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SYSTEMATIC REVIEW AND META-ANALYSIS

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Efficacy of Pregabalin in Acute Postoperative Pain Under Different Surgical Categories

A Meta-Analysis

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Abstract: The efficacy of pregabalin in acute postsurgical pain has been demonstrated in numerous studies; however, the analgesic efficacy and adverse effects of using pregabalin in various surgical procedures remain uncertain. We aim to assess the postsurgical analgesic efficacy and adverse events after pregabalin administration under different surgical categories using a systematic review and meta-analysis of randomized controlled trials.

A search of the literature was performed between August 2014 to April 2015, using PubMed, Ovid via EMBASE, Google Scholar, and ClinicalTrials.gov with no limitation on publication year or language. Studies considered for inclusion were randomized controlled trials, reporting on relevant outcomes (2-, 24-hour pain scores, or 24 hour morphine-equivalent consumption) with treatment with perioperative pregabalin.

Seventy-four studies were included. Pregabalin reduced pain scores at 2 hours in all categories: cardiothoracic (Hedge's g and 95%CI, −0.442 [−0.752 to −0.132], $P = 0.005$), ENT (Hedge g and 95%CI, −0.684 [−1.051 to −0.316], $P < 0.0001$), gynecologic (Hedge g, 95%CI, −0.792 [−1.235 to −0.350], $P < 0.0001$), laparoscopic cholecystectomy (Hedge g, 95%CI, −0.600 [−0.989 to −0.210], $P = 0.003$), orthopedic (Hedge g, 95%CI, −0.507 [−0.812 to −0.202], $P = 0.001$), spine (Hedge g, 95%CI, −0.972 [−1.537 to −0.407], $P = 0.001$), and miscellaneous procedures (Hedge g, 95%CI, −1.976 [−2.654 to −1.297], $P < 0.0001$). Pregabalin reduced 24-hour morphine consumption in gynecologic (Hedge g, 95%CI, −1.085 [−1.582 to −0.441], $P = 0.001$), laparoscopic cholecystectomy (Hedge g, 95%CI, −0.886 [−1.652 to −0.120], $P = 0.023$), orthopedic (Hedge g, 95%CI, −0.720 [−1.118 to −0.323], $P < 0.0001$), spine (Hedge g, 95%CI, −1.016 [−1.732 to −0.300], $P = 0.005$), and miscellaneous procedures (Hedge g, 95%CI, −1.329 [−2.286 to −0.372], $P = 0.006$). Pregabalin resulted in significant sedation in all surgical categories except ENT, laparoscopic cholecystectomy, and gynecologic procedures. Postoperative nausea and vomiting was only significant after pregabalin in miscellaneous procedures.

Analgesic effects and incidence of adverse effects of using pregabalin are not equal in different surgical categories.

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Abbreviations: CI = confidence interval, ENT = ear, nose and throat, NRS = numeric rating scale, OR = odds ratio, PCA = patient-controlled analgesia, PONV = postoperative nausea and vomiting, RCT = randomized controlled trial, SD = standard deviation, VAS = visual analogue scale.

INTRODUCTION

Pregabalin is a structural analogue of gamma-aminobutyric acid that acts as a potent ligand for alpha 2-delta subunits of the voltage-gated calcium channels in the nervous system. Such action results in a reduction in the depolarization-induced influx of calcium, hence a reduction in the release of excitatory neurotransmitters including glutamate, noradrenaline, dopamine, and serotonin.[1] Compared with gabapentin, pregabalin is more potent, is associated with fewer adverse effects, and has a more predictable and linear pharmacokinetic profile.[1,2] Its absorption is extensive, rapid, and proportional to dose.[1,2] Pregabalin is an attractive adjuvant for perioperative analgesia in this regard as it can be taken on an empty stomach, does not lead to gastrointestinal bleeding, and is generally well-tolerated.[3]

A multimodal analgesic technique is now often employed in acute postsurgical pain management in an attempt to improve analgesic efficacy and decrease requirement for opioids that are associated with undesirable adverse effects.[4] Uses of pregabalin therefore range from treatment of neuropathic pain to being an adjunct in the multimodal management of postsurgical pain.[4]

The efficacy of pregabalin in treating acute postsurgical pain has been demonstrated in numerous studies. A recent meta-analysis has suggested that pregabalin, at all doses and administration regimens, has opioid-sparing effects and reduces pain scores in the postsurgical setting,[5] at the expense of increased sedation and visual disturbances; however, the efficacy of pregabalin in providing such in various surgical categories remains uncertain, and it is not known whether the risk : benefit ratio is greater for certain surgical categories. Therefore, the aim of this meta-analysis was to evaluate the analgesic efficacy of pregabalin in reducing postsurgical pain in terms of 2- and 24-hour postsurgical visual analogue scale (VAS) pain scores and 24-hour accumulative morphine-equivalent consumption, in various surgical categories to provide a useful reference in perioperative care.

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MATERIALS AND METHODS

Protocol

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting meta-analyses, http://links.lww.com/MD/A495.[6] Approval by ethics committee or written consent were not required for the extraction of data on studies already conducted for the purposes of this meta-analysis. Before commencing this meta-analysis, all authors agreed on the inclusion and exclusion criteria, which were articles with at least the abstract published in English, and gave data on at least 1 of the primary outcomes. This protocol was not published.

Eligibility Criteria

Studies considered for inclusion in the meta-analysis were randomized, double-blinded, controlled trials (RCTs) that investigated a minimum of 10 subjects in each group[6] and reported on relevant pain outcomes with intervention or treatment with perioperative pregabalin. These studies had to present data for at least 1 of our prespecified outcome variables, which were 2- or 24-hour postsurgical pain or 24-hour morphine-equivalent consumption.

Systematic Search

A comprehensive search for literature for pregabalin was performed between August 2014 to April 2015, using PubMed, Ovid via EMBASE, Google Scholar, and ClinicalTrials.gov with no limitation on the year of publication or language. Attempts were made at accessing www.clinicalstudyresults.org to identify potentially relevant studies that have not been published in medical journals, but the website is no longer in use. The keywords used in the search included ''pregabalin,'' ''lyrica,'' ''analgesia,'' ''acute pain,'' ''post-surgical pain,'' and ''post-operative pain.'' Identified references were screened using title, abstract, and keywords. Searches of the reference lists of identified studies were also made.

Study Selection and Data Collection

Two primary investigators (D.M.H.L. and S.W.C.) screened the titles independently and removed the studies that did not meet the specified screening criteria. Abstracts, literature reviews, and meta-analyses were excluded. Potentially eligible trials were analyzed in detail on the basis of the full text and disagreements were discussed between D.M.H.L. and S.W.C. Data extraction was performed by the 2 reviewers (D.M.H.L. and S.W.C.) independently and included data on the patient (number of subjects, type of surgery, and type of anesthesia), data on the intervention and control (dose and frequency of pregabalin administered), and data on the outcomes (pain intensity, given as acute pain scores at rest, total opioid-equivalent consumption, and adverse effects including nausea, vomiting, sedation, and visual disturbance). Assessing each study for surgical category was performed by D.M.H.L. and C.-W.C.

Data Extraction

The pain intensity measured by either VAS or numeric rating scale (NRS) was extracted as pain scores. These scales have been shown to correlate well.[7] The cumulative opioid consumption at the closest time to 24 hours postsurgery was extracted and converted to an equianalgesic dose of parenteral morphine in mg, based on the following scale: 15 : 1 for hydromorphone, 1.3 : 1 for oxycodone, 1 : 100 for fentanyl, 20 : 1 for codeine, 10 : 1 for tramadol, 10 : 1 for pethidine, 4 : 1 for hydrocodone, 1 : 100 for remifentanil, 1 : 1 for piritramide, and 1 : 1 for nalbuphine.[8–11] If results were presented as the number of doses given, data were extracted from the methods section to ascertain the dosage and then converted to equianalgesic dose of parenteral morphine in mg for inclusion in the meta-analysis. Data regarding postsurgical analgesic consumption were not included from studies that did not utilize opioids during the postsurgical period[12–14] or if data were presented as the number of patients who required rescue analgesics, although pain scores and other information from these studies were included in the analysis whenever given.

The primary outcomes of this present study were pain scores at rest at 2 and 24 hours postsurgery, and morphine-equivalent consumption in the first 24 hours postsurgery. Secondary outcomes were sedation at first assessment and adverse effects. Pain scores at 2 hours postsurgery were selected as the first time point for analysis because pain prior to that time point might be reduced by the effects of analgesics administered during anesthesia. Where pain scores were not available at 2 hours postsurgery, the closest time point was used. Pain scores and opioid consumption at 24 hours postsurgery were chosen in this study as most trials assessed here ceased data collection after 24 hours. Where data were presented graphically, the originals were obtained from the authors or extracted from graphs if no response was obtained from the authors. Twenty-eight corresponding authors were emailed for further details regarding data in the published studies. Seventeen of the emailed authors replied with further data not available in the published articles.

