The Analgesic Efficacy of Celecoxib, Pregabalin, and Their Combination for Spinal Fusion Surgery

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BACKGROUND: As optimal pain relief after surgery is difficult to achieve with the use of just one drug, many pain experts advocate the use of two or more classes of medications so as to reduce the side effects from any one drug. In this trial, we assessed the analgesic efficacy of administering perioperative celecoxib, pregabalin, or both after spinal fusion surgery.

METHODS: Eighty patients scheduled to undergo elective decompressive lumbar laminectomy with posterior spinal fusion were randomized to receive oral medications: placebo 1 h before and 12 h after surgery, celecoxib 400 mg 1 h before and celecoxib 200 mg 12 h after surgery, pregabalin 150 mg 1 h before and 12 h after surgery, or a pregabalin/celecoxib combination of 400 mg/150 mg 1 h before and 200 mg/150 mg 12 h after surgery.

RESULTS: The pregabalin/celecoxib group consumed the least patient-controlled morphine. Celecoxib alone or pregabalin alone also reduced opioid use compared with placebo, but not as much as when combined. The pregabalin/celecoxib combination was the most effective treatment for reducing pain both at rest and with movement over the 24-h postoperative time period. Hemodynamics and respiratory rate did not differ among the four treatment groups. Fewer patients experienced nausea in the pregabalin/celecoxib group compared with that in the placebo group.

CONCLUSION: The perioperative administration of the combination of celecoxib and pregabalin improved analgesia and caused fewer side effects, than either analgesic drug alone after spinal fusion surgery.

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Despite major improvements in our understanding of acute pain physiology over the past decade, approximately 80% of patients undergoing surgical procedures experience postoperative pain (1). Acute postoperative pain is a predictor of chronic pain syndromes as a result of surgery (2). Although opioids are an important component of postoperative pain management, they are associated with side effects (3), and so, the multimodal analgesic approach has been recommended for the management of acute postoperative pain (4,5).

Cyclooxygenase (COX)-2 specific nonsteroidal antiinflammatory drugs (NSAIDs) and α_2-δ subunit calcium channel ligands (gabapentin and pregabalin) are two mechanistically different types of analgesics that have demonstrated efficacy after a variety of surgical procedures (6,7). Gabapentin can enhance the analgesic effect of morphine in both animal models (8) and volunteers (9). Both α_2-δ ligands and NSAIDs can interact synergistically or additively to reverse hyperalgesia associated with peripheral inflammation (10). The combination of gabapentin and rofecoxib, a COX-2 selective NSAID, was shown to be superior to either single drug alone for postoperative pain management (7). Recently, both celecoxib (11,12) and gabapentin (13) have been demonstrated to have analgesic efficacy after spinal fusion surgery.

Although structurally similar to gabapentin, pregabalin has greater analgesic efficacy in rodent models of neuropathic pain (14,15), and exhibits linear pharmacokinetics across its therapeutic dose range with low intersubject variability (14,15). No study has evaluated the efficacy of administering pregabalin with or without a NSAID for postsurgical analgesia.

The hypothesis of this prospective, double-blind, randomized, placebo-controlled trial is that after spinal fusion surgery, a combination of celecoxib and pregabalin will demonstrate superior analgesic efficacy than either drug alone and cause fewer side effects.

METHODS

Patients

After IRB approval, written informed consent was obtained between July 2004 and October 2005 from

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patients scheduled to undergo elective decompressive lumbar laminectomy with instrumented posterior spinal fusion. Patients were eligible for participation if they were at least 18 years old, weighed more than 40 kg, and could operate a patient-controlled analgesia (PCA) device after presurgery instructions. Exclusion criteria included known allergy, sensitivity, or contraindications to sulfa, morphine, or any NSAID; renal insufficiency; a history of peptic ulcer; a history of alcohol or substance abuse; ongoing therapy with sustained-release opioids; seizure disorder; and pregnancy.

Study Design

Study medications were celecoxib 200 mg capsules, pregabalin 150 mg capsules, and placebo capsules that matched the celecoxib or pregabalin capsules in color and size. Patients were assigned to one of four treatment groups in a parallel double-blind randomized manner:

1. The placebo group received placebo capsules (2) 1 h before the anesthetic induction and 12 h after surgery (identically matched to study drugs).
2. The celecoxib group received celecoxib 400 mg and a placebo capsule 1 h before the anesthetic induction and celecoxib 200 mg and placebo capsules, 12 h after surgery.
3. The pregabalin group received pregabalin 150 mg and placebo capsules 1 h before the anesthetic induction and pregabalin 150 mg and placebo capsules, 12 h after surgery.
4. The pregabalin/celecoxib group received celecoxib 400 mg and pregabalin 150 mg 1 h before the anesthetic induction and celecoxib 200 mg and pregabalin 150 mg 12 h after surgery.

