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ORIGINAL ARTICLE

Adding pregabalin to a multimodal analgesic regimen does not reduce pain scores following cosmetic surgery: a randomized trial

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Abstract
Purpose Multimodal analgesia increases the chance of successful discharge and pain control after surgery, and pregabalin is being promoted as an effective analgesic, based on placebo-controlled studies. We investigated whether adding pregabalin improved pain control and reduced opioid requests when it was added to a multimodal analgesic regimen for cosmetic surgery.
Methods One hundred and ten women who underwent same-day cosmetic surgery were randomized to receive oral pregabalin, 75 mg q12 h for five consecutive days starting the night before surgery, or identical placebos. Participants, outcomes assessors, and the statistician were blinded. The primary outcome was postoperative numerical movement-evoked pain scores at 2, 24, 48, 72, and 96 h after surgery. The secondary outcomes included pain scores at rest; incidence of moderate to severe pain; and analgesic and antiemetic requirements; as well as the incidence of nausea, vomiting, and somnolence.
Results Based on 99 patients who completed the study, we found no difference between the groups in the primary outcome; 72 h after surgery, movement-evoked median pain scores were <4/10 in both groups. We found no differences in opioid requirements ($p = 0.95$) or anti-inflammatory requirements ($p = 0.45$), and no difference in opioid-related adverse events.
Conclusion Perioperative pregabalin 75 mg twice a day does not increase benefit when it is added to an already multimodal analgesic regimen for patients undergoing cosmetic surgery. Several factors could explain our findings, including the possibility of publication bias in the current literature.

Keywords Double-blind method · Female · Pain, postoperative/drug therapy · Gamma-aminobutyric acid/therapeutic use · Lipectomy/methods

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Introduction

Medical tourism has increased the economic interest in and surgical expertise of cosmetic surgery in South America [1]. The preferred anesthesia technique is general, and the vast majority of the procedures are ambulatories. In cosmetic surgery, some common demographic features, including middle-aged women [2], extroversion [3], and anxiety [4], have been associated with decreased pain tolerance.

Multimodal analgesia [5], the combination of drugs that differ in their mechanism of action, is the standard practice for postoperative pain. Multimodal analgesia has demonstrated significant benefits such as better pain control, decreased opioid consumption, fewer opioid-related side effects, and earlier return to activities of daily living [6, 7].

Gabapentin is a medication that has demonstrated a significant benefit in placebo-controlled studies [8] for pain at rest and movement-evoked pain after surgery; however, the evidence for adding gabapentin in multimodal analgesic schemes is not consistent [9, 10]. Pregabalin, similar to gabapentin, is another calcium channel blocker that has demonstrated some benefit in the postoperative setting based on several placebo-controlled studies [11].

The primary aim of this study was to examine whether the addition of pregabalin to a multimodal analgesic regimen in patients undergoing cosmetic surgery would have a significant impact on the movement-evoked pain scores. Secondary aims included the potential reduction in supplemental analgesia, nausea, vomiting, and somnolence.

Patients, materials, and methods

The study was approved by the Institutional Review board of the IPS-Universitaria, University of Antioquia in Medellin, Colombia (Comité de Ética Médica de la IPS Universitaria. Act 02-08-2006; Date of Issue: March 6/2006; Contact Information: Maria Teresa Aristizabal. Address: Carrera 51A#62-42, Medellin, Colombia. Tel: 2630171). All patients read the instructions of the research group, agreed to follow the instructions, and signed the consent form to participate in the trial. The study was registered at Current Controlled Trials: ISRCTN89891413.

Study design

This was a randomized, double-blind, placebo-controlled, parallel design study. The study was conceived to include participants who underwent cosmetic liposuction only; however, given the high rate of additional esthetic augmentation mammoplasty or abdominoplasty, we decided to include combined procedures too.

Selection and description of participants

Our patients were enrolled during the pre-anesthesia visit. Our inclusion criteria were women aged 18-60 years, with an American Society of Anesthesiologists (ASA) physical status score of I or II, who were scheduled for cosmetic surgery under general anesthesia at one of the three participating centers (Unidad de Cirugia Ambulatoria-IPS Universitaria, Clinica Bioforma, and Clinica El Rosario). We excluded patients with allergies to the study medications; psychiatric illness; diabetes; history of opioid or alcohol abuse; recent use of steroids; and hypertension with target organ damage.