Studies were classified according to surgical categories, these were gynecologic, orthopedic (not including spine surgery), spine, ear, nose and throat (ENT), cardiothoracic surgery, and laparoscopic cholecystectomy. Where studies reported cumulative data on several different surgical categories or if the authors were only able to find 1 or 2 studies of that surgical category (eg, eye surgeries and breast surgeries), these were included in a miscellaneous, or >1 surgical category, group.

Assessment of Risk of Bias

The quality of the studies was assessed by 2 investigators (D.M.H.L. and S.W.C.) independently, using the Cochrane Collaboration's tool for assessing risk of bias.[15]

Statistical Analysis

Meta-analysis was used to assess the pooled effects of pregabalin 2 hours and 24 hours postsurgery. If the study included different doses of pregabalin, the higher dosage was used in this analysis. Data were analyzed using Comprehensive Meta-Analysis software (version 2.2.064, Englewood, NJ). Meta-regression was not performed in this review as a minimum number of 10 studies per subgroup is required.[16]

VAS pain scores or NRS pain scores were extracted from each study. Mean and standard deviation (SD) values were used when available, but when median and range data were presented, the mean was estimated using the median value, or the median value itself was used if the sample size exceeded 25 subjects in each group.[17] In addition to the various different scoring methods used to assess pain, another major consideration was the heterogeneity of the studies, which included different types of patients, different pregabalin regimens in

terms of time, dose and frequency, and method of administration. To take into consideration the heterogeneity of the studies, Hedge *g* standardized mean difference, which is the difference between the 2 means divided by the pooled SD, with a correction for small sample bias, using a random-effects model was computated and reported as the effect size between the pregabalin and the control groups. Hedge *g* was chosen as most of the studies investigated in this meta-analysis were small (<40 subjects per group). Hedge *g* is also an index of treatment efficacy independent of the scoring system used to measure efficacy, which is particularly useful in the present study as VAS 0–10, VAS 0–100 and NRS have all been used as pain scoring systems.

With regard to the analysis of adverse effects of pregabalin, in studies that have categorized patients according to a score (eg, sedation score) and if continuous data were available, this was inputted as means (SD). For studies that have categorized patients according to none, slight, moderate, or severe sedation, all patients, except those who had been classified as ''none'' by the investigators were regarded as being sedated for the purposes of this present meta-analysis, and these data were inputted using dichotomous data handling techniques. A Forest plot was generated for each endpoint and Hedge *g* with 95% confidence intervals (CIs) were reported. Effects on dichotomous outcomes such as visual disturbances, nausea, vomiting, and postsurgical nausea and vomiting were reported using odds ratio (OR) with a random-effects model. Publication bias was assessed using Funnel plots (Comphrensive Meta-Analysis).[18] Sensitivity analysis was assessed using the 1 study removed technique. For all tests, statistical significance was defined as a 2-tailed *P* value of < 0.05.

RESULTS

Our primary search strategy identified 1700 publications. Seventy-four studies were included in this meta-analysis (Supplementary Figure 1, http://links.lww.com/MD/A495). Results here were presented as all included studies and then according to the surgical category.

Risk of Bias

The results of the risk of bias assessment are summarized in Supplementary Table 1, http://links.lww.com/MD/A495.

Study Protocols

The study protocols of the included trials varied significantly and led to considerable heterogeneity.

It is important to note that the primary outcomes as defined in this meta-analysis were not necessarily the primary outcomes of the published trials, and therefore those trials might not be powered to detect significant differences for the variables included in this meta-analysis. The primary outcomes of the trials are given in Tables 1–7.

Effect of Pregabalin on Primary Outcomes in all Surgical Categories

Two-Hour VAS pain scores

A total of 60 studies with a total of 2019 patients taking pregabalin and 2019 patients on the control treatment that reported pains scores at or around 2 hours postsurgery were included. Overall, pregabalin reduced VAS pain scores at 2 hours postsurgery (Hedge *g* and 95%CI, −0.970 [−1.197 to −0.743], *z* score −8.389, $P < 0.0001$), Figure 1.

Twenty-Four Hour VAS Pain Scores

A total of 57 studies with a total of 2033 patients taking pregabalin and 2033 patients on the control treatment that reported pains scores at 24 hours postsurgery were included. Overall, pregabalin reduced pain scores at 24 hours postsurgery (Hedge *g* and 95%CI, −0.442 [−0.665 to −0.220], *z* score −3.894, $P < 0.0001$), Figure 2.

Subgroup Analysis According to Dosing Regimen

Fifty-five studies that provided information on 24-hour pain scores were categorized according to whether a single dose (prior to surgery) or multiple doses (starting from the night, or days prior to surgery) were administered. There was no difference seen in 24-hour pain scores in these 2 subgroups. Pregabalin reduced pain scores at 24 hours postsurgery regardless of whether a single dose (Hedge *g* and 95%CI, −0.566 [−0.914 to −0.218], *z* score −3.191, $P = 0.001$), or multiple doses were administered (Hedge *g* and 95%CI, −0.322 [−0.571 to −0.073], *z* score −2.536, $P = 0.011$).

Twenty-Four Hour Morphine-Equivalent Consumption

Forty-six studies with a total of 1610 patients taking pregabalin and 1636 patients on the control treatment that reported morphine-equivalent consumption at 24 hours postsurgery were included. Overall, pregabalin reduced morphine-equivalent consumption at 24 hours postsurgery (Hedge *g* and 95%CI, −0.932 [−1.212 to −0.652], *z* score −6.519, $P < 0.0001$), Figure 3.

Effect of Pregabalin on Primary Outcomes in Different Surgical Categories

Cardiothoracic Procedures

There were 4 studies[19–22] with a total of 107 patients taking pregabalin and 110 patients on the control treatment in this group. Pregabalin reduced the pain score at rest 2 hours postsurgery ($P = 0.005$). No significant difference was seen in pain score at rest at 24 hours postsurgery ($P = 0.537$) or morphine-equivalent consumption ($P = 0.239$), Figure 4 (Table 8).

ENT Procedures

There were 6 studies[12–14,23–25] with a total of 265 patients taking pregabalin and 266 patients on the control treatment in this group. Pregabalin reduced the pain score at rest 2 hours postsurgery ($P < 0.0001$) and pain score at rest at 24 hours postsurgery ($P = 0.004$). No statistically significant reduction in morphine-equivalent consumption was seen ($P = 0.568$), Figure 5.

Gynecologic Procedures

There were 17 studies[26–42] with a total of 980 patients taking pregabalin and 730 patients on the control treatment in this group. Pregabalin reduced the pain score at rest 2 hours postsurgery ($P < 0.0001$), pain score at rest at 24 hours postsurgery ($P = 0.001$), and the morphine-equivalent consumption ($P = 0.001$), Figure 6A.

Due to the heterogeneity within the gynecologic group, a subanalysis was performed on open hysterectomy studies only.[27–33,36,37,41,42] There were 11 studies with a total of 468 patients taking pregabalin and 485 patients on the control

TABLE 1. Characteristics of Studies in the Cardiothoracic Surgery Category

Cardiothoracic surgery			Intervention	Outcomes	Results
Reference	**Procedure**	**Anaesthesia and Post-surgical analgesia**	**Experimental and comparison group(s) (n), pregabalin dose and administration**	**Primary outcome, follow-up time and pain scoring system**	**2 h pain score mean (SD) 24 h pain score mean (SD) 24 h total morphine consumption mean (SD)**
Fawzi, 2013[19]	Thoracotomy	*General anaesthesia.* Post-surgery: Oral paracetamol 1g every 6 h, oral tramadol 50 mg every 8 h. i.v morphine 0.1 mg kg^{-1} if required.	Pregabalin 75 mg (30), Placebo (30), Orally twice daily for 5 days pre-surgery until last dose at 2 h prior to surgery	Pain score up to 48 h post-surgery, 6 months, (VAS scores)	Only morphine consumption data available, Pregabalin 26.2 (4.6), Control 41.8 (8.2).
Joshi, 2013[20]	Off-pump coronary artery bypass	*General anaesthesia.* Post-surgery: Tramadol 1 mg kg^{-1}, if required, paracetamol 1 g every 6 h post-surgery.	Pregabalin 150 mg (20), Placebo (20), Orally 2 h prior to surgery (150 mg), then every 12 h (75 mg) for 2 days post-surgery	Pain scores 0-48 h post-surgery, 48 h, (VAS scores)	Only p values given for pain scores at 2 and 24 h, both timepoints with pregabalin group pain scores lower than control group $p < .05$. Morphine consumption; Pregabalin 41.00 (6.00), Control 42.00 (10.00).
Pesonen, 2011[21]	Primary elective coronary artery bypass grafting with cardiopulmonary bypass or single valve repair or replacement with cardiopulmonary bypass	*General anaesthesia.* Post-surgery: i.v oxycodone, 0.05 mg kg^{-1} when required i.v paracetamol 1 g 2 h post-surgery and 3 times daily.	Pregabalin 150 mg (27), Placebo (30), Orally 60 mins prior to surgery 150 mg, and 75 mg twice daily for 5 post-operative days.	Reduction in oxycodone consumption; 3 months; (VRS scores)	Only 2 h pain scores given as $p = .02$.
Sundar, 2012[22]	Elective off-pump coronary artery bypass surgery	*General anaesthesia.* Post-surgery: i.v. fentanyl 0.5 μg/kg.	Pregabalin 150 mg (30), Placebo (30), Orally 60 mins prior to surgery.	Fentanyl consumption during and 24 h post-surgery; 24 h; (VAS scores)	2 h pain, pregabalin 2.03 (0.61), Control 2.20 (0.61). 24 h pain, pregabalin 2.07 (0.74), Control 2.00 (0.64). Morphine, pregabalin 18.00 (13.00), Control, 19.00 (14.00).