Before the start of the study, a medical center pharmacist prepared an allocation protocol which randomized these four drug treatments among 100 patients. Each new patient was assigned a consecutive study number. The study medications were administered at the medical center on the day of surgery by a nurse. The celecoxib dose of 400 mg 1 h before anesthetic induction and 200 mg 12 h after surgery was based on a previous study in which these doses and daily timing were administered after spinal fusion surgery (11). The pregabalin dose of 150 mg 1 h before anesthetic induction and 150 g 12 h after surgery was based on the product information sheet that recommends a maximum dose of 300 mg/day for pain syndromes (14,15).

Spinal fusion was performed at either one or two levels from L4 to S1 using similar carbon fiber cages with pedicle screw and plate instrumentation. All procedures were performed by use of a partial-thickness, posterior iliac-crest bone graft harvested through a lateral oblique incision just cephalad to the crest. Before surgery, both the laminectomy and iliac-crest harvest incision sites were infiltrated with 10 mL bupivacaine 0.25%.

Anesthesia was induced with propofol (2 mg/kg), morphine 0.3 mg/kg, and maintained with isoflurane 70% N_2O in O_2. Patients were connected to a PCA pump (Abbott PCA Plus, Abbott Park, Chicago, IL) on arrival in the postanesthesia care unit. Initial settings were as follows: incremental dose, 2 mg; lockout interval, 8 min; and 4-h limit, 40 mg. The incremental dose was increased to 2.5 mg, and the 4-h limit was increased to 50 mg if analgesia was inadequate after 1 h. If analgesia remained inadequate after an additional hour, the incremental dose was further increased to 3.0 mg, and the 4-h limit was increased to 60 mg.

No other analgesic supplement was given. However, any patient with severe pain that was not adequately controlled by PCA morphine could, by agreement with the principal investigator, be withdrawn from the study so that alternative analgesic dosing could be offered. Any patient in this category would not be replaced with a newly enrolled patient.

Outcomes

Outcome measures for the study were assessed by a research or acute pain service nurse who was blinded to patients' group assignments. Patients were asked to quantify their pain on a verbal rating scale between 0 and 10, with 0 representing no pain and 10 the worst imaginable pain. Pain assessments were made both at rest and with movement. Pain with movement was recorded after the patient completed a 90° logroll while in bed.

Intraoperative blood loss was determined by combining the blood collected in the suction canister as well as by estimating the blood present in the surgical sponges.

Sedation scores were measured on a numerical score of 1–5 (1, completely awake; 2, awake but drowsy; 3, asleep but responsive to verbal commands; 4, asleep but responsive to tactile stimulus; 5, asleep and not responsive to any stimulus).

Pain scores, sedation scores, heart rate, oxygen saturation (SpO_2), mean arterial blood pressure, respiratory rate, and morphine use were recorded by a study nurse 1 h after arrival in the postanesthesia care unit and subsequently at 4, 8, 12, 16, 20, and 24 h. Bed rest was enforced for the first 24 h postoperatively. The incidences of respiratory depression (respiratory rate < 8 breaths/min or $SpO_2 < 90\%$ without oxygen supplementation) and hypotension (mean arterial blood pressure $< 80\%$ of baseline) were recorded. Other symptoms were assessed, including nausea, vomiting, constipation, difficulty passing urine, difficulty concentrating, drowsiness or difficulty staying awake, feeling light-headed or dizzy, feeling confused, feelings of general fatigue or weakness, itchiness, dry mouth, and headache.

Table 1. Patient Demographics and Surgical Data

Treatment group	Placebo	Celecoxib	Pregabalin	Pregabalin/ Celecoxib
Number	20	20	20	20
Gender (M/F)	13/7	12/8	13/7	11/9
Age (yr)	43 ± 14	46 ± 18	42 ± 12	44 ± 16
Weight (kg)	79 ± 17	83 ± 17	82 ± 15	84 ± 17
Height (cm)	169 ± 14	172 ± 17	172 ± 15	171 ± 19
Duration of surgery (min)	181 ± 29	188 ± 34	186 ± 27	190 ± 36
Spinal levels fused				
1 level	12	11	10	11
2 levels	8	9	10	9
Blood loss (mL)	395 ± 55	388 ± 62	410 ± 75	403 ± 65

Data are presented as mean ± SD.