Interventions

After reading and signing the consent form, patients were instructed to start the treatment (pregabalin [Lyrica®-Pfizer, New York, NY, USA] 75 mg or placebo) by taking one capsule of the study medication before going to bed the night before surgery. A second capsule was administered 1 h before the surgery, and the treatment was continued twice a day until the fourth postsurgical day (10 capsules in total). All patients had an anesthesia induction that included the intravenous injection of midazolam 2–3 mg, dexamethasone 8 mg, and propofol 1–2 mg/kg; for anesthesia maintenance, remifentanil 0.2–0.5 μg/kg/min plus an inhaled agent (sevoflurane or desflurane), were used and balanced ad libitum. Nitrous oxide was not allowed. A tumescent technique (1:1,000,000 epinephrine in Ringer's lactate), free of lidocaine, was used for the liposuction. The procedure included, in most of the patients, the abdominal area, hips, and thighs. The plastic surgeon was allowed to perform intercostal injections (bupivacaine 0.25 %, 2–3 cc per intercostal level) of local anesthetic for augmentation mammoplasty. Routine monitoring included heart rate and rhythm, pulse-oximetry, and non-invasive blood pressure. Approximately 30 min before the end of surgery, the patients received a validated intravenous analgesic regimen [12] that included morphine 0.05 mg/kg, diclofenac 75 mg, and/or dipyrone 2 g.

In the postoperative care unit, patients stating that they had moderate or severe pain received intravenous morphine (3 mg q10 min). Morphine was put on hold if there was moderate/severe nausea or vomiting, which was treated with 4 mg of ondansetron. The morphine titration was stopped in patients with no response to verbal commands.

The plastic surgeon in charge prescribed, ad libitum, one of the following analgesic treatments: Winadeine F® 2 tablets po q8h (acetaminophen 500 mg plus codeine 30 mg; Sanofi Aventis, Paris, France); Zaldiar® 2 capsules po q8h (acetaminophen 325 mg plus tramadol 37.5 mg; Grunenthal, Aachen, Germany); Sinalgen® 1 tablet q8h (acetaminophen 500 mg plus hydrocodone 5 mg; Grunenthal). Patients were allowed to take ibuprofen 200 mg or diclofenac 25 mg for analgesic rescue only.

Randomization, allocation, and blinding

Pregabalin and placebo capsules were identical (white and green) in appearance; a capsule-in-capsule technique was used for pregabalin; placebo capsules were flour-filled. Bottles of ten capsules were prepared and tagged with an

alphanumeric code by a nurse (L.D.), who randomized treatments based on a computer-generated sequence. We used simple randomization with 1:1 allocation. The bottles were supplied to the surgical centers and subsequently to the patients during the preoperative anesthesia visit. Nobody but the nurse knew the sequence and content of the bottles; L.D. did not participate in the outcomes assessment or data collection. Nobody, except for her, was aware of the interventions administered to each patient.

Outcomes assessment

Patients were followed at 2, 24, 48, 72, and 96 h after surgery. Except for the 2-h postoperative time-point evaluation, all outcomes assessments were performed by telephone calls. The primary outcome was the reported movement-evoked pain, defined as a transitional movement from the supine to the sitting position, using a 0–10 numerical rating scale. Secondary outcomes included reported pain score at rest; incidence of moderate to severe pain; and incidence of nausea, vomiting, and somnolence; as well as the postoperative analgesic requirement. For data analysis in this trial, the doses of the opioids prescribed were converted to morphine equivalents [13, 14]. Based on the aforementioned publications, 30 mg of codeine, 37.5 mg of tramadol, and 5 mg of hydrocodone are regarded as equivalent to 3, 3.75, and 5 mg of oral morphine, respectively. Meta-analyses have demonstrated, based on the number needed to treat (NNT), that these opioids are equally effective [15–17]. Ibuprofen and diclofenac have also been demonstrated to be equally effective [18, 19]. The protocol included the outcome "return to activities of daily living"; however, a significant number of participants were on medical leave, which introduced bias.

Sample size

The sample was calculated based on the alternative hypothesis that the addition of pregabalin to an already established multimodal analgesic regimen would significantly reduce pain. Based on our experience, we assumed an incidence of moderate to severe pain in the placebo group of 40 % in the first 24 h; we calculated that a sample of 48 patients per arm would provide 80 % power (alpha level of 0.05) to detect a pain reduction incidence of up to 20 % favoring the pregabalin group. No interim analysis was planned. We initially calculated the sample size required to find a difference of at least 2 points on a 0–10 pain scale, assuming 6/10 (standard deviation of 3) in the placebo group and 4/10 (standard deviation of 3) in the pregabalin group; however, based on this calculation, fewer patients (44 per group) were required.