i.v. = intravenous, SD = standard deviation, VAS = visual analogue scale, VRS = verbal rating scale.

TABLE 2. Characteristics of Studies in the ENT Surgery Category

Ear, nose and throat surgery			Intervention	Outcomes	Results
Reference	**Procedure**	**Anaesthesia and Post-surgical analgesia**	**Experimental and comparison group(s) (n), pregabalin dose and administration**	**Primary outcome, follow-up time and pain scoring system**	**2 h pain score mean (SD) 24 h pain score mean (SD) 24 h total morphine consumption mean (SD)**
Demirhan, 2013[23]	Elective rhinoplasty	*General anaesthesia*. Post-surgery: PCA tramadol 20 mg bolus, i.v pethidine 50 mg if required	Pregabalin 300 mg (20), Placebo (20), Pregabalin and dexamethasone (20), Orally 60 mins prior to surgery	Reduction in tramadol consumption 0-24 h post-surgery; 24 h; (NRS scores)	2 h pain score given as $p = .058$. Morphine consumption, mean value given, pregabalin 2.00, control, 4.00.
Demirhan, 2014[24]	Elective septoplasty	*General anaesthesia*. Post-surgery: PCA tramadol 20 mg bolus i.v Pethidine 0.5mg/kg as required	Pregabalin 300 mg (30), Placebo (30), Pregabalin + dexamethasone (30), Orally 60 mins prior to surgery	Reduction in tramadol consumption; 24 h; (NRS scores)	2 h pain score, pregabalin 1.00 (1.095), control 1.60 (1.562). No pain scores at 24 h recorded for pregabalin group, control group, 0.30 (0.9). Morphine consumption, mean value given, pregabalin 1.80, control 4.00.
Jadeja, 2014[13]	Elective middle ear surgery	*General anaesthesia*. Post-surgery: i.v diclofenac 1.5 mg/kg bolus, i.v tramadol 50 mg if required.	Pregabalin 150 mg (30), Placebo (30), Orally 60 mins prior to surgery.	Reduction in VAS; 24 h; (VAS scores)	2 h pain score, pregabalin, 3.78 (0.92), control, 6.13 (1.74). 24 h pain score, pregabalin, 2.78 (0.39), control 3.46 (0.48).
Kim, 2014[14]	Septoplasty	*General anaesthesia*. Post-surgery: Acetaminophen 650 mg 3 times daily, i.v Pethidine 50 μg as required.	Pregabalin 150 mg (24), Placebo (vitamin complex) (23), Orally 60 mins prior to surgery and 12 h after initial dose.	Reduction in VNRS; 48 h; (VNRS scores)	Pain scores at 2 and 24 h given as $p < .05$ with pregabalin lower than control group. No morphine consumption data given.
Mathiesen, 2011[25]	Bilateral tonsillectomy	*General anaesthesia*. Post-surgery: First hr post-surgery, i.v morphine on request, 2.5 mg. Oral paracetamol, 1000 mg from 1 h post-surgery and then every 8 h. 1st 24 hrs post-surgery, ketobemidone as necessary.	Pregabalin (300mg) + paracetamol (45), Placebo + paracetamol (43), Pregabalin + paracetamol + dexamethasone (43), Orally 60 mins prior to surgery.	Pain during swallowing at 2 h post-surgery; (VAS scores)	2 h pain score, pregabalin 37.3 (25.2), control 45.0 (23.8). 24 h pain score, pregabalin 37.1 (25.6), control 46.7 (28.3). Morphine consumption not different between two groups, given as $p > .05$.
Sagit, 2013[12]	Elective septoplasty	*General anaesthesia*. Post-surgery: i.v diclofenac 75 mg if required.	Pregabalin 75 mg (50), Pregabalin 150 mg (46), Placebo (47), Orally 60 mins prior to surgery.	Reduction in pain scores; 24 h; (VAS scores)	2 h pain score, pregabalin 40.0 (23.0), control 57.2 (21.9). 24 h pain score, pregabalin 3.3 (6.6), control 20.9 (14.5). No morphine consumption data.

ENT = ear, nose, and throat, i.v. = intravenous, NRS = numeric rating scale, PCA = patient-controlled analgesia, SD = standard deviation, VAS = visual analogue scale, VNRS = verbal numerical rating scale.

TABLE 3. Characteristics of Studies in the Gynecologic Surgery Category

Gynaecological surgery			Intervention	Outcomes	
Reference	**Procedure**	**Anaesthesia and Post-surgical analgesia**	**Experimental and comparison group(s) (n), pregabalin dose and administration**	**Primary outcome, follow-up time and pain scoring system**	**2 h pain score mean (SD) 24 h pain score mean (SD) 24 h total morphine consumption mean (SD)**
Bafna, 2014[26]	Elective gynaecological surgeries (no further details given)	*Spinal anaesthesia.* Post-surgery: Intramuscular diclofenac 75 mg.	Pregabalin 150 mg (30), Placebo (30), Gabapentin (30), Orally 1 h prior to surgery.	Doses of rescue analgesic in first 24 h post-surgery; 24 h; (VAS scores)	2 h pain score, pregabalin 2.3 (0.7), control 2.8 (0.6). No data for 24 h pain score. No morphine consumption data.
Chotton, 2014[27]	Elective abdominal hysterectomy	*General anaesthesia.* Post-surgery: Ketorolac.	Pregabalin 150 mg (45), Placebo (45), Orally 1 h prior to surgery.	Severity of post-operative pain; 24 ; (VAS scores)	2 h pain score, pregabalin vs control, p = .001. 24 h pain score, pregabalin vs control, p = .013. No morphine consumption data.
Eman, 2014[28]	Total abdominal hysterectomy	*General anaesthesia.* Post-surgery: PCA morphine.	Pregabalin 150 mg (20), Placebo capsule (20), Single dose given orally 60 mins prior to surgery.	Not stated; 24 ; (VAS scores)	2 h pain score, pregabalin 7.3, control 8.0. 24 h pain score, pregabalin 0.8, control 2.7. Morphine consumption data, pregabalin 19.9 (6.5), control 35.1 (5.5).
Fassoulaki, 2012[29]	Abdominal hysterectomy or myomectomy	*General anaesthesia.* Post-surgery: PCA i.v morphine.	Pregabalin 150 mg (39), Placebo (41), Orally every 8 h starting from one day prior to surgery at 14:00 and continuing for 5 days post-surgery.	Morphine consumption from 0-48 h post-surgery; 3 months; (VAS scores)	2 h pain score, pregabalin 6.4 (2.4), control 7.3 (2.5). 24 h pain score, pregabalin 2.5 (1.9), control 3.1 (1.8). Morphine consumption data, pregabalin 21.0 (12.0), control 33.0 (16.0).
George, 2014[30]	Open abdominal hysterectomy	*General anaesthesia.* Post-surgery: PCA morphine 1 mg, naproxen 500 mg orally on request.	Pregabalin 75 mg (31), Pregabalin 150 mg (28), Placebo (30), Orally 2 h prior to surgery and 2 h after initial dose.	Cumulative morphine consumption at 24 h post-surgery; 6 months; (NRS scores)	2 h pain score, pregabalin 4.3 (2.1), control 5.4 (2.2). 24 h pain score, pregabalin 1.1 (1.2), control 1.9 (1.6). Morphine consumption data, pregabalin 44.3 (20.9), control 54.0 (26.2).
Ghai, 2011[31]	Abdominal hysterectomy	*General anaesthesia.* Post-surgery: Diclofenac sodium 1 mg/kg intramuscular, and tramadol 10 mg i.v if required.	Pregabalin 300 mg (30), Placebo (30), Given orally 1-2 h prior to surgery.	Pain scores at rest and during cough 1-24 h post-surgery; 24 h; (VAS scores)	2 h pain score, pregabalin 1.5, control 2.5. 24 h pain score, pregabalin 2.0, control 2.0. No morphine consumption data.
Ittichaikulthol, 2009[32]	Elective abdominal hysterectomy with or without salphingo-oophorectomy	*General anaesthesia.* Post-surgery: Morphine 3 mg i.v as required.	Pregabalin 300 mg (38), Oral lorazepam (40), Given orally 1 h prior to surgery.	Pain scores at rest 0-24 post-surgery; 24 h; (VNRS scores)	2 h pain score, pregabalin 5.5, control 3.5. 24 h pain score, pregabalin 2.0, control 3.5. Morphine consumption data, pregabalin 5.0 (6.0), control 20.0 (6.0).
Jo, 2011[33]	Total abdominal hysterectomy	*General anaesthesia.* Post-surgery: i.v fentanyl 25 μg and ondansetron 4 mg. PCA fentanyl 0.3 μg/kg.	Pregabalin 150 mg + remifentanil 5 ng/ml (20), Placebo (20), Remifentanil (20), Oral pregabalin 1 h prior to surgery and 12 hrs post-surgery, total 3 doses.	VAS at rest and coughing 48 h post-surgery; Cumulative fentanyl consumption; 3 months; (VAS scores)	2 h pain score, pregabalin 2.75 (0.35), control 3.6 (0.65). No data for 24 h pain score. Morphine consumption data, pregabalin 42.0 (18.0), control 31.0 (19.0).
Jokela, 2008[34]	Laparoscopic hysterectomy	*General anaesthesia.* Post-surgery: 0.025 mg doses fentanyl i.v on request, in recovery room, oral ibuprofen 800 mg.	Pregabalin 75 mg + ibuprofen 800 mg (30), Pregabalin 150 mg + ibuprofen 800 mg (26), Ibuprofen 800 mg (28), All medications given orally 60 mins prior to surgery.	Pain scores at rest and in motion 1-8 h post-surgery; 24 h; (VAS scores)	No pain score data. Morphine consumption data, pregabalin 13.0 (8.0), control 14.0 (8.0).
Jokela, 2008[35]	Day-case gynaecological laparoscopic surgery	*General anaesthesia.* Post-surgery: PCA oxycodone, oral ibuprofen 800 mg, paracetamol and codeine on request.	Pregabalin 150 mg (27), Pregabalin 300 mg (29), Diazepam (29), Given orally 60 mins prior to surgery and 12 hours post-surgery.	Pain scores and analgesic consumption; 3 days; (VAS scores)	N/A.

