

STUDII CLINICE

Pregabalin as an adjunct to a multimodal analgesic regimen to achieve opioid sparing in arthroscopic rotator cuff repair

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Abstract

Background: Arthroscopic rotator cuff repair of the shoulder is associated with a significant amount of pain, especially the first 36-48 postoperative hours [1]. Previous studies have demonstrated that an interscalene block is an effective analgesic technique for shoulder surgery [2-5]. However, even with the use of a long-acting local anesthetic, the analgesic effect of a single injection is limited to the first 6 to 12 hours [6]. Our objective was to determine the value of pregabalin as an opioid-sparing adjunct when used in combination with regional anesthesia techniques. **Methods:** We prospectively studied 50 patients undergoing primary arthroscopic rotator cuff repair under general anesthesia. Patients received a single-injection interscalene brachial plexus block with 30 mL of 0.5% ropivacaine, and oral celecoxib 200 mg and acetaminophen 500 mg. The patients were provided with a prescription for oral oxycodone 5 mg and acetaminophen 325 mg, 1-2 tablets every 4-6 hours as needed for postoperative supplemental analgesia. Patients were randomized to receive pregabalin (150 mg, twice daily, administered orally) or a placebo. The primary end point of the study was total opioid (oxycodone) consumption in the first 48 postoperative hours. Secondary end points included pain (evaluated with a 0-10 numeric rating scale anchored with 0 as “no pain” and 10 as “worst pain imaginable”), opioid- and pregabalin-related adverse effects, and duration of hospitalization. **Results:** Median opioid consumption during the first 48 postoperative hours was 51 mg (standard deviation [SD]: 40, interquartile range [IQR], 23-80 mg) in the pregabalin group and 64 mg (SD: 41, IQR: 35-90) in the placebo group ($p = 0.26$). Pain scores, adverse effects, and other secondary end points were similar between the groups. **Conclusions:** Pregabalin, at the dosage used in this study, resulted in a minimal or negligible decrease in opioid consumption when used as an adjunct to a multimodal, regional, analgesic regimen. The apparently lack of additive analgesia effect of pregabalin in this setting may be explained by the analgesic effects of the oral analgesics that were administered postoperatively. These nonsteroidal anti-inflammatory analgesics may have masked the pregabalin-induced analgesia by preventing postoperative central sensitization.

Keywords: rotator cuff repair, interscalene block, pregabalin, oxycodone, multimodal postoperative analgesia

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Introduction

Arthroscopic rotator cuff repair is a procedure associated with a significant amount of pain, especially the first 36-48 postoperative hours [1]. Previous studies

have demonstrated that interscalene blocks are an effective analgesic technique for shoulder surgery [2-5]. However, even with the use of a long-acting local anesthetic, the analgesic effect of a single injection is limited to the first 6 to 12 hours after a single injection [6].

Currently at Mayo Clinic Florida, a single-injection interscalene block is utilized to decrease postoperative oral and intravenous opioid consumption. The nerve block technique is intended both to improve analgesia

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and decrease opioid consumption. A decrease in total opioid consumption is considered beneficial because it reduces opioid side effects and the potential for respiratory depression from drug accumulation [7].

Gabapentin and pregabalin are α_2/δ voltage-dependent calcium channel blocking agents that appear to decrease central sensitization at the dorsal root ganglion and spinal interneuronal levels in both experimental and clinical models of neuropathic, inflammatory, and post-surgical pain [7-10]. Clinical studies have shown significant decreases in both opioid consumption and visual analog scales (VAS) of pain when these agents are used in the postoperative setting [7, 10]. Pregabalin is particularly appealing because of its high bioavailability, lack of drug interactions, and linear dose-response characteristics [11]. In this study, we evaluated the use of pregabalin as an opioid-sparing perioperative co-analgesic in the setting of an arthroscopic rotator cuff repair.

