Journal of Anesthesia & Clinical Research
ISSN: 2155-6148

George et al., J Anesth Clin Res 2014, 5:2
DOI: 10.4172/2155-6148.1000383

Research Article Open Access

Pregabalin Confers No Added Benefit to a Non-steroid Anti-inflammatory Drug and Acetaminophen Regimen in Outpatient Breast Cancer Surgery: A Randomized Controlled Trial

Ronald B. George[1,2*], **Dolores M. McKeen**[2], **Colin Boyd J**[1,2] **and Geoff A. Porter**[1,3]

[1]*IWK Health Centre, Dalhousie University, Canada*

[2]*Department of Women's & Obstetric Anesthesia, Dalhousie University, Canada*

[3]*Department of Surgery, Dalhousie University, Canada*

[*]**Corresponding author:** Ronald B. George, IWK Health Centre, Department of Women's & Obstetric Anesthesia, 5850/5980 University Avenue, P.O. Box 9700, Halifax, NS, B3K 6R8, Canada, B3K 6R8, Tel: (902) 470-6627; Fax: (902) 470-6626; E-mail: rbgeorge@dal.ca

Rec date: Jan 20, 2014; **Acc date:** Feb 17, 2014; **Pub date:** Feb 19, 2014

Abstract

Objectives: Multimodal analgesia may reduce both postoperative pain and the risk of adverse effects associated with opioid-use. Pregabalin has emerged as a potential perioperative analgesic with an improved pharmacokinetic profile. However, data regarding its analgesic efficacy and optimal dose following breast surgeries are conflicting. This study was designed to determine if perioperative treatment with pregabalin could reduce pain scores and oxycodone consumption following elective surgery for possible breast cancer.

Methods: Fifty-nine women undergoing elective breast cancer surgery (mastectomies and lumpectomies) were recruited for this study. Patients were randomized to pregabalin (150 mg) or placebo, both administered prior to surgery and 12 hours postoperatively. Pain and nausea intensity were measured using an 11-point numerical rating scale 2, 24, and 48 h postoperatively. Acetaminophen, naprosyn, and oxycodone were available in both groups postoperatively.

Results: At 24 hours post-op there were no differences in average pain intensity at rest (placebo 1.3 vs pregabalin 0.6; difference=0.65, 95% CI: -0.09 to 1.39, p=0.08), pain following movement (placebo 1.3 vs P150 1.2; difference=0.14, 95% CI: -0.59 to 0.88, p=0.70, or average oxycodone tablet consumption (placebo 0.7 vs P150 1.0, difference=0.26, 95% CI: -1.86 to 1.35, p=0.72) postoperatively.

Conclusion: Pregabalin given preoperatively and 12 h postoperatively did not improve pain or oxycodone consumption 24 h following breast surgery. Further research regarding the appropriate dose and timing of pregabalin administration surrounding breast surgery is required.

Keywords: Pregabalin; Breast cancer surgery; Pain; Nausea; Vomiting; Opioids; Oxycodone

Introduction

Breast cancer is the most commonly diagnosed non-skin cancer in women with the majority of such women requiring breast surgery. Acute and chronic postoperative pain is prevalent after breast cancer surgery [1-4]. Acute pain following surgery limits the function of patients in the post-operative period and is a risk factor for development of chronic pain [5,6]. Opioids continue to have a major role in pain management despite contributing to increased in-hospital morbidity and costs and pose a significant risk to patients for opioid-related adverse effects including post-operative nausea and vomiting, sedation, sleep disturbances, urinary retention and respiratory depression [7-9]. Management of postoperative pain and reduction of opioid-related adverse effects can be achieved through multimodal, balanced analgesia [10].

Recently, gabapentin and pregabalin have emerged as potentially important members of a multimodal perioperative analgesia regimen [11]. Pregabalin, a calcium channel blocker, has been shown to improve pain management and reduce opioid consumption in the postoperative period [12]. Upon binding to calcium channels, gabapentin and pregabalin reduce the release of excitatory neurotransmitters to inhibit central sensitization and potentially reducing hyperalgesia [13]. However, reports on the efficacy and adverse effect profile of pregabalin have been conflicting [14-17]. Currently, evidence of pregabalin use for improved analgesia after breast surgery is limited to two reports [14,17], with only one of those reports relating specifically to breast cancer [17]. Among those studies, pregabalin has shown varying effectiveness at improving analgesia and decreasing opioid consumption while limiting side effects. There are also discrepancies among those studies in the total dose of pregabalin and the timing of administration. Accordingly, the optimal timing and dose of pregabalin administration for pain management, reducing opioid consumption, and patient well-being are unclear. The current study uses a dosage and administration structure relatable to the breast cancer report and is consistent with more established research for procedures such as hysterectomy and cholecystecomy [18-21].