Gynaecological surgery			Intervention	Outcomes	
Reference	**Procedure**	**Anaesthesia and Post-surgical analgesia**	**Experimental and comparison group(s) (n), pregabalin dose and administration**	**Primary outcome, follow-up time and pain scoring system**	**2 h pain score mean (SD) 24 h pain score mean (SD) 24 h total morphine consumption mean (SD)**
Lalenoh, 2015[36]	Hysterectomy (no other details given)	*General anaesthesia.* Post-surgery: PCA morphine.	Pregabalin 3mg/kg (26), Placebo (26), Orally 1 h before surgery.	VAS, Morphine consumption, blood pressure & heart rate, glutamate and substance-P levels in blood. 24; (VAS scores)	2 h pain score, pregabalin 40.0, control 55.0. 24 h pain score, pregabalin 20.0, control 30.0. Morphine consumption data, pregabalin 7.0, control 10.0.
Mathiesen, 2009[37]	Abdominal hysterectomy with or without salphingo-oophorectomy	*General anaesthesia.* Post-surgery: Oral paracetamol 1000 mg/6 h PCA morphine.	Pregabalin 300 mg + paracetamol 1000 mg (39) Pregabalin 300 mg + paracetamol 1000 mg + dexamethasone 8 mg (37), Paracetamol 1000 mg + placebo (40), Pregabalin and paracetamol given orally, dexamethasone intravenous, 60 mins prior to GA.	PCA morphine consumption from 0-4 h and 0-24 h post-surgery; 24 h; (VAS scores)	2 h pain score, pregabalin 3.828 (2.197), control 4.025 (2.042) 24 h pain score, pregabalin 1.20 (2.00), control 1.50 (2.00), Morphine consumption data, pregabalin 32.0 (20.0), control 35.0 (18.0).
Nutthachote, 2014[38]	Elective laparoscopic gynaecological surgery	*General anaesthesia.* Post-surgery: Oral etoricoxib 120 mg, once daily. Acetaminophen 1000 mg on request. Meperidine 1mg/kg i.v as necessary.	Pregabalin 75 mg (27), Placebo (27), Orally 2 h prior to surgery.	Pain VAS at 24 and 48 h post-surgery; 48; (VAS scores)	2 h pain score, pregabalin vs control, $p < .05$, Morphine consumption data, pregabalin 0.1 (0.37), control 0.8 (0.269).
Paech, 2007[39]	Minor gynaecological surgery involving the uterus	*General anaesthesia.* Post-surgery: Fentanyl 20 or 30 μg if required. i.v tramadol 50 mg and oral diclofenac 50 mg if required.	Pregabalin 100 mg (41), Placebo (45), Orally 60 mins prior to surgery.	Pain at discharge; 24 h;	2 h and 24 h pain scores, pregabalin vs control, $p = .80$ No data on morphine consumption.
Prasad, 2014[40]	Vaginal hysterectomy	*Spinal anaesthesia.* Post-surgery: Diclofenac sodium 1 mg/kg intramuscular.	Pregabalin 150 mg (30), Placebo (30), Clonidine (30), Orally 1.5 h prior to surgery.	VAS score 0-24 h post-surgery; 24 h; (VAS scores).	2 h pain score, pregabalin 4.94 (1.34), control 6.48 (0.630). 24 h pain score, pregabalin 3.58 (0.96), control 6.0 (1.18). No data on morphine consumption.
Singla, 2014[41]	Elective abdominal hysterectomy with or without salphingo-oophorectomy using transverse section	*General anaesthesia.* Post-surgery: PCA morphine.	Pregabalin 150 mg (161), Pregabalin 300 mg (166), Placebo (169), Oral, 12h and 2 h before surgery; continued treatment for 4 weeks post-surgery.	Mean worst pain over past 24 h; 6 months; (NRS scores).	No data on 2 h pain score. 24 h pain score, pregabalin 3.76 (0.184), control 3.93 (0.18). Morphine consumption data, pregabalin 111.27 (7.211), control 124.44 (7.16).
Yücel, 2011[42]	Abdominal hysterectomy	*General anaesthesia.* Post-surgery: PCA i.v morphine.	Pregabalin 300 mg (30), Pregabalin 600 mg (30), Placebo (30), Orally 4 prior to surgery.	Cumulative morphine consumption at 24 h post-surgery; 24 h; (VAS scores).	2 h pain score, pregabalin 4.37 (0.49), control 6.23 (0.46). 24 h pain score, pregabalin 1.47 (0.50), control 1.73 (0.9). Morphine consumption, pregabalin vs control, $p = .001$.

GA = general anaesthesia, i.v. = intravenous, NRS = numeric rating scale, PCA = patient-controlled analgesia, SD = standard deviation, VAS = visual analogue scale, VNRS = verbal numerical rating scale.