Statistical analysis

We have expressed the pain scores (non-normally distributed) as medians and inter-quartile ranges. The association of treatment and its interaction with time and continuous outcomes (pain scores, medication dose) were analyzed with the use of mixed models. An inter-patient random effect was used, combined with an intra-patient autoregressive correlation structure that decreases with increasing lags between measures. In the model, in addition to treatment and time and treatment-time interaction, a number of covariates (age, body mass index [BMI], type of surgery) were also used as potential confounders. Dichotomous outcomes were analyzed using generalized estimating equations (using a binomial distribution for the outcome and a logit link function). As with the continuous outcomes, an intra-patient autoregressive correlation structure was used. The statistician (N.M.) was blinded to treatment allocation.

Results

Recruitment and retention of patients

Figure 1 shows the flow chart outlining the recruitment and retention of the study patients. Three hundred and ninety-seven patients were screened for the trial.

Demographic and clinical variables

Table 1 shows that the groups were comparable with respect to age, BMI, smoking, history of postoperative nausea/vomiting, and surgical time. Almost one-third of the patients who completed the study (31/99) had a combined liposuction with augmentation mammoplasty or abdominoplasty.

Effect of treatments

The primary analysis for the 99 study completers showed that the pain scores were not normally distributed at rest or with movement throughout the trial, so our main results are reported as medians and interquartile ranges (IQRs). Even assuming a normal distribution, our findings showed no differences in movement-evoked pain scores (see Table 2). Notably, a median movement-evoked pain score of 3/10 was reached at 72 h in both groups; however, based on categorical pain score, 12/50 patients in the pregabalin group and 14/49 in the placebo group were still reporting moderate or severe movement-evoked pain at the same time point. On the last observation day, 4 days after the