Materials and Methods

Subjects and study design

This study was approved by the Mayo Clinic and the Medical Education and Research Institute of Colorado Institutional Review Boards. Arthroscopic rotator cuff repair is a similar procedure at the Mayo Clinic (Jacksonville, Florida) and the Surgical Center at Premier (Colorado Springs, CO). All patients scheduled to undergo primary arthroscopic rotator cuff repair of the shoulder at the Mayo Clinic Florida and the Surgical Center in Colorado Springs were considered eligible and offered enrollment into the study. The minor variation between surgical techniques, if any, was dictated by the patient's pathology and not the geographic location of the procedure. Exclusion criteria were previous rotator cuff repair, patients currently taking pregabalin or gabapentin, contraindication to interscalene block, and patients with seizure disorders on antiepileptic medications. Written, informed consent was obtained from all patients.

Fifty patients were recruited to participate in the study, which was performed in a prospective, randomized, placebo-controlled, and double-blind fashion. Each patient was randomized to a control (placebo) or treatment (pregabalin) arm of the study. Randomization was computer-generated using the permuted blocks method to ensure equal numbers in the two groups. Block permutation randomization was used with stratification by site to ensure that the numbers of patients in each group were balanced appropriately. The patients were given an identification number during the randomization process, and the pharmacy kept a list so when an order was received to randomize patients, they were assigned to the next sequentially

available randomization group. The pharmacist pre-packed the bulk of required doses in advance to minimize turn around time once a patient was identified and randomized.

The surgeon and staff were blinded to the group assignment. Each patient underwent a standard preoperative preparation for the procedure. Before sedation, each patient received 200 mg of oral celecoxib and either 150 mg pregabalin or the placebo. The patients received titrated intravenous midazolam (1-4 mg) and fentanyl (50-200 mcg) for comfort during placement of the interscalene block. An anesthesiologist experienced in the interscalene block technique performed the block. An insulated 22-gauge, 2½-inch Braun needle was used, and 30 mL of 0.5% ropivacaine was administered after appropriate muscle stimulation was obtained. The intraoperative general anesthetic technique was chosen at the discretion of the supervising anesthesiologist.

Postoperative scheduled analgesia was provided with 200 mg oral celecoxib every 12 hours, and oral placebo or pregabalin 150 mg every 12 hours for a total of four doses. Supplemental analgesia was provided with oral oxycodone 5 mg and acetaminophen 325 mg, 1-2 tablets every 4-6 hours as needed. The total amount of opioid (oxycodone) required during the first 48 hours was the primary comparison variable in the two groups.

Data acquisition

Patient characteristics were archived at the time of randomization. Postoperative data were recorded every 6 hours, starting from the time of patient arrival in the postanesthesia care unit (time = 0 hours) until 48 hours postoperatively. The primary end point of the study was total opioid (oxycodone) consumption. Secondary end points were overall pain scores, pain score at each time point (6-hour intervals), and adverse events. Patients were assessed for pain intensity using a self-administered standard 0-10 visual analog score (VAS) scale (11-point NRS scale, whereby 0 = "no pain" and 10 = "worst pain imaginable"). VAS scores were obtained every 6 hours while patients were awake. Other side effects known to be attributable to pregabalin (sedation, dizziness, nausea) were recorded on a 4-point numerical scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) every 6 hours, and the frequency of side effects was compared between the two groups.

Sample size

In determining the sample size of the study, the aim was to have 90% power to detect a 25% reduction of opioid use relative to placebo. Power was calculated at greater than 80% if the final sample sizes in each group were 19 or greater. The goal was to recruit 25 patients scheduled for arthroscopic rotator cuff repair per group (placebo and pregabalin). Within each group

of 25 patients, 10 were to be recruited from Mayo Clinic Florida and 15 from Surgical Center in Colorado, for totals of 20 and 30 patients, respectively. Mayo Clinic recruited 18 patients; however, three did not meet inclusion criteria and could not be included, and three did not complete the treatment as assigned. The Surgical Center in Colorado recruited 32 patients, but three did not complete the treatment as assigned. This resulted in a combined total of 47 patients recruited, of which 41 completed the treatment (19/24 in the placebo group and 22/23 in the pregabalin group completed treatment).