TABLE 4. Characteristics of Studies in the Laparoscopic Cholecystectomy Category

Laparoscopic Cholecystectomy surgery		Intervention	Outcomes	Results
Reference	**Anaesthesia and Post-surgical analgesia**	**Experimental and comparison group(s) (n), pregabalin dose and administration**	**Primary outcome, follow-up time and pain scoring system**	**2 h pain score mean (SD) 24 h pain score mean (SD) 24 h total morphine consumption mean (SD)**
Agarwal, 2008[43]	General anaesthesia. Post-surgery: PCA fentanyl 2 μg kg^{-1} h^{-1}.	Pregabalin 150 mg (27), Placebo (29), Orally 60 mins prior to surgery.	Post-operative VAS score; 24 ; (VAS scores).	Median pain scores given, with pregabalin lower than control at 2 and 24 h $p < .05$. Morphine consumption, pregabalin group 17.0 (4.00), control 23.0 (3.00).
Balaban, 2011[44]	General anaesthesia. Post-surgery: i.v fentanyl 25 μg if required.	Pregabalin 150 mg (30), Pregabalin 300 mg (30), Placebo (30), Orally 60 mins prior to surgery.	Pain 0-6 h post-surgery; 36 h; (VAS scores).	2 h pain score, pregabalin 0.30 (0.7), control 1.03 (0.8). No data on 24 h pain scores or morphine consumption.
Bekawi, 2014[45]	General anaesthesia. Post-surgery: i.m pethidine 1mg/kg. i.m diclofenac 75 mg if required.	Pregabalin 150 mg (30), Placebo (30), Gabapentin (30). Orally pregabalin 2 h prior to surgery and 12 h post-surgery, then twice daily for 2 days.	Reduction in opioid consumption; 24 h; (VAS scores).	2 h pain score, pregabalin 1.07 (0.7), control 1.27 (0.6). 24 h pain score, pregabalin 0.60 (0.6), control 1.13 (0.6). No data on morphine consumption.
Chang, 2009[46]	General anaesthesia. Post-surgery: i.v pethidine 25 mg 10 min before end of surgery, i.v ketorolac 30 mg on patient request.	Pregabalin (40), Placebo (40), Orally 60 mins prior to surgery and 12 h after first dose.	Post-operative shoulder pain; 48 h; (NRS scores).	2 pain score, pregabalin 0.50 (1.1), control 0.5 (1.3). 24 pain score, pregabalin 2.80 (2.5), control 2.3 (1.8). No data on morphine consumption.
Peng, 2010[47]	General anaesthesia. Post-surgery: Fentanyl bolus, 25-50 μg. i.v Dimenhydrinate 25-50 mg upon request, acetaminophen 325 mg with codeine 30 mg as required.	Pregabalin 50 mg (48), Pregabalin 75 mg (48), Placebo (46). Orally 60 mins prior to surgery 12 and 24 h post −surgery.	Post-operative pain scores; (NRS scores).	2 h pain score given as $p = .05$. 24 h pain score given as $p = .054$. Morphine consumption, pregabalin, 16.0, control, 30.0.
Sarakatsianou, 2013[48]	General anaesthesia Post-surgery: PCA morphine max dose of 12 mg per 4 h. Paracetamol 1g every 8 h.	Pregabalin 300 mg (20), Placebo (20), Orally 300 mg one night prior to surgery and orally 300 mg 1 h prior to surgery.	Post-operative pain; 24 h; (VAS scores).	2 h pain score, pregabalin 2.30 (1.7), control 4.90 (1.8). 24 h pain score, pregabalin 1.00 (1.1), control 3.25 (2.0) Morphine consumption, pregabalin, 1.50, control, 3.75.

i.m. = intramuscular, i.v. = intravenous, NRS = numeric rating scale, PCA = patient-controlled analgesia, PCEA = patient controlled epidural anaesthesia, SD = standard deviation, VAS = visual analogue scale.

TABLE 5. Characteristics of Studies in the Orthopedic Surgery Category

Orthopaedic surgery (excluding spine surgery)			Intervention	Outcomes	Results
Reference	**Procedure**	**Anaesthesia and Post-surgical analgesia**	**Experimental and comparison group(s) (n), pregabalin dose and administration**	**Primary outcome, follow-up time and pain scoring system**	**2 h pain score mean (SD) 24 h pain score mean (SD) 24 h total morphine consumption mean (SD)**
Akhavanakbari, 2013[49]	Lower limb orthopaedic surgery (no further details given)	Spinal anaesthesia. Post-surgery: i.v pethidine 50 mg bolus if required.	Pregabalin 150 mg (30), Placebo (30), Orally 2 h prior to surgery.	Reduction in VAS; 24 h; (VAS scores).	No data on 2 h pain scores. 24 h pain score, pregabalin 2.560 (0.1), control 5.730 (0.2). Morphine consumption, pregabalin, 0.312 (0.27), control, 0.121 (0.39).
Buvanendran, 2010[50]	Total knee arthroplasty	Spinal-epidural anaesthesia. Post-surgery: PCEA basal infusion fentanyl 5 μg/ml, bupivacaine 1 mg/ml/6 ml per h for 32 to 42 h. Oral opioids (morphine, oxycodone and hydromorphone) as required.	Pregabalin 300, 150, 75, 50 mg (113), Placebo (115), Orally 300 mg 1 to 2 h prior to surgery. 150 mg twice daily for 10 post-operative days, 75 mg twice daily on days 11 and 12, 50 mg twice daily on days 13 and 14.	Reduction in neuropathic pain; 1 month; (NRS scores).	No data on pain scores. Morphine consumption, pregabalin, 4.55, control, 7.32.
Eskandar, 2013[51]	Elective shoulder arthroscopy	General anaesthesia. Post-surgery: Nalbuphine 4 mg/dose.	Pregabalin 300 mg (40), Placebo (40), Orally 12 h and 1 h prior to surgery.	Pain scores at 24 h post-surgery; 24 h; (VAS scores).	2 h pain score, pregabalin 4.65 (1.5), control 5.80 (1.3). 24 h pain score, pregabalin 2.10 (0.8), control 1.95 (0.8). Morphine consumption, pregabalin, 33.8 (6.9) control, 46.4 (5.7).
Ghoghari, 2014[52]	Lower limb surgery (no further details given)	Spinal anaesthesia. Post-surgery: i.v tramadol 75 mg if required.	Pregabalin 300 mg (25), Placebo (25), i.v. dexamethasone 8 mg + pregabalin 300 mg (25). Orally 60 mins prior to surgery.	VAS score; 24 h; (VAS scores).	2 h pain score, pregabalin 3.04 (0.7), control 4.56 (1.0) 24 h pain score, pregabalin 1.80 (1.0), control 2.72 (0.5) Morphine consumption, pregabalin, 80.0, control, 180.0.
Gonano, 2011[53]	Elective arthroscopic knee surgery for partial meniscectomy	General anaesthesia. Post-surgery: i.v piritramide in 2 mg increments at patients' request.	Pregabalin 300 mg (20), Placebo (20), Orally prior to surgery, time not stated.	VAS anxiety, and VAS pain; (VAS scores).	2 h pain score, pregabalin 2.70 (1.1), control 2.60 (1.2). 24 h pain score, pregabalin 2.60 (1.20), control 2.60 (1.20). Morphine consumption, pregabalin, 2.00 (2.00) control, 4.00 (3.00).
Jain, 2012[54]	Total knee arthroplasty	Spinal epidural block. Post-surgery: Patient controlled epidural analgesia bupivacaine 0.0625% and morphine 0.05 mg/ml. Continuous infusion at 4 ml/hr, bolus dose of 6 ml.	Pregabalin 75 mg (20), Placebo (20), Orally 2 h prior to surgery and at 6am and 6pm on first two post-operative days.	Reduction in morphine consumption; 48 h; (VAS scores).	No data on 2 h pain scores. 24 h pain score, pregabalin 2.20 (0.69), control 3.50 (1.20). Morphine consumption, pregabalin, 3.60 (1.180), control, 7.20 (2.97).
Lee, 2014[55]	Elective, primary total knee arthroplasty for osteoarthritis	General anaesthesia. Post-surgery: PCA fentanyl 20 μg loading and 10 μg boluses at basal background infusion rate of 10 μg/h for 48 hrs. Celecoxib 200 mg every 12 h Hydromorphone 2 mg every 8 h. Oral tramadol 50 mg upon request.	Pregabalin 150 mg + celecoxib 400 mg (21), Celecoxib 400 mg (20), Orally 1 h prior to surgery.	Reduction in pain scores and fentanyl consumption; 48 h; (NRS scores).	2 h pain score, pregabalin 2.67 (0.73), control 3.55 (1.50). 24 h pain score, pregabalin 2.76 (1.14), control 3.40 (1.39). Morphine consumption, pregabalin, 31.0, control, 43.0.
Martinez, 2014[56]	Total hip arthroplasty	General anaesthesia. Post-surgery: PCA morphine 1 to 3 mg.	Pregabalin 150 mg (35), Placebo (38), Ketamine (34), Pregabalin + Ketamine (35), Single dose, time of administration unclear.	Total morphine consumption 0–48 h post-surgery; 48 h; (NRS scores).	2 h pain score, pregabalin 5.0, control 6.0. 24 h pain score, pregabalin 2.5, control 3.0. Morphine consumption, pregabalin, 44.0, control, 77.0.