Fig. 1 Trial profile

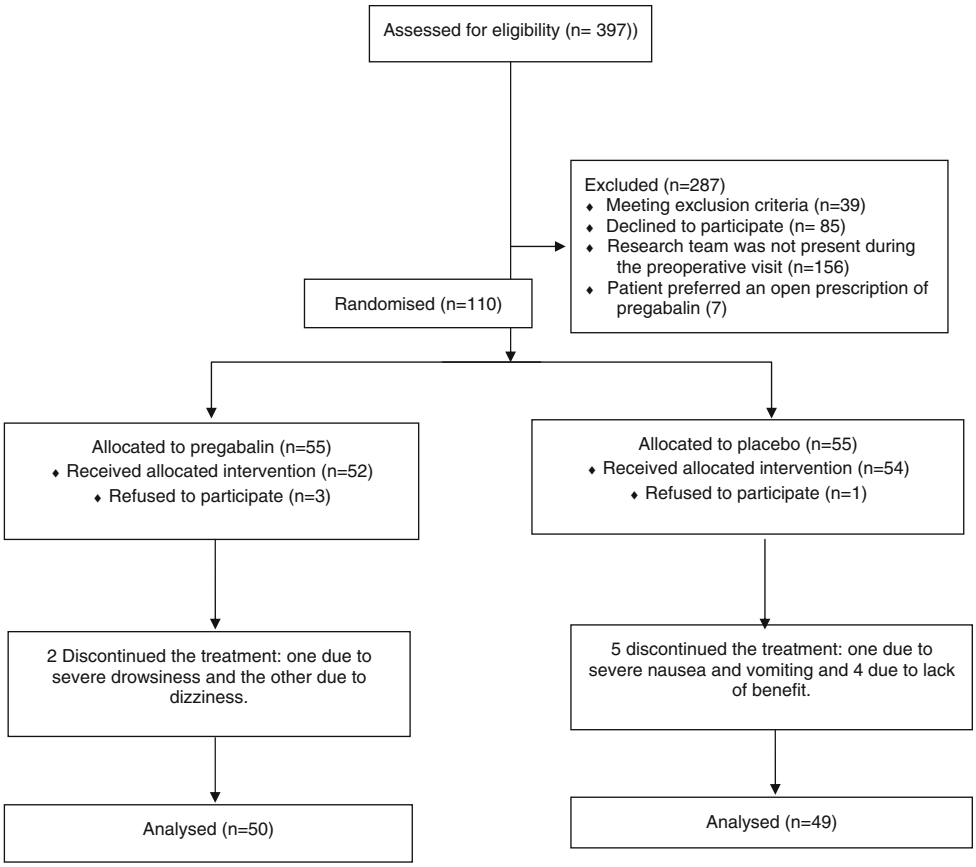

Table 1 Demographic characteristics of the patients

	Placebo group ($n = 49$)	Pregabalin ($n = 50$)
Age, years, mean (SD)	34.3 (9.81)	32.8 (8.73)
BMI, mean (SD)	24 (2.98)	23.59 (3.08)
Surgical time (min), mean (SD)	206.73 (67.61)	218.5 (80.9)
Smokers	7/49	12/50
History of PONV	8/49	9/50
Motion sickness	10/49	12/50
Liposuction only	36	32
Liposuction + mammoplasty	6	15
Liposuction + abdominoplasty	7	3

BMI Body mass index, *PONV* postoperative nausea/vomiting

surgery, 14 % of the pregabalin and 10.2 % of the placebo group had persistent moderate/severe pain (see Table 2).

We found no differences between the groups in postoperative opioid consumption ($p = 0.95$; see Table 2) or in nonsteroidal anti-inflammatory drug (NSAID) use ($p = 0.45$; see Table 2). Of note, the cumulative incidences of nausea (18/50 vs. 14/49; p value 0.276); vomiting (12/50 vs. 12/49; p value 0.955); antiemetic requirement (18/50 vs. 13/49; p value 0.314); and somnolence (9/50 vs. 6/49; p value 0.429) were similar in the pregabalin and placebo groups.

Discussion

In this clinical trial, adding pregabalin to a multimodal regimen for postoperative pain management after cosmetic surgery showed no difference in the primary outcome of movement-evoked pain scores as compared with the placebo group. The groups remained comparable even after multiple analyses for potential confounders such as age, BMI, or type of surgery (liposuction alone versus liposuction + mammoplasty versus liposuction + abdominoplasty). We also found no differences in analgesic requirements or adverse effects.

Our analgesic regimen included, in addition to an opioid, analgesics such as dexamethasone [20], NSAIDs [21], local anesthetic injections [22], and acetaminophen [23, 24] that have been demonstrated, by meta-analyses, to exert significant pain control and clinically relevant opioid-sparing effects. Our experience has also demonstrated the benefit of dexamethasone as a means of decreasing the incidence of long-term sensory abnormalities after augmentation

Table 2 Pain scores and analgesic requirements

	2 h		24 h		48 h		72 h		96 h	
	Pregabalin	Placebo	Pregabalin	Placebo	Pregabalin	Placebo	Pregabalin	Placebo	Pregabalin	Placebo
Median pain scores (IQR)	6 (5–8)	6 (5–7)	5 (4–7)	5 (4–7)	4 (3–6)	4 (3–6)	3 (2–5)	3 (2–5)	2 (1–3)	2 (1–3)
Dynamic moderate or severe pain	37/50	36/49	31/50	36/49	24/50	21/49	12/50	14/49	7/50	5/49
Rest moderate or severe pain	24/50	18/49	11/50	15/49	6/50	10/49	2/50	5/49	2/50	1/49
Mean pain scores (SD)[a]	6.1 (2.30)	5.6 (2.25)	5.3 (2.68)	5.4 (2.34)	4.2 (2.40)	4.2 (2.12)	3.1 (2.13)	3.1 (2.01)	2.3 (1.97)	2.1 (1.77)
Median (IQR) morphine equivalent request (mg)	6 (3–9)	6 (3–9)	7.5 (0–12)	6 (0–12)	5.5 (0–12)	8 (0–12)	5.5 (0–12)	6 (0–12)	0 (0–6)	6 (0–12)
Median NSAID request (# tablets)	[b]	[b]	6 (4–6)	6 (2–6)	5 (3–6)	6 (3–6)	4 (2–6)	4 (2–6)	4 (2–6)	4 (2–6)

IQR Interquartile range, *NSAID* nonsteroidal anti-inflammatory drug

[a] Although this value was calculated, pain scores were not normally distributed

[b] Pain management using intravenous morphine; NSAID tablets were ibuprofen 200 mg or diclofenac 25 mg

mammoplasty [25]. The tumescent technique did not include lidocaine, given the potential risk of late toxicity already documented by Klein and Kassarjdian [26].