There were no statistical differences among groups.

Statistical Analysis

Sample size was estimated by analyzing previous data from studies comparing verbal rating-scale pain scores between patients receiving a COX-2 selective inhibitor and those receiving placebo after spinal fusion surgery (11,12). With 90% power, a mean difference of 2.9, a standard deviation of 1.0, and $\alpha = 0.05$, a power analysis of ANOVA testing on four independent means would require 16 patients per group. To be conservative, we planned to initially enroll 20 patients per group. At the end of the study, if there was a drop-out in any group due to a protocol violation, new patients would be enrolled and randomly assigned to treatment groups to increase the total to 20 per group. Morphine consumption, pain at rest, pain with movement, heart rate, mean arterial blood pressure, and respiratory rate were compared among the four groups over the postoperative time points, with repeated measures linear fixed model. If group differences were significant ($P < 0.05$), then treatment groups were compared at each time point with Tukey-Kramer *post hoc* testing. Sedation scores were compared among the four groups by repeated measures analysis of variance for assessment of time and treatment effects. If differences were found, a Bonferroni *post hoc* test was performed. Total PCA morphine use, duration of surgery, and intraoperative blood loss were compared among the four groups with ANOVA, and Tukey-B *post hoc* testing. Demographic data were analyzed using ANOVA or χ^2 test, as appropriate. The incidence of each side effect was compared with an omnibus χ^2 test, and if significant ($P < 0.05$), pairwise *post hoc* comparisons of each of the three drug groups to the placebo group were made with Fisher's exact test ($P < 0.0167$ for significance).

RESULTS

Patients

The clinical trial was conducted between July 2004 and October 2005. Seven patients were withdrawn from the study due to protocol violation: two patients had more than two levels of fusion, two patients used cadaver rather than autogenous iliac crest graft, and three patients were not administered their study drugs according to protocol. These subjects were replaced by new study patients to make the number of patients in each group = 20. No patient was withdrawn from the study because of severe pain requiring additional analgesic beyond the PCA protocol. Table 1 lists the characteristics of the 80 patients completing the clinical trial. There were no differences in demographic characteristics, surgical duration, or number of spinal levels fused.

Morphine Consumption

Figure 1 shows the average PCA-administered drug consumption at each of the postoperative time intervals up to 24 h. Repeated measure analysis demonstrated a difference among the four treatment groups ($F = 283.3$, $P < 0.001$), and also a group by time interaction ($F = 17.83$, $P < 0.001$). *Post hoc* analysis showed that the pregabalin/celecoxib group required the least amount of opioid. Celecoxib alone or pregabalin alone also reduced morphine consumption

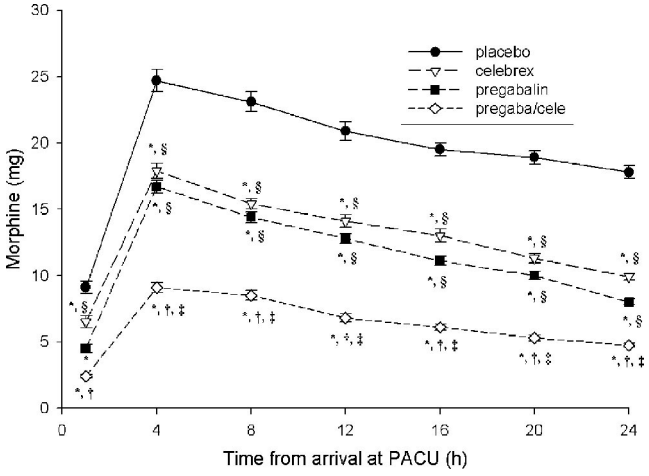

Figure 1. Morphine delivered by patient-controlled analgesia (PCA) after arrival in the postanesthesia care unit (PACU). The group receiving perioperative pregabalin/celecoxib consumed the least amount of morphine over this 24-h postoperative period. Data are shown as mean ± SEM; *different from placebo ($P < 0.01$); †different from celecoxib ($P < 0.01$); ‡different from pregabalin ($P < 0.01$); §different from pregabalin/celecoxib combination ($P < 0.01$).