There is a need for clinical research to further refine the evidence supporting the use of pregabalin in the perioperative pain management setting and specifically women undergoing breast cancer

surgery. In particular, as evidence suggests that adverse events with pregabalin are dose dependent [22], we sought to determine if a relatively low dose of pregabalin can protect against side effects while remaining an effective analgesic. Accordingly, this study was designed to determine if the addition of perioperative pregabalin to a standard postoperative analgesia regimen can reduce pain and oxycodone consumption compared to placebo in women undergoing surgery for suspected breast cancer with general anesthesia. We hypothesized that pregabalin would decrease postoperative pain as measured by postoperative rating scores and postoperative opioid consumption in the first 24 hours following breast cancer surgery compared to placebo.

Methods

Our main objective was to determine if perioperative pregabalin could reduce pain at 24 h postoperatively. Patients scheduled to undergo outpatient elective breast cancer surgery at the IWK Health Centre were recruited for participation. Recruitment was limited to lumpectomies and simple mastectomies concurrently with and without concomitant sentinel lymph node biopsy. To be eligible patients had to have an ASA status of I or II, be less than 65 years old, and speak English. Exclusion criteria were extensive surgery that included axillary node dissection or bilateral procedures, known or suspected allergies or contraindications to pregabalin or any standardized medications, abnormal body mass (BMI<20 kg/m2 or ≥45 kg/m2), history of a seizure disorder, pregnancy, current therapy with any gabapentanoids or opioids, or renal dysfunction (CrCl less than 60 mL/min). Patients were randomized into either a control (placebo) or pregabalin 150 mg (P150) group, and randomization was stratified on mastectomies and lumpectomies. A screening log was maintained to document the number of patients approached for study enrollment and reasons for refusal based on the suggested format given in the CONSORT Statement [23]. Study protocol was approved by the IWK Health Centre Research Ethics Board (REB# 1005405, Approved June 4th, 2008) and registered on ClinicalTrials.gov (NCT00785382). All participants provided informed written consent prior to participation.

Study Protocol

Patients were enrolled into the study by research personnel after an introduction by a member of their care team. Consented patients were randomized to a treatment arm by opening a sealed opaque envelope that corresponded to their study number which contained their group assignment (Group A or Group B). The IWK Health Centre Pharmacy allocated patients using a computer-generated randomization sequence and assigned a department staff member uninvolved with any research activities to create the allocation envelopes. Randomization codes were concealed from investigators, nurses, and patients until the end of the study and data analysis.

Trial capsules were compounded and prepared by the pharmacy such that all study medications were identical in appearance. Blinded investigators administered the study medication – pregabalin 150 mg (P150) or placebo 2 hours prior to surgery. The standardized anesthetic technique consisted of induction (propofol [0.5-2.0 mg/kg) & fentanyl [1-3 mcg/kg]) and maintenance (desflurane [0.6–1.4 MAC] & fentanyl [25-100 mcg] boluses for >30% increase in heart rate or blood pressure from baseline values). In the post-anesthesia care unit (PACU) patients could receive intravenous morphine up to 10 mg to achieve a numerical rating scale (NRS) pain score of ≤3/10. The NRS was anchored by 0 = no pain and 10 = worst possible pain [24]. Once institutional PACU discharge criteria were met, patients were discharged home and instructed to take their second dose of study drug 12 hours after the initial dose at a time confirmed with them by a member of the research staff. Patients were also given a package of naprosyn (500 mg x 6 tablets) distributed by the hospital pharmacy as part of their analgesia regimen. Patients were encouraged to use acetaminophen and received a prescription for oxycodone (5 mg Q6H PRN) for breakthrough analgesia. Confirmation of the second dose of study tablet and the number of oxycodone tablets used during the first 48 hours following surgery were recorded during a follow-up phone interview.