Orthopaedic surgery (excluding spine surgery)			Intervention	Outcomes	Results
Reference	Procedure	Anaesthesia and Post-surgical analgesia	Experimental and comparison group(s) (n), pregabalin dose and administration	Primary outcome, follow-up time and pain scoring system	2 h pain score mean (SD) 24 h pain score mean (SD) 24 h total morphine consumption mean (SD)
Mathiesen, 2008[57]	Primary alloplastic hip joint replacement surgery	Spinal anaesthesia. Post-surgery: Oral acetaminophen 1g every 8 h, PCA morphine 2.5 mg per bolus.	Pregabalin 300 mg (42), Placebo (42), Pregabalin + dexamethasone (42), Orally 60 mins prior to surgery.	Reduction in morphine consumption; 24 h; (VAS scores).	2 h pain score, pregabalin 0.45 (0.93), control 0.56 (0.101). 24 h pain score, pregabalin 1.28 (1.12), control 1.29 (1.29). Morphine consumption, pregabalin, 25.0 (15.0), control, 50.0 (30.0).
Niruthisard, 2013[58]	Primary total knee arthroplasty for osteoarthritis	Spinal anaesthesia. Post-surgery: PCA morphine 1 mg per bolus.	Pregabalin 150 mg (25), Placebo (27), Placebo + celecoxib 400 mg (23), Pregabalin + celecoxib 400 mg (24), Orally 60 mins prior to surgery.	Reduction in morphine consumption 0-48 h post-surgery; 48 h; (VAS scores).	2 h pain score, pregabalin 0.90 (1.30), control 1.70 (2.50). 24 h pain score, pregabalin 3.30 (2.10), control 2.70 (2.20). Morphine consumption, pregabalin, 18.4 (9.90), control, 18.4 (15.8).
Wang, 2010[59]	Primary, unilateral, first metatarsal bunionectomy surgery with osteotomy	Regional anaesthesia. Post-surgery: PCA hydromorphone. Oral hydrocodone 7.5 mg/ acetaminophen 500 mg if required.	Pregabalin 300 mg (31), Placebo (27), Naproxen (27), Orally 60 mins prior to surgery.	Reduction in opioid consumption; 24 h; (NRS scores).	2 h pain score, pregabalin 4.08, control 5.12. 24 h pain score, pregabalin 4.57, control 5.08. Unable to calculation morphine equivalent consumption.
YaDeau, 2012[60]	Foot or ankle surgery	Spinal-epidural, peripheral nerve-block. Post-surgery: PCA hydromorphone 0.2 mg/ml, 1 to 3 ml bolus. oral oxycodone/ acetaminophen 5/325 mg.	Pregabalin 100 mg (28), Placebo (28), Orally 60 mins prior to surgery 100 mg, then 50 mg every 12 h for 3 days post-surgery.	No. of hours of moderate to severe pain post-surgery; 48 h; (NRS scores).	2 h pain score, pregabalin 0.60 (1.50), control 0.40 (1.10). 24 h pain score, pregabalin 3.40 (2.40), control 2.60 (2.00). Morphine consumption, pregabalin, 9.00 (8.00), control, 14.00 (15.00).

i.m. = intramuscular, i.v. = intravenous, NRS = numeric rating scale, PCA = patient-controlled analgesia, PCEA = patient controlled epidural anaesthesia, SD = standard deviation, VAS = visual analogue scale.

TABLE 6. Characteristics of Studies in the Spine Surgery Category

Spine surgery			Intervention	Outcomes	Results
Reference	**Procedure**	**Anaesthesia and Post-surgical analgesia**	**Experimental and comparison group(s) (n), pregabalin dose and administration**	**Primary outcome, follow-up time and pain scoring system**	**2 h pain score mean (SD) 24 h pain score mean (SD) 24 h total morphine consumption mean (SD)**
Burke, 2010[61]	Elective lumbar discectomy for chronic lumbar sacral radiculopathy	*General anaesthesia.* Post-surgery: Morphine in 2 mg aliquots (recovery), oral codeine and paracetamol with diclofenac 75 mg twice daily. i.m dihydrocodeine, tramadol and morphine and necessary.	Pregabalin 300 mg (18), Placebo (20), Orally 1.5 h prior to surgery (300 mg) and 12 and 24 h post-operatively (150mg).	Cumulative analgesic requirement 0-24 h post-operation; 3 months; (VAS scores).	No data on pain scores. Morphine consumption, pregabalin, 1.55 (2.10), control, 3.30 (3.80).
Choi, 2013[62]	Elective lumbar laminectomy with or without fusion, for chronic lumbo-sacral radiculopathy due to herniated lumbar disc or degenerative spinal stenosis	*General anaesthesia.* Post-surgery: Fentanyl 1 μg/kg administered 20 mins before end of surgery.	Pregabalin 150 mg (36), Placebo (36), Placebo with dexamethasone (36), Orally 60 mins prior to surgery.	Post-operative pain 6 – 24 h post-surgery; 1 month; (VAS scores).	2 h pain score, pregabalin 3.30 (2.4), control 3.70 (2.5). 24 h pain score, pregabalin 2.20 (2.1), control 3.00 (2.1). No data on morphine consumption.
Gianesello, 2012[63]	Elective decompressive lumbar laminectomy with spinal fusion for degenerative spinal stenosis	*General anaesthesia.* Post-surgery: i.v morphine 0.01 mg/kg/h and ketorolac 2.5 mg/h continuous till 48 h post-surgery. i.v morphine 2 mg as required.	Pregabalin 300 mg (30), Placebo (30), Pregabalin 150 mg twice daily for 48 hrs post-surgery. Orally 60 mins prior to surgery.	Reduction in morphine consumption; 1 year; (VAS scores).	2 h pain score, pregabalin 1.80 (0.4), control 3.10 (0.7). 24 h pain score, pregabalin 0.60 (0.8), control 0.20 (0.5). Morphine consumption, pregabalin, 3.00 (2.00), control, 9.50 (2.50).
Hegarty, 2011[64]	Elective lumbar discectomy	*Paracetamol 1 g and diclofenac 75 mg i.v prior to surgery.* Post-surgery: PCA morphine 2 mg per bolus. Oral paracetamol 1 g every 6 h.	Pregabalin 300 mg (14), Placebo (18), Orally 60 mins prior to surgery.	Reduction in morphine consumption; 24 h; (VAS scores).	No data on pain scores. Morphine consumption, pregabalin, 5.00, control, 9.00.
Khurana, 2014[65]	Lumbar discectomy for intervertebral disc prolapse without ligament hypertrophy	*General anaesthesia.* Post-surgery: i.v tramadol.	Pregabalin 75 mg (30), Gabapentin 300 mg (30), Placebo (30), 60 mins prior to surgery and every 8 h post-surgery for 7 days.	Pain score up to 72 h post-surgery; 3 months; (VAS scores).	2 h pain score, pregabalin 3.0, control 9.0. 24 h pain score, pregabalin 0.3, control 1.0.
Kim, 2011[66]	Elective posterior lumbar spinal fusion	*General anaesthesia.* Post-surgery: i.v PCA fentanyl 25 μg/kg, ketorolac 120 mg, ondansetron 8 mg.	Pregabalin 75 mg (28), Pregabalin 150 mg (28), Placebo (28), Orally 1 h prior to surgery and 12 h post-surgery.	Cumulative fentanyl PCA; 48 h; (VAS scores).	2 h pain score, pregabalin 3.0 (2.0), control 4.0 (2.0). 24 h pain score, pregabalin 3.0 (2.0), control 3.0 (2.0).
Kumar, 2013[67]	Elective decompressive lumbar laminectomy	*General anaesthesia.* Post-surgery: Fentanyl and diclofenac.	Pregabalin 150 mg (25), Placebo (25), Tramadol 100 mg (25), Orally 1 h prior to surgery.	Pain score up to 6 h post-surgery; 6 h; (VAS scores).	2 h pain score, pregabalin 2.9 (1.2), control 5.5 (1.3). No data on 24 h pain scores. Morphine consumption, pregabalin, 1.9 (1.6), control, 2.0 (2.0).
Ozgencil, 2011[68]	Elective decompressive lumbar laminectomy and discectomy	*General anaesthesia.* Post-surgery: PCA morphine 2.5 mg.	Pregabalin 150 mg (30), Placebo (30), Gabapentin 600 mg (30), 2 h prior to surgery, and 10 and 22 h post-surgery.	VAS from 0-24 h post-surgery; 24 h; (VAS scores).	2 h pain score, pregabalin 4.5 (1.3), control 5.7 (1.1). 24 h pain score, pregabalin 1.1 (1.2), control 1.5 (0.8). Morphine consumption, pregabalin, 0.36 (0.13), control, 0.51 (0.14).
Spreng, 2011[69]	Elective lumbar single-level microdiscectomy	*General anaesthesia.* Post-surgery: Paracetamol 1000 mg and diclofenac 50 mg. PCA morphine for first 24 h post-surgery.	Pregabalin 150 mg (22), Placebo (24), 60 mins prior to surgery.	VAS up to 120 mins post-surgery; 24 h; (VAS scores).	2 h pain score, pregabalin 2.72 (2.0), control 3.78 (2.5). 24 h pain score, pregabalin 2.36 (1.5), control 2.62 (1.4) Morphine consumption, pregabalin, 25.0, control, 36.0.

i.m. = intramuscular, i.v. = intravenous, PCA = patient-controlled analgesia, SD = standard deviation, VAS = visual analogue scale.

