functional outcomes 3 months after lumbar discectomy, compared to gabapentin and placebo.[18] In this study, we used 150 mg pregabalin 2 hrs before surgery. It is similar to some recent studies.[19,20] In addition to these desirable effects, preoperative pregabalin also reduces intraoperative anesthetic agent requirements in patients who received general anesthesia by a total intravenous anesthesia technique. A reduction in pain at rest and during movement, and persistent neuropathic pain are additional benefits.[21] For patients receiving general anesthesia, its use also decreases fentanyl consumption. Furthermore, it improves the quality of life up to 3 months after surgery.[22]

A prospective randomized double-blind controlled study of single preoperative oral dose (120 mg) of Etoricoxib showed that reducing significantly post operative pain at rest and movement and improving sleep without any side effects in patient who had single-level discectomy.[23] A

The preemptive analgesia group (blue line) had statistically significant lower VAS at time point (H0.5, H1, H4, H8, H16, H24, H36, H48) than the control group (red line).
*P* values are shown in Table 4.

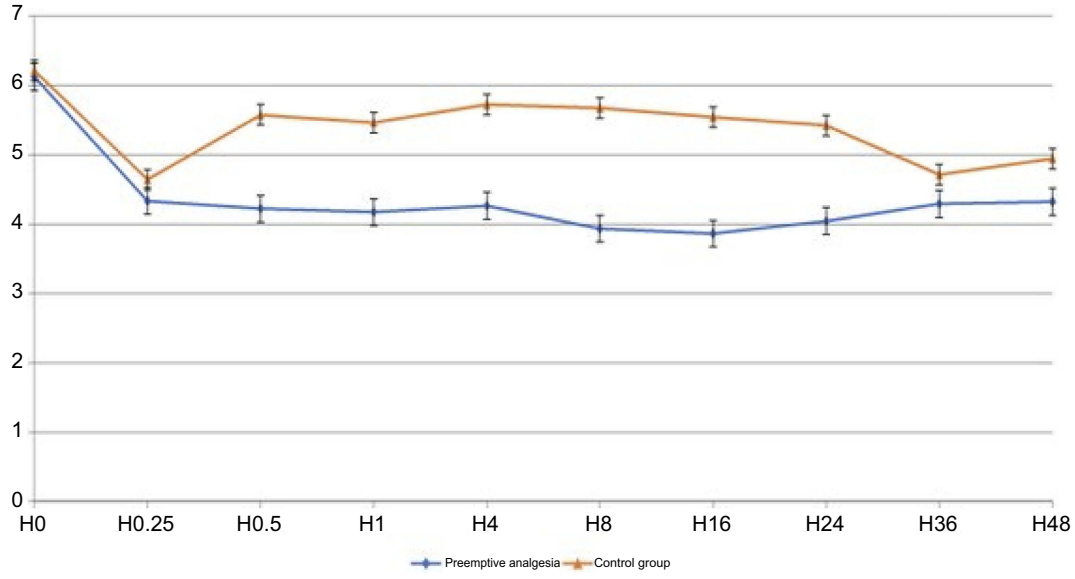


**Figure 3** VAS score during lower legs movement.

**Table 5** Postoperative heart rate, mean arterial blood pressure and respiratory rate

| Time after surgery | Preemptive analgesia group (n=30) | Control group (n=30) |
|---|---|---|
| Preoperative | | |
| HR | 83.60±5.11 | 83.87±5.07 |
| MAP | 85.17±4.95 | 85.62±3.08 |
| RR | 18.93±0.90 | 18.63±0.76 |
| $SpO_2$ | 96.83±1.31 | 97.33±1.18 |
| 0.25 hr | | |
| HR | 82.70±5.23 | 83.10±5.62 |
| MAP | 84.70±5.47 | 85.24±3.99 |
| R R | 17.93±0.74 | 18.00±0.78 |
| $SpO_2$ | 96.70±1.12 | 97.37±1.21 |
| 0.5 hr | | |
| HR | 81.40±5.05 | 82.70±5.65 |
| MAP | 84.60±6.07 | 84.83±3.44 |
| RR | 17.83±1.20 | 17.57±1.22 |
| $SpO_2$ | 96.60±1.16 | 96.63±0.99 |
| 1 hr | | |
| HR | 81.20±5.94 | 82.67±6.62 |
| MAP | 85.60±5.65 | 85.86±3.49 |
| RR | 18.40±0.62 | 18.17±0.83 |
| $SpO_2$ | 96.70±1.34 | 97.00±1.08 |
| 4 hrs | | |
| HR | 81.73±6.29 | 82.70±6.07 |
| MAP | 83.57±5.11 | 84.69±4.67 |
| RR | 18.30±0.87 | 18.43±0.85 |
| $SpO_2$ | 96.77±1.04 | 97.00±0.94 |
| 8 hrs | | |
| HR | 81.83±6.24 | 82.40±5.77 |
| MAP | 83.30±5.15 | 84.72±5.09 |
| RR | 17.90±1.06 | 18.20±0.99 |
| $SpO_2$ | 96.70±1.08 | 97.10±1.29 |
| 16 hrs | | |
| HR | 81.93±5.71 | 82.47±5.50 |
| MAP | 82.10±5.17 | 83.55±5.65 |
| RR | 18.70±0.70 | 18.70±0.83 |
| $SpO_2$ | 97.03±0.93 | 97.07±1.05 |
| 24 hrs | | |
| HR | 82.07±5.68 | 83.10±5.71 |
| MAP | 83.70±5.41 | 85.31±5.47 |
| RR | 19.10±0.71 | 19.17±0.87 |
| $SpO_2$ | 96.60±0.89 | 96.53±0.68 |
| 36 hrs | | |
| HR | 82.17±5.90 | 82.70±5.39 |
| MAP | 84.17±5.093 | 85.45±5.22 |
| RR | 18.53±0.86 | 18.63±0.85 |
| $SpO_2$ | 96.70±1.02 | 97.30±1.29 |
| 48 hrs | | |
| HR | 81.87±5.86 | 82.50±6.73 |
| MAP | 84.43±6.06 | 84.31±6.32 |
| RR | 19.30±0.95 | 18.93±0.98 |
| $SpO_2$ | 96.90±1.27 | 96.67±1.29 |