Measures

Blinded research personnel collected patient data until discharged from the PACU (minimum 2 hours) then at 24 and 48 h postoperatively via telephone interview. In the PACU sedation was assessed with the modified Ramsay scale; 1 = patient anxious, agitated, or restless, 2 = patient cooperative, oriented, and tranquil, 3 = patient responds to commands only, 4 = patient responds to gentle shaking, 5 = patient responds to noxious stimulus, 6 = patient has no response to firm nail bed pressure or other noxious stimuli [25]. Pain at rest and after movement (standing) as well as nausea were assessed using an 11-point NRS (0 = no pain/nausea, 10 = worst possible pain/nausea) and a verbal rating scale (VRS) for pain (none, mild, moderate, severe) [26]. Pruritus was measured on a scale from 0 to 3 (0 = no pruritus, 3 = worst possible pruritus). Respiratory depression was defined as a respiratory rate <8 breaths per minute and/or oxygen saturation < 90%. At the 48-h assessment, patients were asked about their satisfaction with postoperative pain relief using an NRS (0 = completely dissatisfied, 10 = completely satisfied). Urinary retention was defined as any need for a urinary catheter within 48 hours following surgery.

Statistical Analysis

Descriptive statistics are expressed as mean ± standard deviation. The student's t-test was used for comparison of the means of continuous variables. The Mann-Whitney U-test was used for ordinal data. Categorical data were analyzed using $\chi 2$ test analysis or Fisher's exact test where any expected cell frequency was less than 5. The statistical analysis was performed by the investigators using GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA) and α set at 0.05.

Our primary outcome was pain at 24 h postoperatively on the NRS. Accordingly, the sample size calculation was performed based on the outcome of NRS assessment of pain at 24 hours. A one-tailed, t-test for independent groups sample size calculation, testing for a significance level of $\alpha = 0.05$ and $\beta=0.20$ (i.e. 80% power), was completed to detect a 30% reduction in the NRS. Based upon data from Turan et al. [27] (NRS = 1.6 ± 0.7), assuming $\alpha = 0.05$, $\beta=0.20$, and a 30% reduction in NRS at 24 hours determined 26 patients per group were necessary. Our secondary outcome was cumulative opioid consumption at 24 h postoperatively.

Results

Patient characteristics

Eighty-eight patients were screened for participation from September 2008 to November 2011 until sufficient sample size was

achieved. Sixty-two patients were subsequently randomized with fifty-nine patients completing the study and included in the analyses (Figure 1).

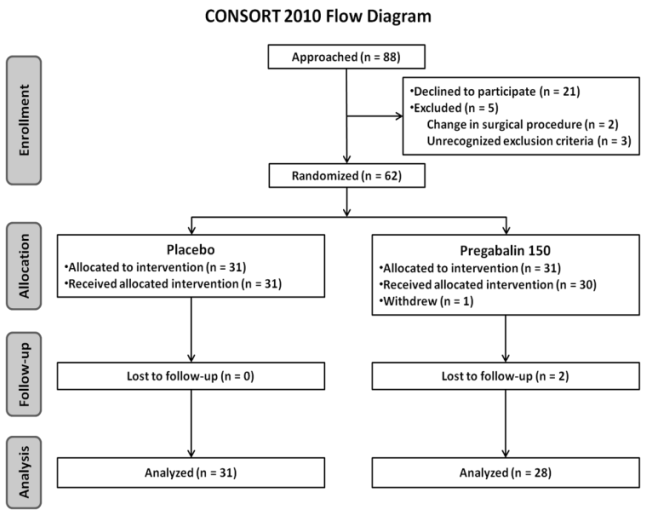

Figure 1: Flow diagram of patient recruitment, randomization, treatment and data analysis

There were no clinically relevant differences among demographic characteristics between groups (Table 1).

Measure		Placebo (n = 31)	P150 (n = 28)
Age (years)		52 ± 8	53 ± 7
Weight (kg)		80 ± 20	80 ± 17
Height (cm)		163 ± 6	162 ± 6
Procedure	Lumpectomy	24 (77.4%)	23 (82.1%)
	Mastectomy	7 (22.6%)	5 (17.9%)
ASA Status	1	15 (48.4%)	15 (53.6%)
	2	16 (51.6%)	13 (46.4%)

Table 1: Patient Characteristics; Data presented as mean ± SD or n (%)

Intensity of Pain

The average (sd) pain scores at rest at 24 hours were 1.3 (1.8) in the placebo group and 0.6 (0.8) in the P150 group (difference = 0.65, 95% CI: -0.09 to 1.39, p = 0.08) Similarly, the average pain scores after movement at 24 hours were 1.3 (1.5) in the placebo group and 1.2 (1.3) in the P150 group (difference = 0.14, 95% CI: -0.59 to 0.88, p = 0.70). Pain scores over time are shown in Figure 2.