Statistical analysis

Numerical variables were summarized with the sample mean, standard deviation (SD), and interquartile range (IQR) and were compared between patients receiving pregabalin and patients receiving a placebo using a Wilcoxon rank sum test. Categorical variables were summarized with number and percent

of patients, and were compared between patients those receiving pregabalin and those receiving a placebo using Fisher’s exact test. Statistical significance was determined at the 5% level.

Results

Table 1 shows patient demographic data, hospitalization information, and opioid (oxycodone) consumption according to treatment group. Total opioid consumption in patients that completed treatment over the first 48 postoperative hours in the pregabalin group was a mean of 51 mg (SD: 40, IQR: 23-80) and 64 mg (SD: 41, IQR: 35-90) in the placebo group (p = 0.26) (Fig. 1). The acetaminophen was combined with the oxycodone in a single tablet and the ratio of narcotic to acetaminophen was a fixed ratio for both groups. Table 2 shows the VAS pain scores. Table 3 shows the nausea, dizziness, and drowsiness scores, respectively.

Table 1. Patient demographics, hospitalization information, and opioid consumption

Variable	Pregabalin (N = 23)	Placebo (N = 24)	P-value
Age at surgery	63 ± 11 (51-73)	60 ± 10 (54-70)	0.37
Gender			0.74
Male	17 (74%)	19 (79%)	
Female	6 (26%)	5 (21%)	
BMI	29 ± 5 (25-32)	31 ± 6 (25-36)	0.16
Operative site			0.55
Left shoulder	7 (30%)	10 (42%)	
Right shoulder	16 (70%)	14 (58%)	
Patient completed treatment as assigned	22 (96%)	19 (79%)	0.19
Time from surgery to discharge (hours)	3.5 ± 1.4 (2.4-4.4)	4.3 ± 7.1 (2.3-3.4)	0.21
Time from surgery to arrival in PACU (hours)	1.1 ± 0.5 (0.7-1.6)	1.1 ± 0.6 (0.8-1.3)	0.97
Total opioid consumption (mg)*	51 ± 40 (23-80)	64 ± 42 (35-90)	0.26

Numerical variables were summarized as sample mean ± SD (IQR). P values result from Fisher’s exact test or Wilcoxon rank sum test

* Represents patients that completed treatment

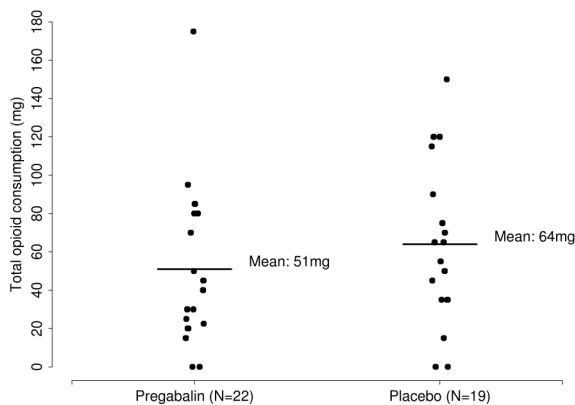


Fig. 1. Total opioid consumption in patients that completed treatment

Table 2. Visual analog scales pain scores overall and at each time point after surgery

Time after surgery	VAS pain score (0-10)		
	Pregabalin (N = 23)	Placebo (N = 24)	P-value
0 hours	0.1 ± 0.6 (0-0)	0 ± 0 (0-0)	0.37
6 hours	1 ± 2.1 (0-0)	0.7 ± 1.9 (0-0)	0.72
12 hours	1.1 ± 2.1 (0-1)	2.4 ± 3.5 (0-6)	0.41
18 hours	2.9 ± 2.9 (0-5)	3.7 ± 2.9 (1-5)	0.35
24 hours	3.1 ± 2.4 (1-5)	3.9 ± 2.7 (1.5-6)	0.34
30 hours	2.5 ± 2.2 (1-4)	3.3 ± 2.5 (1-5)	0.35
36 hours	2.8 ± 2.6 (1-3)	3.3 ± 2.2 (1-5)	0.38
42 hours	1.6 ± 2.1 (0-3)	2.9 ± 2.4 (1-5)	0.063
48 hours	2.7 ± 2.1 (1-4)	2.2 ± 2.3 (1-3)	0.33
Overall	2.0 ± 2.4 (0-4)	2.5 ± 2.7 (0-5)	0.10