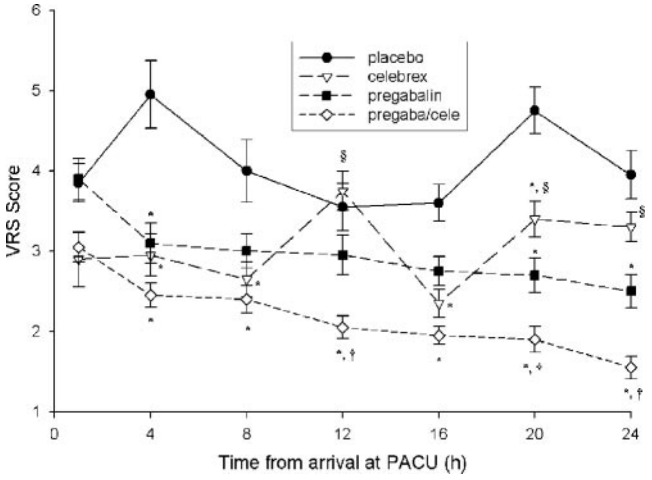

Figure 2. Verbal rating scale (VRS) pain at rest over the 24-h postoperative period after arrival at the postanesthesia care unit (PACU). The group receiving perioperative pregabalin/celecoxib experienced the least amount of pain. Data are shown as mean ± SEM; *different from placebo ($P < 0.05$); †different from celecoxib ($P < 0.05$); §different from pregabalin/celecoxib combination ($P < 0.05$).

compared with placebo, but not as much as when combined. Total 24-h cumulative morphine consumption was different among the four treatment groups ($F = 269.1$, $P < 0.001$), with each group statistically different from each other: placebo 134.0 ± 3.3 mg, celecoxib 88.0 ± 2.4 mg, pregabalin 77.4 ± 1.7 mg, pregabalin/celecoxib 43.0 ± 1.3 mg (mean ± SEM).

Pain Scores

Figures 2 and 3 display postoperative pain scores over time both at rest and with movement. At rest, pain scores differed among the four groups ($F = 28.9$, $P < 0.001$), and also group by time ($F = 5.64$, $P < 0.001$). Post hoc testing showed that the pregabalin/celecoxib treatment group consistently reduced pain intensity at rest throughout the postoperative period. With movement, pain scores differed by group ($F = 69.6$, $P < 0.001$), and group by time ($F = 2.25$, $P = 0.003$). *Post hoc* testing demonstrated that the pregabalin/celecoxib combination was the most effective treatment for reducing pain with movement.

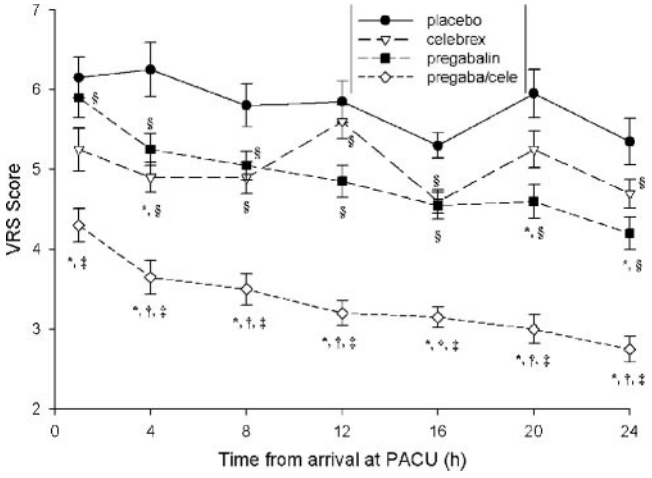

Figure 3. Verbal rating scale (VRS) pain with movement over the 24-h postoperative period after arrival at the postanesthesia care unit (PACU). The group receiving perioperative pregabalin/celecoxib experienced the least amount of pain. Data are shown as mean ± SEM; *different from placebo ($P < 0.05$); †different from celecoxib ($P < 0.05$); ‡different from pregabalin ($P < 0.05$); §different from pregabalin/celecoxib combination ($P < 0.05$).

Side Effects

Hemodynamics and respiratory rate did not differ among the four treatment groups during the postoperative period (Table 2). The level of sedation during the postoperative period was less in the celecoxib group and the pregabalin/celecoxib group when compared with that in the placebo or pregabalin group (Table 3). The overall incidence of side effects is summarized in Table 4. Fewer patients experienced nausea in the pregabalin/celecoxib group compared with that in the placebo group. Drowsiness was less frequent with pregabalin/celecoxib or celecoxib alone than placebo. There were fewer occurrences of excessive sedation in the pregabalin/celecoxib group than in the placebo group.