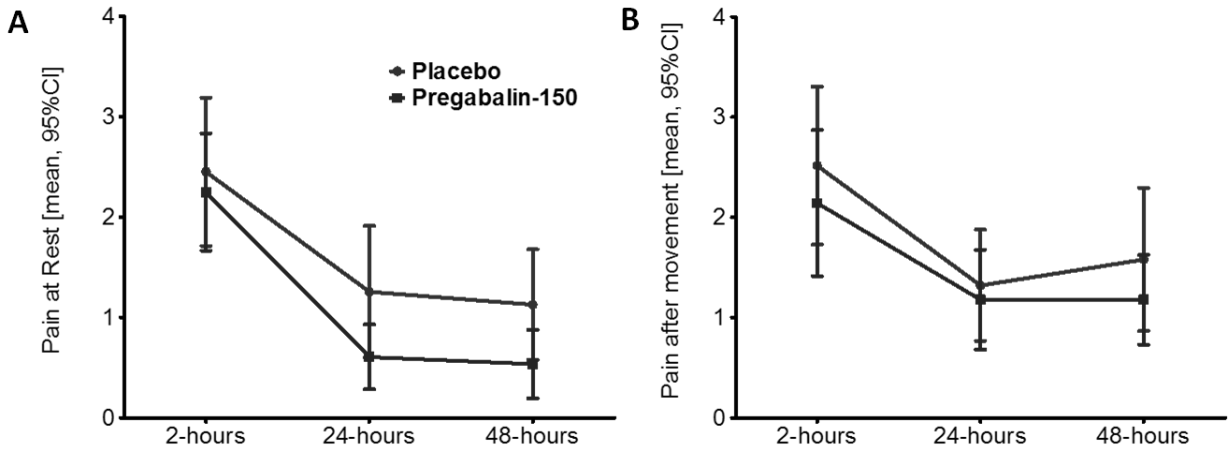

Figure 2: Mean profiles of pain scores over time. Pain scores were assessed with an 11-point Numerical Rating Scale (NRS) 2, 24, and 48 hours postoperatively A) at rest and B) after movement (standing)

Oxycodone tablet consumption

Additionally, the average (sd) oxycodone tablet consumption from 24 to 48 h following surgery was 0.10 (0.4) in the placebo group and 0.68 (2.9) in the P150 group (difference = -0.58, 95% CI: -1.64 to 0.47, p = 0.27, data not shown). Twenty-nine (94%) patients in the placebo group and 22 (76%) patients in the P150 group took no oxycodone tablets within 24 h postoperatively. Further, 29 (94%) and 26 (90%) of patients in the placebo and P150 groups, respectively took no oxycodone tablets between 24 and 48 h following surgery.

The average (sd) oxycodone tablet consumption 24 h postoperatively was 0.71 (3.6) in the placebo group and 0.96 (2.3) in the P150 group (difference = -0.26, 95% CI: -1.86 to 1.35, p = 0.72, Table 2).

Measure	Placebo (n = 31)	P150 (n = 28)	Estimated between-group difference	95% Confidence interval	p-value
Pain at rest	1.3 ± 1.8	0.6 ± 0.8	0.65 ± 0.37	-0.09 to 1.39	0.08
Pain after movement	1.3 ± 1.5	1.2 ± 1.3	0.14 ± 0.37	-0.59 to 0.88	0.70
Oxycodone tablet consumption	0 (0–20)	0 (0–10)	-0.26 ± 0.80	-1.86 to 1.35	0.72

Table 2: Primary outcomes at 24 h follow-up; Data presented as mean ± SE or median (range); Pain and oxycodone data analyzed by Mann-Whitney U-test.

Outcome data

There was no difference in total intraoperative fentanyl (mcg) administered between groups during surgery. Further, there were no differences between groups in total morphine received or sedation level 2 hours following surgery. Patient satisfaction was not statistically different between groups 48 h following surgery (Table 3).