Data are summarized as mean ± SD (IQR). P values result from Wilcoxon rank sum test

Table 3. Nausea, dizziness and drowsiness after surgery

Time after surgery	Nausea			Dizziness			Drowsiness		
	Pregabalin (N = 23)	Placebo (N = 24)	P-value	Pregabalin (N = 23)	Placebo (N = 24)	P-value	Pregabalin (N = 23)	Placebo (N = 24)	P-value
0 hours	0 (0%)	0 (0%)	NA	12 (52%)	15 (75%)	0.20	10 (43%)	5 (25%)	0.15
6 hours	4 (19%)	2 (10%)	0.43	11 (50%)	8 (42%)	0.67	13 (59%)	6 (30%)	0.043
12 hours	3 (14%)	1 (5%)	0.37	13 (59%)	8 (42%)	0.41	11 (50%)	3 (16%)	0.016
18 hours	3 (14%)	2 (11%)	0.72	9 (43%)	4 (24%)	0.21	11 (52%)	1 (6%)	0.002
24 hours	6 (29%)	4 (20%)	0.38	6 (30%)	7 (35%)	0.87	10 (50%)	8 (40%)	0.19
30 hours	3 (14%)	2 (11%)	0.74	7 (33%)	5 (26%)	0.48	9 (43%)	3 (16%)	0.074
36 hours	2 (10%)	1 (5%)	0.64	5 (24%)	5 (26%)	0.97	7 (33%)	2 (11%)	0.074
42 hours	2 (11%)	1 (6%)	0.63	3 (16%)	3 (17%)	0.98	6 (32%)	3 (17%)	0.28
48 hours	1 (5%)	2 (11%)	0.46	3 (14%)	5 (28%)	0.40	6 (27%)	5 (28%)	0.84
Overall	9 (39%)	6 (30%)	0.32	19 (83%)	18 (90%)	0.49	19 (83%)	12 (60%)	0.006

Data are summarized as number (%) experiencing any nausea, dizziness or drowsiness (a score of 1 or higher). P values result from Wilcoxon rank sum test using scores on 0 to 3 scale

Discussion

Of the 47 total patients, 41 (87%) completed their treatment as assigned. When considering only these patients, the evidence is insufficient for an opioid-sparing effect of pregabalin when added to a multimodal analgesic regimen of peripheral nerve blocks, celecoxib, and acetaminophen. This result contrasts with observations from other perioperative studies that used both pregabalin and gabapentin [12-19]. However, other researchers had findings similar to ours when studying the perioperative use of gabapentin in conjunction with an interscalene block during arthroscopic shoulder surgery [20].

Perioperative pain is thought to involve primary hyperalgesia (peripheral nociceptor sensitization) and secondary hyperalgesia (central sensitization) [21, 22]. Pregabalin and gabapentin appear to have no effect on primary nociception in animal and human models. However, they may mitigate the hyperexcitability of dorsal horn neurons that is induced by tissue damage [23-29], and thereby decrease secondary hyperalgesia.

Pregabalin may have clinically significant additive analgesic effects for patients with incomplete or no neural block, in whom antagonism of central sensitization would mitigate the hyperalgesic consequences of incoming nociception [30]. Additionally, pregabalin may have a role during the transition from the perioperative regimen of local anesthetic agents and nerve block to a therapeutic program of oral analgesics. Interscalene blocks have been associated with a 100% incidence of a temporary block of the phrenic nerve [31] associated with mild respiratory dysfunction [32]. Despite the respiratory side effect, interscalene blocks are associated with decreased narcotic consumption with subsequent decrease in nausea, vomiting and

overnight hospital admissions [33]. This period of transition may be of major importance because after the effects of perioperative analgesia abate, the surgical wound may reinitiate the central sensitization process [28], hinder rehabilitation, and possibly contribute to chronic postoperative pain [34-38]. Older patients who are more prone to the adverse effects of opioids may be well served by a transition phase that uses an aggressive, nonopioid oral analgesic approach that includes pregabalin [35, 36]. Further studies should investigate the timing and efficacy of pregabalin and other agents during this transition phase.