DISCUSSION

This study revealed that the perioperative administration of the combination of celecoxib and pregabalin resulted in improved analgesia compared with either analgesic drug alone after spinal fusion surgery. This combination produced a significant reduction in pain scores and in morphine use during the first 24 postoperative hours. The pregabalin/celecoxib combination was the only treatment that significantly reduced the incidence of nausea and excess sedation.

Pregabalin has demonstrated analgesic efficacy for neuropathic pain (14,15), fibromyalgia syndrome (16), and in a postdental pain model (17). Biochemical studies have identified the α_2-δ (Type 1) receptor as the primary binding site for both gabapentin and pregabalin (18,19). Binding of pregabalin to the α_2-δ subunit of voltage-gated calcium channels alters the kinetics and voltage dependence of calcium currents (20). By reducing calcium influx at nerve terminals, pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, calcitonin gene-related peptide, and substance P (21–23). This reduction in neurotransmitter release is presumed to account for pregabalin's analgesic actions. As demonstrated in the present study, pregabalin had no effect on arterial blood pressure or heart rate, which is consistent with animal experiments showing that intrathecal administration of the related compound gabapentin does not alter resting or acutely evoked autonomic outflow (24).

Although parenteral opioids are still considered the foundation for the treatment of moderate to severe pain (25), sufficient analgesia cannot be achieved without the risk of significant adverse events (26). The

Table 2. Postoperative Heart Rate, Mean Arterial Blood Pressure, and Respiratory Rate

Hours after surgery	Placebo (n = 20)	Celecoxib (n = 20)	Pregabalin (n = 20)	Pregabalin/ Celecoxib (n = 20)
Preoperative				
HR (bpm)	85 ± 16	81 ± 13	78 ± 21	79 ± 17
MAP (mm Hg)	110 ± 25	107 ± 21	113 ± 23	111 ± 21
RR (breaths/min)	15 ± 5	16 ± 6	16 ± 4	15 ± 5
1 h				
HR (bpm)	88 ± 19	84 ± 15	79 ± 23	81 ± 21
MAP (mm Hg)	107 ± 23	105 ± 25	110 ± 21	108 ± 23
RR (breaths/min)	14 ± 4	15 ± 3	13 ± 2	15 ± 3
4 h				
HR (bpm)	85 ± 17	81 ± 13	77 ± 22	78 ± 19
MAP (mm Hg)	110 ± 21	105 ± 21	112 ± 23	107 ± 21
RR (breaths/min)	12 ± 3	14 ± 3	15 ± 3	15 ± 2
8 h				
HR (bpm)	84 ± 18	82 ± 13	77 ± 21	80 ± 19
MAP (mm Hg)	111 ± 21	108 ± 23	113 ± 22	109 ± 21
RR (breaths/min)	11 ± 3	14 ± 3	16 ± 3	15 ± 4
12 h				
HR (bpm)	84 ± 16	83 ± 14	78 ± 23	79 ± 17
MAP (mm Hg)	109 ± 23	110 ± 21	111 ± 24	110 ± 19
RR (breaths/min)	12 ± 2	15 ± 3	14 ± 2	14 ± 2
16 h				
HR (bpm)	81 ± 16	79 ± 15	78 ± 21	79 ± 18
MAP (mm Hg)	108 ± 19	107 ± 21	111 ± 20	107 ± 18
RR (breaths/min)	11 ± 2	14 ± 3	14 ± 3	13 ± 4
20 h				
HR (bpm)	80 ± 13	81 ± 11	78 ± 16	78 ± 14
MAP (mm Hg)	89 ± 11	89 ± 13	90 ± 14	91 ± 15
RR (breaths/min)	10 ± 2	13 ± 2	13 ± 2	14 ± 3
24 h				
HR (bpm)	81 ± 14	78 ± 12	79 ± 11	80 ± 13
MAP (mm Hg)	88 ± 11	89 ± 11	87 ± 12	86 ± 14
RR (breaths/min)	10 ± 3	13 ± 3	14 ± 1	13 ± 1

Data are presented as mean ± SD.

HR = heart rate; MAP = mean arterial blood pressure; RR = respiratory rate.