Measure	Placebo (n = 31)	P150 (n = 28)	Estimated between-group difference	95% confidence interval	p-value
Intraoperative Fentanyl (mcg)	193 ± 56	178 ± 69	14.88 ± 16.31	-17.79 to 47.56	0.36
PACU Morphine (mg)	1.0 [0.0, 8.0]	3.5 [0.5, 6.8]	-0.67 ± 1.06	-2.79 to 1.45	0.53
2-hour Sedation*	2 (2–3)	2 (2–2)	–	–	0.36
48-hour Patient Satisfaction	10 (5–10)	10 (7–10)	0.04 ± 0.26	-0.47 to 0.56	0.86

Table 3: Outcome Data by Group Allocation: Data presented as mean ± SD; median [IQR]; or median (Range); Sedation scores analyzed by Mann Whitney U-test; *Modified Ramsay: 2 = patient cooperative; oriented; and tranquil.

Prevalence of nausea, pruritus, vomiting, and urine retention

There were no differences in nausea or pruritus between groups at any timepoint (Table 4). Vomiting occurred in three instances in the placebo group and four instances in the P150 group at the 2 h time point.

Measure	Time	Groups		Difference	95% CI	Bonferroni
		Placebo	P150			
Nausea	2	0 [0, 2]	0 [0, 1.5]	0.2189	-1.16 to 0.72	ns
	24	0 [0, 1]	0 [0, 0]	0.5772	-1.51 to 0.36	ns
	48	0 [0, 0]	0 [0, 0]	0.2224	-1.16 to 0.71	ns
Pruritus	2	0 [0, 0]	0 [0, 0]	0.129	-0.32 to 0.07	ns
	24	0 [0, 0]	0 [0, 0]	0.0219	-0.22 to 0.17	ns
	48	0 [0, 0]	0 [0, 0]	0.0288	-0.22 to 0.17	ns
				Relative Risk		p-value
Vomiting	2	3 (9.7%)	4 (14.3%)	0.68	0.17 to 2.77	0.7
	24	2 (6.5%)	1 (3.6%)	1.81	0.17 to 18.87	1
	48	0 (0%)	0 (0%)	–	–	–
Urine Retention	24	0 (0%)	1 (3.6%)	0	∞	0.47
	48	0 (0%)	0 (0%)	–	–	–

Table 4: Group Wise Comparison of Nausea, Pruritus, and Vomiting Scores 2, 24, and 48 h Postoperatively; Nausea and pruritus scores analyzed by repeated measures ANOVA; Vomiting and Urine Retention scores analyzed by Fisher's exact test; Data presented as median [IQR] or total n (%).

Analysis by Fisher's exact test determined the incidences of vomiting were not statistically different between groups at any time point (Table 4). The only reported incidence of urinary retention occurred in the P150 group at the 24 h time point, with no other cases of urinary retention reported in either group at any time point (Table 4).

Discussion

This study sought to determine whether 150 mg of pregabalin administered 2 h prior to surgery and 12 hours later was able to reduce acute pain and oxycodone tablet consumption in women undergoing breast cancer surgery with general anesthesia. Our results suggest that perioperative pregabalin is not effective in reducing pain either at rest or after movement at 24 h postoperatively in this patient cohort whose pain expectations were likely low to begin with. Administration of pregabalin also did not appear to reduce any side effects in the recovery period.

We observed no differences in postoperative pain at rest or after movement between the P150 and placebo groups at any timepoint during their perioperative pregabalin administration (Table 2 and Figure 2). The upper limits of the confidence intervals for the between-group differences were all less than 1.5, essentially ruling out any clinically important difference. This is consistent with some previous pregabalin research in breast and related surgeries, although these findings are controversial with various reports of limited or no benefit [15,18,28]. Additionally, the relatively low pain scores (0-3 out of 10) in both study groups suggest that likely no clinically significant impact of low dose pregabalin could be achieved. Previously published research describes reductions in postoperative pain following perioperative pregabalin administration [14,17,29]. However, in the only other report of pregabalin use for breast cancer surgery, median

pain scores were higher in both study groups both at rest (Placebo: 3 [2, 4] vs 1 [0, 2], Pregabalin: 2 [0, 2] vs. 0 [0, 1]) and after movement (Placebo: 5 [3, 6] vs 1 [0, 2], Pregabalin: 3 [2, 4] vs. 1 [0, 2]) 24 h following surgery [17]. Disagreement among results is currently quite common as new research on the analgesic efficacy and effective dose of pregabalin emerges.