A recent systematic review evaluated the efficacy and safety profile of pregabalin in acute pain based on 18 published trials [11]. The authors of that review concluded that any daily dose between 50 and 300 mg was effective for rest pain; however, for movement-evoked pain, at least 225 mg/day would be required. When we started our study in 2006, there were no published trials on the use of pregabalin for acute pain, although 150 mg bid had been proven to be safe and effective for neuropathic pain [27]. The minimum dose of pregabalin required for acute pain is still difficult to pinpoint, given that the meta-analysis [11] of the higher recommended dose, 600–750 mg, including data from 4 trials, failed to demonstrate a significant effect. We observed that our trial's sample size did not differ from the sample size of those trials that did reach statistical difference. Furthermore, three positive but non-multimodal studies used our chosen regimen, 150 mg/day, and these have been recently published [28–30].

A publication bias [31] favoring positive trials is feasible given that we identified three negative clinical trials that were supported by Pfizer but have not been published yet: one study including 487 patients evaluated pregabalin for acute pain after hysterectomy (http://www.clinicalstudyresults.org/documents/company-study_11355_0.pdf; accessed on 8 December 2011); in another study, 413 patients received pregabalin for inguinal herniorrhaphy (http://www.clinicalstudyresults.org/documents/company-study_10223_0.pdf; accessed on 8 December 2011); and in the last one, 292 patients received pregabalin for pain treatment after knee arthroplasty (http://www.clinicalstudyresults.org/documents/company-study_9843_0.pdf; accessed on 8 December 2011). We believe that the conclusions of the aforementioned systematic review [11] would change if it had included the data of these studies.

The same review highlighted that pregabalin can decrease opioid consumption. As we know, an opioid-sparing effect is a surrogate endpoint that is clinically significant only when a concomitant decrease in opioid-related side effects such as constipation, respiratory depression, urinary retention, pruritus, nausea, vomiting, or sedation, is detected [32]. Gabapentin decreases the incidence of postoperative vomiting with a number-needed-to-treat (NNT) of 11 [33]; however, pregabalin can induce similar effects only when antiemetic prophylaxis is omitted [11]. On the other hand, NSAIDs decrease the chance of sedation with an NNT of 27 [21], but gabapentin increases the frequency of sedation with an NNT of −5 [32]. We calculated the NNT for sedation/somnolence based on the data reported by the above review [11] and we found an NNT of −31 for a daily dose of 150 mg pregabalin (non-significant given that the confidence interval was between positive and negative values). Of note, analysis of the data of the trials using between 225 and 300 mg pregabalin [11] showed that the chance of sedation would increase with an NNT of −10 (−5 to −42). In other words, increasing the dose of pregabalin can decrease the pain scores but can also increase the chance of sedation.

One of the limitations of our trial is that our postoperative assessments were completed by telephone interviews; so we cannot confirm that our patients took all the study

medications as ordered. Serum measurements of pregabalin were not considered. Another limitation is the lack of homogeneity in the postoperative analgesic prescriptions; however, we believe that calculating the morphine equivalents is a reliable approach and is valuable for the external validity of the results.

The analgesic properties of pregabalin should be evaluated in future studies including specific populations that have contraindications for common analgesics or even opioids. Opioid abusers are another population that could potentially benefit from the use of perioperative pregabalin.

This study did not demonstrate an analgesic effect of pregabalin when it was added to a multimodal analgesic regimen following cosmetic surgery.