There were no statistical differences among the four groups.

opioid doses necessary for complete relief of spontaneous pain at rest (tonic pain) have no effect on movement-associated (phasic) pain (27,28). Both COX-2 NSAIDs (29) and α_2-δ ligands (6) have been demonstrated to have analgesic efficacy during pain at rest and with movement. Although both analgesics alone are capable of reducing postoperative opioid use by 20–50%, it remains to be determined whether this can result in a significant reduction in opioid-related adverse events, thereby accelerating the rehabilitation process and reducing postoperative morbidity (30). Only one clinical study evaluating the perioperative analgesic effect of gabapentin (13) demonstrated a reduction in opioid-related side effects (vomiting and urinary retention). Meta-analysis studies of NSAIDs and COX-2 inhibitors highlight the importance of

Table 3. Postoperative Sedation Scores

Time period (h)	Placebo (n = 20)	Celecoxib (n = 20)	Pregabalin (n = 20)	Pregabalin/ Celecoxib (n = 20)
1	3.3 ± 0.5	3.1 ± 0.7	3.2 ± 0.9	3.0 ± 0.7
4	3.4 ± 0.7	2.4 ± 0.8*	3.3 ± 0.6	2.3 ± 0.7*
8	3.2 ± 0.6	2.3 ± 0.5*	3.1 ± 0.7	2.2 ± 0.6*
12	3.4 ± 1.1	2.4 ± 0.6*	3.4 ± 0.7	2.3 ± 0.7*
16	3.3 ± 0.9	2.3 ± 0.9*	3.4 ± 1.1	2.4 ± 0.8*
20	3.4 ± 0.9	2.4 ± 0.8*	3.3 ± 0.5	2.3 ± 0.7*
24	3.5 ± 0.7	2.5 ± 0.9*	3.4 ± 0.8	2.4 ± 0.6*

Data are presented as mean ± SD.

* $P < 0.05$ when compared with placebo and pregabalin.

Table 4. Incidence of Side Effects

Side effect	Placebo ($n = 20$)	Celecoxib ($n = 20$)	Pregabalin ($n = 20$)	Pregabalin/ Celecoxib ($n = 20$)	P
Nausea	10 (50)	5 (25)	6 (30)	2 (10)*	0.046
Vomiting	7 (35)	4 (20)	4 (20)	1 (5)	0.131
Constipation	2 (10)	1 (5)	1 (5)	2 (10)	0.868
Difficulty passing urine	4 (20)	2 (10)	2 (10)	0 (0)	0.217
Difficulty concentrating	5 (25)	3 (15)	2 (10)	1 (5)	0.297
Drowsiness	10 (50)	2 (10)*	5 (25)	2 (10)*	0.008
Feeling light-headed or dizzy	6 (30)	2 (10)	4 (25)	3 (15)	0.412
Feeling confused	3 (15)	1 (5)	2 (10)	1 (5)	0.632
Feeling of general fatigue	5 (25)	2 (10)	2 (10)	1 (5)	0.249
Itchiness	4 (20)	2 (10)	1 (10)	0 (0)	0.140
Dry mouth	5 (25)	2 (10)	2 (10)	0 (0)	0.094
Headache	5 (25)	1 (5)	2 (10)	1 (5)	0.146
Respiratory depression	3 (15)	0 (0)	0 (0)	0 (0)	0.025
Excessive sedation	7 (35)	1 (5)	5 (25)	0 (0)*	0.007
Hypoxemia	6 (30)	0 (0)	1 (5)	0 (0)	0.001
Hypotension	0 (0)	0 (0)	0 (0)	0 (0)	NA

Data inside the parentheses are percentages.

Respiratory depression, $\leq$8 breaths/min.

Excessive sedation, sedation score ≥ 4.

Hypoxemia, $Spo_2 < 90\%$.

Hypotension, mean arterial blood pressure $< 80\%$ of baseline.

P, χ^2 P value for full contingency table.

* Different from placebo ($P < 0.0167$).

using more than one nonopioid analgesic in the multimodal management of acute pain (31,32).

Without a full dose-response study and associated ED50s, it is not possible to infer that the combination of celecoxib and pregabalin has more than just an additive effect. Another study with rofecoxib and gabapentin perioperative administration for abdominal hysterectomy did not support synergy between a COX-2 inhibitor and a α_2-δ ligand (7). Another limitation of our study is that preoperative narcotic usage was not used as a covariant in analyzing postoperative opioid requirements.

In summary, the present study demonstrates that the perioperative administration of the pregabalin/celecoxib combination reduces both postoperative pain and opioid-related side effects more effectively than either drug alone. These results from spinal fusion surgery support the wider clinical use of this specific drug combination in the postsurgical setting.

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