TABLE 7. Characteristics of Studies in the Miscellaneous Surgery Category

Miscellaneous surgery			Intervention	Outcomes	Results
Reference	Procedure	Anaesthesia and Post-surgical analgesia	Experimental and comparison group(s) (n), pregabalin dose and administration	Primary outcome, follow-up time and pain scoring system	2 h pain score mean (SD) 24 h pain score mean (SD) 24 h total morphine consumption mean (SD)
Alimian, 2012[70]	Laparoscopic gastric bypass	*General anaesthesia.* Post-surgery: PCA morphine.	Pregabalin 300 mg (30), Placebo (30), Orally 60 min prior to surgery.	Pain score up to 24 h post-surgery; 24 h; (VAS scores).	2 h pain score, pregabalin, 1.30 (0.6), control 4.10 (1.0). 24 h pain score, pregabalin, 1.20 (0.4), control 1.90 (0.5).
Alimian, 2012[71]	Dacryocysto-rhinostomy	*General anaesthesia.* Post-surgery: Pethidine intramuscularly 25 mg if required.	Pregabalin 300 mg (40), Placebo (40), Orally 60 mins prior to surgery.	VAS pain scores at 0-24 h post-surgery; 24 h; (VAS scores).	2 h pain score, pregabalin, 2.70 (1.4), control 5.40 (1.6). 24 h pain score, pregabalin, 0.60 (0.8), control 1.60 (1.5).
Aydogan, 2014[72]	Percutaneous nephrolithotomy	Post-surgery: PCA morphine 2.5 mg loading dose. i.v tenoxicam 20 mg if required.	Pregabalin 75 mg (30), Placebo (30), Orally 60 mins prior to surgery.	Reduction in morphine consumption; 24 h; (VAS scores).	2 h pain score, pregabalin, 1.85 (0.8), control 2.40 (0.9). 24 h pain score, pregabalin, 1.00 (0.8), control 0.80 (0.4).
Bornemann-Cimenti, 2012[73]	Elective transperitoneal nephrectomy	*General anaesthesia.* Post-surgery: PCA piritramide, 0.02 mg kg^{-1}.	Pregabalin 300 mg (13), Placebo (13), Orally 60 mins prior to surgery.	Reduction in opioid consumption post-surgery; 48 h; (NRS scores).	Morphine consumption, pregabalin, 4.00 (2.00), control, 7.00 (3.00).
Cabrera Schulmeyer, 2010[74]	Laparoscopic sleeve gastrectomy	*General anaesthesia.* Post-surgery: i.v ketoprofen 300 mg in 24 h, rescue i.v morphine 2 mg per bolus.	Pregabalin 150 mg (39), Placebo (41), 2 h prior to surgery.	Reduction in post-surgical morphine consumption and severity of post-surgical pain; 24 h; (VAS scores).	2 h pain score, pregabalin group lower than control, $p = .04$. 24 h pain score, pregabalin group lower than control, $p = .04$. Morphine consumption, pregabalin, 11.51 (7.93), control, 23.07 (9.59).
Chaparro, 2012[75]	Liposuction with or without mammoplasty and abdominoplasty	*General anaesthesia.* Post-surgery: Multimodal, acetaminophen, codeine, tramadol, hydrocodone Ibuprofen or diclofenac as required.	Pregabalin 75 mg (50), Placebo (49), Orally 75 mg one night prior to surgery, then 1 h prior to surgery, then twice a day until 4 days post-surgery.	Post-operative pain at 2-96 h; 96 h; (NRS scores).	2 h pain score, no difference between two groups $p < .05$. 24 h pain score, no difference between two groups $p < .05$. Morphine consumption, pregabalin, 7.50, control, 6.00.
Freedman, 2008[76]	Augmentation mammoplasty	*General anaesthesia.* Post-surgery: Hydrocodone 5 mg as required.	Pregabalin 75 mg (40), Hydrocodone 5 mg (40), Orally 2 h prior to surgery and twice daily for 7 days post-surgery.	Reduction in post-surgical opioid use; 6 months; (Rogers' Pain Scale).	No data on pain scores. Morphine consumption, pregabalin, 10.00 (8.00), control, 34.00 (10.00).
Hemjit Singh, 2014[77]	Open cholecystectomy with right subcostal incision	*General anaesthesia.* Post-surgery: i.v tramadol 1 mg/kg if required.	Pregabalin 150 mg (40), Pregabalin 300 mg (40), Placebo (40), Orally 60 mins prior to surgery.	Reduction in pain scores; 24 h; (VAS scores).	2 h pain score, pregabalin, 0.20 (0.5), control 4.98 (0.5). 24 h pain score, pregabalin, 0.78 (0.5), control 3.60 (0.6)
Hill, 2001[78]	Removal of one or two ipsilateral third molars at least one of which was mandibular and fully or partially impacted in bone	*Local anaesthetic.* Post-surgery: none.	Pregabalin 300 mg (50), Pregabalin 50 mg (49), Placebo (50), Ibuprofen 400 mg (49), Orally post-surgery when pain had reached moderate intensity.	Pain score up to 12 h post-surgery; 12 h; (Pain relief, Pain intensity difference).	2 h pain score, pregabalin group lower than control, $p < .05$.
Kim, 2010[79]	Elective robot-assisted endoscopic thyroidectomy for thyroid cancer	*General anaesthesia.* Post-surgery: i.v fentanyl 50 μg, i.m tramadol 50 mg, ibuprofen 200 mg twice per day, as required.	Pregabalin 150 mg (47), Placebo (47), Orally 60 mins prior to surgery and 12 h after initial dose.	Reduction in VNRS; 3 months; (VNRS scores).	2 h pain score, pregabalin, 2.06 (1.2), control 2.6 (1.4). 24 h pain score, pregabalin group lower than control, $p = .021$.
Kim, 2011[66]	Elective partial or total mastectomy with or without lymph node dissection	*General anaesthesia.* Post-surgery: i.v Fentanyl 50 μg or i.m tramadol 50 mg if required. All patients, aceclofenac 100 mg twice daily on day following surgery.	Pregabalin 75 mg (40), Placebo (40), Orally 60 mins prior to surgery, and 12 h after initial dose.	Reduction in pain scores; 1 month; (VNRS scores).	2 h pain score, pregabalin, 1.54 (1.5), control 2.97 (1.4).