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References

1. Horowitz MD, Rosensweig JA, Jones CA. Medical tourism: globalization of the healthcare marketplace. MedGenMed. 2007;9:33.
2. Kalkman CJ, Visser K, Moen J, Bonsel GJ, Grobbee DE, Moons KG. Preoperative prediction of severe postoperative pain. Pain. 2003;105:415–23.
3. Taenzer P, Melzack R, Jeans ME. Influence of psychological factors on postoperative pain, mood and analgesic requirements. Pain. 1986;24:331–42.
4. Rankin M, Borah GL. Anxiety disorders in plastic surgery. Plast Reconstr Surg. 1997;100:535–42.
5. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg. 1993;77: 1048–56.
6. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg. 2008;248:189–98.
7. White PF. The changing role of non-opioid analgesic techniques in the management of postoperative pain. Anesth Analg. 2005;101: S5–22.
8. Peng PW, Wijeysundera DN, Li CC. Use of gabapentin for perioperative pain control—a meta-analysis. Pain Res Manag. 2007;12:85–92.
9. Clarke H, Pereira S, Kennedy D, Andrion J, Mitsakakis N, Gollish J, Katz J, Kay J. Adding gabapentin to a multimodal regimen does not reduce acute pain, opioid consumption or chronic pain after total hip arthroplasty. Acta Anaesthesiol Scand. 2009;53:1073–83.
10. Rasmussen ML, Mathiesen O, Dierking G, Christensen BV, Hilsted KL, Larsen TK, Dahl JB. Multimodal analgesia with gabapentin, ketamine and dexamethasone in combination with paracetamol and ketorolac after hip arthroplasty: a preliminary study. Eur J Anaesthesiol. 2010;27:324–30.
11. Engelman E, Cateloy F. Efficacy and safety of perioperative pregabalin for post-operative pain: a meta-analysis of randomized-controlled trials. Acta Anaesthesiol Scand. 2011;55:927–43.
12. Chaparro LE, Lezcano W, Alvarez HD, Joaqui W. Analgesic effectiveness of dipyrone (metamizol) for postoperative pain after herniorrhaphy: a randomized, double-blind, dose–response study. Pain Pract. 2012;12:142–7.
13. Foley KM. The treatment of cancer pain. N Engl J Med. 1985;313:84–95.
14. Schug SA, Gandham N. Opioids: clinical use. In: McMahon SB, Koltzenburg M, editors. Wall and Melzack's Textbook of Pain. London: Elsevier; 2006. pp. 443–57.
15. Edwards JE, McQuay HJ, Moore RA. Combination analgesic efficacy: individual patient data meta-analysis of single-dose oral tramadol plus acetaminophen in acute postoperative pain. J Pain Symptom Manag. 2002;23:121–30.
16. Fricke JR Jr, Karim R, Jordan D, Rosenthal N. A double-blind, single-dose comparison of the analgesic efficacy of tramadol/acetaminophen combination tablets, hydrocodone/acetaminophen combination tablets, and placebo after oral surgery. Clin Ther. 2002;24:953–68.
17. Toms L, Derry S, Moore RA, McQuay HJ. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. Cochrane Database Syst Rev 2009;CD001547.
18. Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral ibuprofen for acute postoperative pain in adults. Cochrane Database Syst Rev 2009;CD001548.
19. Derry P, Derry S, Moore RA, McQuay HJ. Single dose oral diclofenac for acute postoperative pain in adults. Cochrane Database Syst Rev 2009;CD004768.
20. De Oliveira GS Jr, Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology. 2011;115:575–88.
21. Marret E, Kurdi O, Zufferey P, Bonnet F. Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. Anesthesiology. 2005;102:1249–60.
22. Mahabir RC, Peterson BD, Williamson JS, Valnicek SM, Williamson DG, East WE. Locally administered ketorolac and bupivacaine for control of postoperative pain in breast augmentation patients. Plast Reconstr Surg. 2004;114:1910–6.
23. Elia N, Lysakowski C, Tramer MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. Anesthesiology. 2005;103:1296–304.
24. Ong CK, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesth Analg. 2010;110:1170–9.
25. Chaparro LE, Muñoz Y, Gallo CA, Alvarez HA, Restrepo SM, Perez N, Restrepo L. Pain and sensory symptoms following augmentation mammaplasty: a long-term follow up study with intraoperative ketamine use. Revista Colombiana de Anestesiologia 2010;38:204–12.
26. Klein JA, Kassarjdian N. Lidocaine toxicity with tumescent liposuction. A case report of probable drug interactions. Dermatol Surg. 1997;23:1169–74.
27. Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain. 2005;115: 254–63.
28. Kim JC, Choi YS, Kim KN, Shim JK, Lee JY, Kwak YL. Effective dose of peri-operative oral pregabalin as an adjunct to multimodal analgesic regimen in lumbar spinal fusion surgery. Spine (Phila Pa 1976) 2011;36: 428–33.

29. Kim SY, Song JW, Park B, Park S, An YJ, Shim YH. Pregabalin reduces post-operative pain after mastectomy: a double-blind, randomized, placebo-controlled study. Acta Anaesthesiol Scand. 2011;55:290–6.
30. Pesonen A, Suojaranta-Ylinen R, Hammaren E, Kontinen VK, Raivio P, Tarkkila P, Rosenberg PH. Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: a randomized placebo-controlled trial. Br J Anaesth. 2011;106:873–81.
31. Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. Cochrane Database Syst Rev 2009;MR000006.
32. Elia E, Tramer MR. Is opioid sparing clinically relevant? In McQuay HJ, Kalso E, Moore RA, editors. Systematic reviews in pain research: methodology refined. Seattle: IASP Press; 2008. pp. 119–31.
33. Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain–a systematic review of randomized controlled trials. Pain. 2006;126:91–101.