The observed differences in oxycodone consumptions at 24 hours were small (<1 tablet) and the confidence intervals for the difference excluded clinically important differences (Table 2). These findings are in accordance with previous reports of no difference in opioid requirements following pregabalin administration but in contrast to others that demonstrate reduced opioid use with pregabalin [14,15,18,29,30]. Such diversity among findings does not appear to be related to type of surgery as conflicting reports occur in comparable surgeries such as breast surgeries and hysterectomies [14,15,29,30]. It appears that the dose of pregabalin administered in the current study, 150 mg per capsule (300 mg total), was insufficient to reduce postoperative opioid consumption after surgery as studies prescribing greater doses of pregabalin (300 mg per capsule) have demonstrated reduced opioid consumption [18,31]. In particular, Jokela et al. [18] have described less oxycodone consumption, although no difference in pain at rest, with two 300 mg doses of pregabalin compared to two 150 mg doses as prescribed in the current study following laparoscopic hysterectomy.

Current literature describes a weak relationship between pregabalin treatment and the intensity of postoperative pain as well as oxycodone consumption. Perhaps some of this inconsistency can be attributed to variability in timing and dosage of pregabalin administration as well as measurement techniques. While higher doses of pregabalin have demonstrated lower pain scores and opioid consumption, they have been associated with increases in adverse events [18,19,31,32]. The 150 mg dose of pregabalin selected for this research was chosen in an attempt to limit the associated side effects while remaining effective as an analgesic [22]. The apparent failure of pregabalin to improve pain and nausea and reduce opioid consumption up to 48 h postoperatively in the current study conflicts with numerous previous reports of improvements in those outcomes with pregabalin [14,17,33]. Further, Chaparro et al. [15] posit the feasibility of a publication bias towards positive pregabalin trials and suggest an influence of such partiality on the existing view of pregabalin therapy. They direct the reader toward three currently unpublished negative trials supported by Pfizer. We await the publication of those and other trials studying pregabalin as we continue to attempt to resolve the role of pregabalin in a perioperative analgesia regimen.

Nausea was not significantly different between the Placebo and P150 groups at any timepoint postoperatively (Table 4). The inability of this perioperative pregabalin regimen to reduce postoperative nausea compared to placebo in the current study confirms previous reports [15,19,29,34]. However, pregabalin treatment has been shown to reduce postoperative nausea in other work [14,33]. It is difficult to isolate the independent effect of pregabalin on nausea following surgery considering the concomitant consumption of opioids, known for their risk of post-operative nausea and related adverse effects [9]. This confounding variable emphasizes the ultimate goal of improving analgesic regimens for better pain management and a concurrent reduction in opioid consumption. Related indices of patient recovery such as pruritus, vomiting, and urine retention (Table 4) were also similar between groups, with no significant differences in any measure at any timepoint.

Pregabalin is perhaps perceived to have successfully replaced its predecessor, gabapentin, as a potent non-opioid analgesic with a role in multimodal analgesia regimens. While a review of the pharmacokinetics and pharmacodynamics of both drugs has indicated some advantages of pregabalin, very limited data currently exists comparing the two directly [35]. In an investigation comparing the analgesic efficacy of pregabalin to gabapentin after hysterectomy, Ghai et al. [33] report that pregabalin was superior in terms of reducing postoperative analgesic requirements and time to first request for analgesia. In 2012, the same group analyzed the impact of pregabalin and gabapentin on preoperative anxiety and sedation in women having a hysterectomy and found that pregabalin is a better anxiolytic and sedative than gabapentin [36]. In the current study there were no differences between groups in 2-hour sedation, but having patients leave the institution following discharge from PACU made further evaluation of sedation less valid and unfeasible. While enhanced benefits to pregabalin over gabapentin have been suggested, further research is required to explore the differences between gabapentin and pregabalin as well as to corroborate these potential advantages of pregabalin.

This study is limited by having based the sample size calculation on a study of hysterectomies [27], a potentially more painful procedure than those in the current study. Further, using a two-tailed t-test for independent groups in our sample size calculation may have been more appropriate than a one-tailed test. However, a post hoc two-tailed test for a significance level of $\alpha = 0.05$, $\beta = 0.20$, and a 35% reduction in NRS at 24 hours determined that 27 patients per group were necessary, which we have achieved. Additionally, this trial is unable to assess the efficacy of pregabalin in the absence of oxycodone; a scenario that is becoming increasingly common as non-narcotic pain control becomes more prevalent. Finally, this research did not evaluate the potential benefit or harm of pregabalin on specific subpopulations or among patients undergoing more extensive or painful breast cancer surgeries. The low pain scores among all patients in this study may have limited any beneficial effect of pregabalin.