**Notes:** Data are presented as mean ± SD. $SpO_2$ (%): There were no statistical differences between two groups.

**Abbreviations:** HR (bpm), heart rate; MAP (mm Hg), mean arterial blood pressure; RR (breaths/min), respiratory rate.

**Table 6** Sedation score

| Time points | Preemptive analgesia group (n=30) | Control group (n=30) | *P*-value |
|---|---|---|---|
| H0.5 | 0.73±0.58 | 0.87±0.73 | 0.414 |
| H1 | 0.80±0.66 | 0.80±0.66 | 1.00 |
| H4 | 0.63±0.66 | 0.77±0.67 | 0.418 |
| H8 | 1.10±0.40 | 1.47±0.77 | 0.023* |
| H16 | 0.97±0.71 | 0.97±0.80 | 1.00 |
| H24 | 0.93±0.64 | 0.87±0.68 | 0.726 |
| H36 | 0.83±0.64 | 0.83±0.64 | 1.00 |
| H48 | 0.57±0.56 | 0.43±0.50 | 0.311 |

**Notes:** Results: mean ± SD; *$p<0.05$ analysis by Student's *t*-test.

meta-analysis by Gupta et al, showed that NSAIDs do not increase the incidence of adverse effects in the acute period after surgery.[24] This safety profile has also been demonstrated in spinal surgery.[25] In the management of acute postoperative pain, COX-2 inhibitors may impart certain clinical advantages over other NSAIDs due to their reduced effects on platelets.[26] A study in rabbits and meta-analyses in NSAIDs (ketorolac, diclofenac sodium, celecoxib, or rofecoxib) with normal-dose showed celecoxib was safe in the two weeks following spinal fusion.[27,28] In addition, the analgesic effect of celecoxib was exhibited quickly and sustained.[29] Although our results differ from those of Karst et al, (n=34: Celecoxib has no effect on postoperative pain scores after lumbar microdiscectomy),[30] we suspect the reason behind their finding of non-efficacy is related to their concomitant use of anti-inflammatory steroid and a smaller sample size. Recent studies also have shown loxoprofen sodium has superior and rapid effectiveness compared with celecoxib after spinal surgery.[31] Further studies may be needed to detect and more precisely measure undesired side effects after spinal surgery.

The preoperative administration of the combination of pregabalin and celecoxib improved analgesia. Li, Z., et al,

study also showed this combination during the perioperative period can reduce pain after surgery and the incidence of postoperative neuropathic pain.[32] The addition of celecoxib has been shown to be more effective than the use of gabapentinoids alone.[33] In our study, the pain score and morphine consumption of the preemptive analgesia group was significantly lower than the control group (Table 2). In the study of Fujita 2016 also found that administration of 150 mg of pregabalin 2 hrs before spine surgery decreased postoperative pain intensity and morphine consumption.[19] Another study using 150–300 mg orally perioperatively has been shown to reduce both pain and narcotic consumption and improve patient's satisfaction after spinal surgery.[7]

Many studies have demonstrated that multimodal therapy is superior to single agent methods for postoperative pain management. This is the result of action on different sites in the transmitting pain pathways.[34,35] Pinar, H.U., et al, study showed that preemptive analgesia with ibuprofen and pregabalin safely decreased postoperative pain and total morphine consumption in spine surgery.[36] Preemptive multimodal (celecoxib, pregabalin, extended-release oxycodone, and acetaminophen) analgesic regimen have been done with significantly lower VAS in the multimodal analgesia group at all time points within 7 postoperative days.[15]

## Limitations of study

This study aimed to provide the uses of available drug in the clinical context in the Vietnamese population. There were no pharmacokinetics and pharmacodynamics evaluations about combination treatment effect.

## Conclusions

Preoperative administration of pregabalin combined with celecoxib had a good preemptive analgesia effect and reduced intravenous morphine consumption after lumbar spine surgery. Side effects were mild and transient.

## Disclosure

The authors have no funding and conflicts of interest to disclose in this work.

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