One potential limitation of our study is the dosage of oral pregabalin (150 mg, twice daily), which may have been inadequate to effect a difference in opioid consumption. However, animal studies have shown an analgesic potency of pregabalin that is two- to four-fold greater than gabapentin [39], and the dosage used in this study, therefore, should have been equipotent to dosages of gabapentin with known preoperative analgesia effectiveness. Another limitation of the study was the sample size. The study was powered to detect relatively large (25%) differences between groups; however, even smaller differences may still be clinically significant by decreasing the potential for respiratory depression induced by opioids, especially in the elderly.

In summary, the addition of pregabalin to a multimodal regimen interscalene brachial plexus block and celecoxib resulted in minimal decrease in opioid use during the first 48 postoperative hours after arthroscopic rotator cuff repair. Further studies are warranted to examine the benefit of pregabalin during the transition phase from perineural analgesia to oral analgesics with the goal of maintaining the prevention of central sensitization and secondary hyperalgesia.

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Pregabalin, un adjuvant al regimului analgezic multimodal în scopul reducerii necesarului de opioid în refacerea artroscopică a coafei rotatorilor

Rezumat

Scop și obiective. Refacerea artroscopică a coafei rotatorilor articulației umărului este asociată cu durere semnificativă, în special în primele 36-48 de ore postoperator. Studii anterioare au demonstrat că blocul interscalenic este o tehnică analgezică eficientă pentru chirurgia umărului. Totuși, chiar și cu utilizarea

anestezicelor locale cu durată de acțiune lungă, efectul analgezic al unei singure injecții este limitat la primele 6-12 ore. Obiectivul nostru a fost să determinăm valoarea pregabalinului ca adjuvant care reduce necesarul de opioid atunci când este utilizat în combinație cu tehnicile de anestezie regională.

Metode. Am studiat prospectiv 50 de pacienți supuși operației primare de refacere artroscopică a coafei rotatorilor sub anestezie generală. Pacienților li s-a efectuat blocarea plexului brahial pe cale interscalenică printr-o singură injecție cu 30 mL ropivacaină 0,5% și, pe cale orală, 200 mg celecoxib și 500 mg acetaminofen. Pentru suplimentarea analgeziei postoperatorii, pacienților li s-au prescris 5 mg oxycodon și 325 mg acetaminofen, 1-2 tablete la 4-6 ore, în caz de nevoie. Pacienții au fost randomizați să primească fie pregabalin (150 mg de 2 ori pe zi p.o), fie placebo. Obiectivul primar al studiului a fost consumul total de opioid (oxycodon) din primele 48 de ore postoperator. Obiectivele secundare au inclus durerea (evaluată cu o scală numerică 0-10, în care 0 înseamnă „fără durere” și 10 „cea mai mare durere cu putință”), efectele adverse ale opioidului și pregabalinului și durata spitalizării.

Rezultate. Consumul mediu de opioid din cursul primelor 24 de ore postoperator a fost de 51 mg (deviație standard [DS] 40, amplitudine interquartilică 23-80 mg) în grupul pregabalin și 64 mg (DS 41, amplitudine interquartilică 35-90) în grupul placebo ($p = 0,26$). Scorurile de durere, efectele adverse și alte obiective secundare au fost similare în cele două grupuri.

Concluzie. Pregabalinul, în doza utilizată în acest studiu, a produs o reducere minimă sau neglijabilă a consumului de opioid atunci când a fost utilizat ca adjuvant la un regim analgezic multimodal, regional. Lipsa aparentă de efect analgezic suplimentar al pregabalinului poate fi explicată prin efectele analgezice ale analgeticelor administrate postoperator. Aceste analgetice nesteroidiene antiinflamatorii se pare că au mascat analgezia indusă de pregabalin prin prevenirea sensibilizării centrale postoperatorii.

Cuvinte cheie: refacerea coafei rotatorilor, bloc interscalenic, pregabalin, oxycodon, analgezie postoperatorie multimodală