Consideration of the current findings suggests that much work remains to be done in eliciting the optimal effective dose of pregabalin to maximize analgesic efficacy while minimizing adverse events. Though higher doses of pregabalin have previously demonstrated lower pain scores and opioid consumption, such high doses have been associated with increases in adverse events [18,19,31,32]. Future researchers may be well served to isolate the impact of pregabalin on specific subpopulations (ex. the obese) or surgical categories (ex. complete mastectomies) to better enable achievement of this goal. As well, research regarding the mechanistic action of pregabalin in vivo may shed light on its disparate results to this point.

In conclusion, this study showed no improvement in pain intensity or oxycodone tablet consumption 24 h postoperatively with pregabalin compared to placebo after elective breast cancer surgery. Further research is required to isolate the appropriate dose and timing of pregabalin administration surrounding breast cancer surgery. These studies should target a patient population that is experiencing at least moderate pain and/or needing more than minimal opioid medications.

Summary

This study was designed to determine if perioperative pregabalin treatment could reduce pain scores and oxycodone consumption

following elective surgery for possible breast cancer. Fifty-nine women were randomized to pregabalin (150 mg) or placebo, both administered prior to surgery and a second dose 12 hours postoperatively. There were no differences in pain intensity at rest or following movement 24 h postoperatively. Similarly, there were no differences between groups in oxycodone consumption at either 24 or 48 h postoperatively. Therefore, 150 mg of pregabalin given preoperatively and 12 h postoperatively did not improve pain, nausea, or oxycodone consumption up to 48 h following breast surgery.

Disclosures

This study was completed at the IWK Health Centre. Dr. George would like to acknowledge the financial support of the Canadian Anesthesiologists' Society Career Scientist Award and IWK Health Centre Recruitment & Establishment Grant to conduct his research.

None of the authors have any relevant conflicts of interest to disclose. Clinical Trials Registry: NCT00785382

References

1. Kehlet H, Jensen TS, Woolf CJ (2006) Persistent postsurgical pain: risk factors and prevention. Lancet 367: 1618-1625.
2. Pruthi S, Brandt KR, Degnim AC, et al. (2007) A multidisciplinary approach to the management of breast cancer, part 1: prevention and diagnosis. Mayo ClinProc 82: 999-1012.
3. Steegers MA, Wolters B, Evers AW, Strobbe L, Wilder-Smith OH (2008) Effect of axillary lymph node dissection on prevalence and intensity of chronic and phantom pain after breast cancer surgery. J Pain 9: 813-822.
4. Wallace MS, Wallace AM, Lee J, Dobke MK (1996) Pain after breast surgery: a survey of 282 women. Pain 66: 195-205.
5. Katz J, Jackson M, Kavanagh BP, Sandler AN (1996) Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. Clin J Pain 12: 50-55.
6. Poleshuck EL, Katz J, Andrus CH, et al. (2006) Risk factors for chronic pain following breast cancer surgery: a prospective study. J Pain 7: 626-634.
7. Oderda GM, Evans RS, Lloyd J, et al. (2003) Cost of opioid-related adverse drug events in surgical patients. J Pain Symptom Manage 25: 276-283.
8. Philip BK, Reese PR, Burch SP (2002) The economic impact of opioids on postoperative pain management. J ClinAnesth 14: 354-364.
9. Taylor S, Voytovich AE, Kozol RA (2003) Has the pendulum swung too far in postoperative pain control? Am J Surg 186: 472-475.
10. Kehlet H, Dahl JB (1993) The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. AnesthAnalg 77: 1048-1056.
11. Gilron I (2007) Gabapentin and pregabalin for chronic neuropathic and early postsurgical pain: current evidence and future directions. CurrOpinAnaesthesiol 20: 456-472.
12. Zhang J, Ho KY, Wang Y (2011) Efficacy of pregabalin in acute postoperative pain: a meta-analysis. Br J Anaesth 106: 454-462.
13. Field MJ, Holloman EF, McCleary S, Hughes J, Singh L (1997) Evaluation of gabapentin and S-(+)-3-isobutylgaba in a rat model of postoperative pain. The Journal of pharmacology and experimental therapeutics 282: 1242-1246.
14. Freedman BM, O'Hara E (2008) Pregabalin has opioid-sparing effects following augmentation mammaplasty. AesthetSurg J 28: 421-424.
15. Chaparro LE, Clarke H, Valdes PA, Mira M, Duque L, Mitsakakis N (2012) Adding pregabalin to a multimodal analgesic regimen does not reduce pain scores following cosmetic surgery: a randomized trial. J Anesth 26: 829-835.
16. Engelman E, Cateloy F (2011) Efficacy and safety of perioperative pregabalin for post-operative pain: a meta-analysis of randomized-controlled trials. ActaAnaesthesiolScand 55: 927-943.
17. Kim SY, Song JW, Park B, Park S, An YJ, Shim YH (2011) Pregabalin reduces post-operative pain after mastectomy: a double-blind, randomized, placebo-controlled study. ActaAnaesthesiolScand 55: 290-296.
18. Jokela R, Ahonen J, Tallgren M, Haanpaa M, Korttila K (2008) A randomized controlled trial of perioperative administration of pregabalin for pain after laparoscopic hysterectomy. Pain 134: 106-112.
19. Yucel A, Ozturk E, Aygogan MS, Durmus M, Colak C, Ersoy MO (2011) Effects of 2 Different Doses of Pregabalin on Morphine Consumption and Pain After Abdominal Hysterectomy: A Randomized, Double-Blind Clinical Trial. CurrTher Res 72: 173-183.
20. Agarwal A, Gautam S, Gupta D, Agarwal S, Singh PK, Singh U (2008) Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. Br J Anaesth 101: 700-704.
21. Chang SH, Lee HW, Kim HK, Kim SH, Kim DK (2009) An evaluation of perioperative pregabalin for prevention and attenuation of postoperative shoulder pain after laparoscopic cholecystectomy. AnesthAnalg 109: 1284-1286.
22. White PF, Tufanogullari B, Taylor J, Klein K (2009) The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. AnesthAnalg 108: 1140-1145.
23. Schulz KF, Altman DG, Moher D (2010) CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. J ClinEpidemiol 63: 834-840.
24. Gan TJ, Meyer TA, Apfel CC, et al. (2007) Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. AnesthAnalg 105: 1615-1628.
25. Carrasco G (2000) Instruments for monitoring intensive care unit sedation. Crit Care 4: 217-225.
26. Dworkin RH, Turk DC, Farrar JT, et al. (2005) Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 113: 9-19.
27. Turan A, Karamanlioglu B, Memis D, Usar P, Pamukcu Z, Ture M (2004) The analgesic effects of gabapentin after total abdominal hysterectomy. AnesthAnalg 98: 1370-1373, table of contents.
28. Fassoulaki A, Melemeni A, Tsaroucha A, Paraskeva A (2012) Perioperative pregabalin for acute and chronic pain after abdominal hysterectomy or myomectomy: a randomised controlled trial. Eur J Anaesthesiol 29: 531-536.
29. Ittichaikulthol W, Virankabutra T, Kunopart M, Khamhom W, Putarawuthichai P, Rungphet S (2009) Effects of pregabalin on post operative morphine consumption and pain after abdominal hysterectomy with/without salphingo-oophorectomy: a randomized, double-blind trial. Journal of the Medical Association of Thailand = Chotmaihetthangphaet 92: 1318-1323.
30. Mathiesen O, Jacobsen LS, Holm HE, et al. (2008) Pregabalin and dexamethasone for postoperative pain control: a randomized controlled study in hip arthroplasty. Br J Anaesth 101: 535-541.
31. Przesmycki K, Wiater-Koziol E, Kotarski J, et al. (2011) [Effect of pre-emptive pregabalin on pain intensity and morphine requirement after hysterectomy]. Anestezjologiaintensywnaterapia 43: 14-17.
32. Kohli M, Murali T, Gupta R, Khan P, Bogra J (2011) Optimization of subarachanoid block by oral pregabalin for hysterectomy. Journal of anaesthesiology, clinical pharmacology 27: 101-105.
33. Ghai A, Gupta M, Hooda S, Singla D, Wadhera R (2011) A randomized controlled trial to compare pregabalin with gabapentin for postoperative pain in abdominal hysterectomy. Saudi journal of anaesthesia 5: 252-257.
34. Paech MJ, Goy R, Chua S, Scott K, Christmas T, Doherty DA (2007) A randomized, placebo-controlled trial of preoperative oral pregabalin for postoperative pain relief after minor gynecological surgery. AnesthAnalg 105: 1449-1453.

35. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P (2010) A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clinical pharmacokinetics 49: 661-669.

36. Ghai A, Gupta M, Rana N, Wadhera R (2012) The effect of pregabalin and gabapentin on preoperative anxiety and sedation: a double blind study. Anesth, Pain & Intensive Care 16: 257-261.