Miscellaneous surgery			Intervention	Outcomes	Results
Reference	Procedure	Anaesthesia and Post-surgical analgesia	Experimental and comparison group(s) (n), pregabalin dose and administration	Primary outcome, follow-up time and pain scoring system	2 h pain score mean (SD) 24 h pain score mean (SD) 24 h total morphine consumption mean (SD)
Lee, 2013[80]	Laparoendoscopic single-site urologic surgery	*General anaesthesia*. Post-surgery: PCA morphine 60 mg, ketorolac 150 mg, ramosetron 0.6 mg in total volume of 100 ml. 0.5 ml per bolus.	Pregabalin 300 mg + remifentanil 0.3 μg/kg/min (31), Remifentanil 0.3 μg/kg/min (29), Oral pregabalin 60 mins prior to surgery.	Pain intensity during movement, 1, 6, 12, and 24 h post-surgery; 24 h; (Linear VAS scores).	2 h pain score, pregabalin, 5.48 (0.9), control 5.76 (0.9). 24 h pain score, pregabalin, 1.42 (0.5), control 2.38 (0.7). Morphine consumption, pregabalin, 27.42 (3.90), control, 30.84 (2.52).
Meek, 2014[81]	Elective excimer laser photorefractive keratectomy	*Local anaesthesia*. Post-surgery: Oxycodone 5 mg/ acetaminophen 500 mg as required.	Pregabalin 75 mg (67), Placebo (63), Orally 2 h prior to surgery, then every 12 h for 4 post-surgical days.	Reduction in subjective pain scores; 5 days; (VAS score and present pain intensity (PPI) score).	2 h pain score, pregabalin, 0.76 (1.1), control 1.03 (1.7). 24 h pain score, pregabalin, 0.63 (0.91), control 0.10 (0.15).
Rajendran, 2014[82]	Infraumbilical and lower limb surgeries (no further details given)	*Spinal anaesthesia*. Post-surgery: Tramadol 100 mg intramuscular as required.	Pregabalin 300 mg (30), Placebo (30), Gabapentin 900 mg (30), Orally 60 mins prior to surgery.	Time to first rescue analgesia and total analgesia; 72 h; (VAS scores).	2 h pain score, pregabalin, 3.20 (0.4), control 6.53 (0.8). 24 h pain score, pregabalin, 6.77 (0.1), control 6.03 (0.8). Morphine consumption, pregabalin, 3.00, control, 12.00.
Sahu, 2010[83]	Below umbiblical surgeries	*Spinal anaesthesia*. Information not given.	Pregabalin 150 mg (35), Placebo (35), Orally 60 mins prior to surgery.	Post-operative pain at 2-24 h; 24 h; (VAS scores).	Only data on time to first analgesic used.
Saraswat, 2008[84]	Miscellaneous surgical procedures	*Spinal anaesthesia*. i.m diclofenac 1 mg/kg.	Pregabalin 300 mg (30), Gabapentin 1200 mg (30), Orally 60 mins prior to surgery.	VAS score at 24 h; (VAS scores).	Only data on time to first analgesic used.
Singla (Pfizer study, hernia) 2014,[41]	Primary, elective, open, unilateral inguinal herniorrhaphy using Lichtenstein mesh repair	*General anaesthesia*. Post-surgery: Naproxen 500 mg. Tramadol 50 mg and acetaminophen 500-650 mg as needed.	Pregabalin 50 mg (108), Pregabalin 150 mg (106), Pregabalin 300 mg (103), Placebo (108), 12 h and 2 h before surgery, then continued treatment for 1 week.	2 and 24 h NRS; Total morphine consumption; Mean worst pain over past 24 h; 6 months; (NRS scores).	2 h pain score, pregabalin, 2.80 (0.18), control 3.10 (0.18). 24 h pain score, pregabalin, 3.3 (0.22), control 3.3 (0.22). Morphine consumption, pregabalin, 6.58 (2.28), control, 16.03 (2.28).
Upendra Singh, 2014[85]	Open cholecystectomy with right subcostal incision	*General anaesthesia*. Post-surgery: i.v tramadol 1 mg/kg if required.	Pregabalin 150 mg (40), Placebo (40), Orally 60 mins prior to surgery.	Reduction in pain scores; 24 h; (VAS scores).	2 h pain score, pregabalin, 0.28 (0.5), control 4.98 (0.5). 24 h pain score, pregabalin, 2.55 (0.8), control 1.05 (0.2).
Wei, 2014[86]	Blepharoplasty, lateral canthoplasty, eyelid retraction surgery, ptosis surgery, or eyelid reconstruction	*Local anaesthesia*. Post-surgery: Acetaminophen 325 mg per tablet, as required.	Pregabalin 150 mg (26), Placebo (23), Oral pregabalin 15 to 60 mins prior to surgery.	Reduction in pain scores 1-48; 48 h; (Linear VAS scores).	2 h pain score, pregabalin, 12.9, control 2.94. 24 h pain score, pregabalin, 1.13, control 0.97.
White, 2009[87]	Miscellaneous, including ear, nose and throat, laparoscopic, urologic and plastic surgery	*General anaesthesia*. Post-surgery: i.v. fentanyl 25-50 μg bolus.	Pregabalin 75 mg (27), Pregabalin 150 mg (27), Pregabalin 300 mg (27), Placebo (27), Orally 60-90 min prior to surgery.	Reduction of pre-operative anxiety 120 min; Post-surgery 7 days; (VRS scores).	2 h pain score, pregabalin, 4.0 (4.0), control 4.0 (3.0). 24 h pain score, pregabalin, 4.0 (3.0), control 2.0 (2.0). Morphine consumption, pregabalin, 6.0 (10.0), control, 7.0 (6.0).

i.m. = intramuscular, i.v. = intravenous, NRS = numeric rating scale, PCA = patient-controlled analgesia, SD = standard deviation, VAS = visual analogue scale, VRS = verbal rating scale.

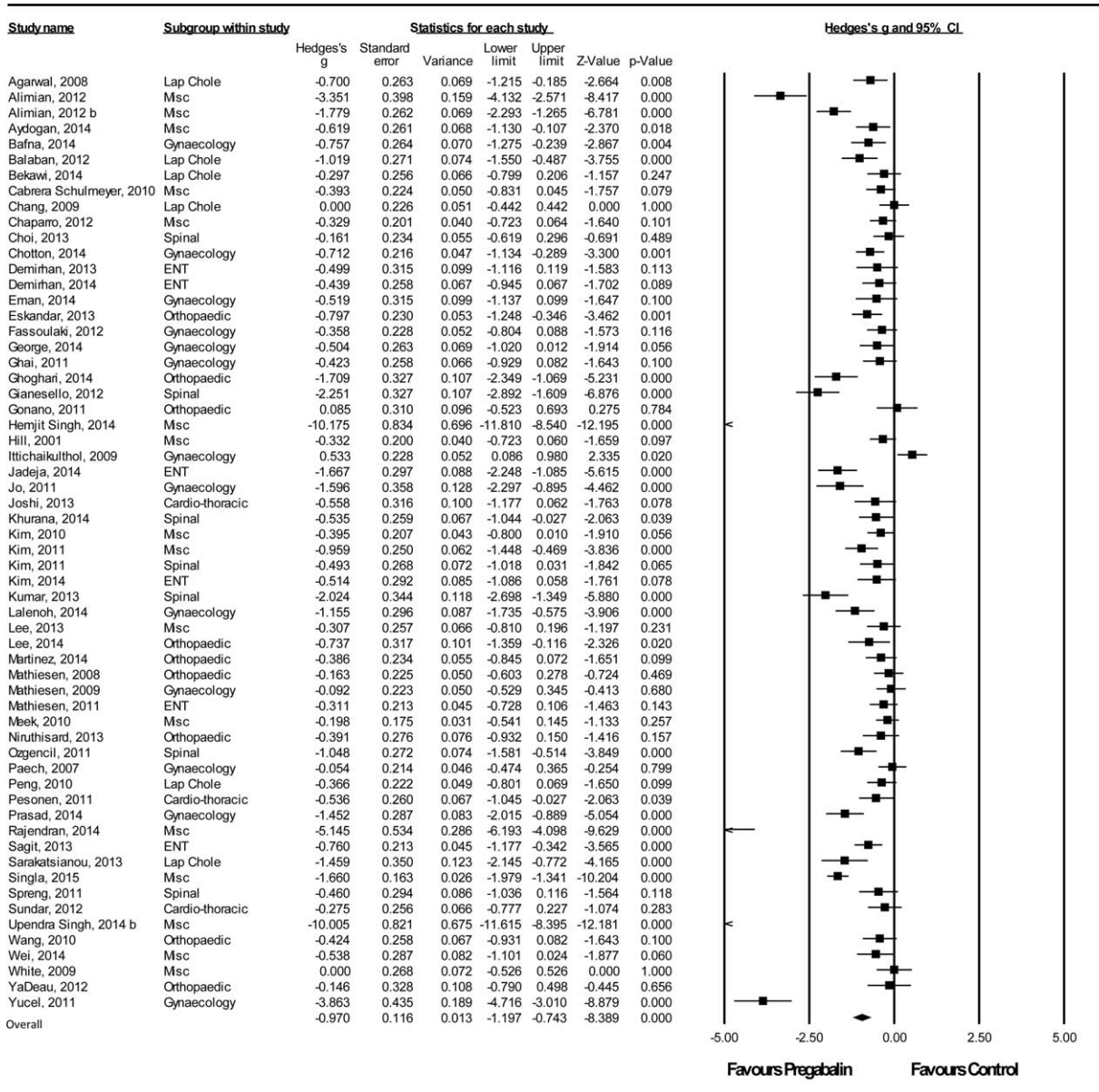


FIGURE 1. Forest plot for 2-hour pain scores.

treatment in this group. Pregabalin reduced the pain score at rest 2 hours postsurgery ($P = 0.004$), pain score at rest at 24 hours postsurgery ($P = 0.003$), and the morphine-equivalent consumption ($P = 0.002$), Figure 6B.

Laparoscopic Cholecystectomy Procedures

There were 6 studies[43–48] with a total of 273 patients taking pregabalin and 225 patients on the control treatment in this group. Pregabalin reduced the pain score at rest 2 hours postsurgery ($P = 0.003$), pain score at rest at 24 hours postsurgery ($P = 0.036$), and the morphine-equivalent consumption ($P = 0.023$), Figure 7.

Orthopedic Procedures

There were 12 studies[49–60] with a total of 430 patients taking pregabalin and 642 patients on the control treatment in this group. Pregabalin reduced the pain score at rest 2 hours postsurgery ($P = 0.001$), pain score at rest at 24 hours postsurgery ($P = 0.013$), and the morphine-equivalent consumption ($P < 0.0001$), Figure 8.

Spine Procedures

There were nine studies[61–65,67–69,88] with a total of 291 patients taking pregabalin and 332 patients on the control treatment in this group. Pregabalin reduced the pain score at

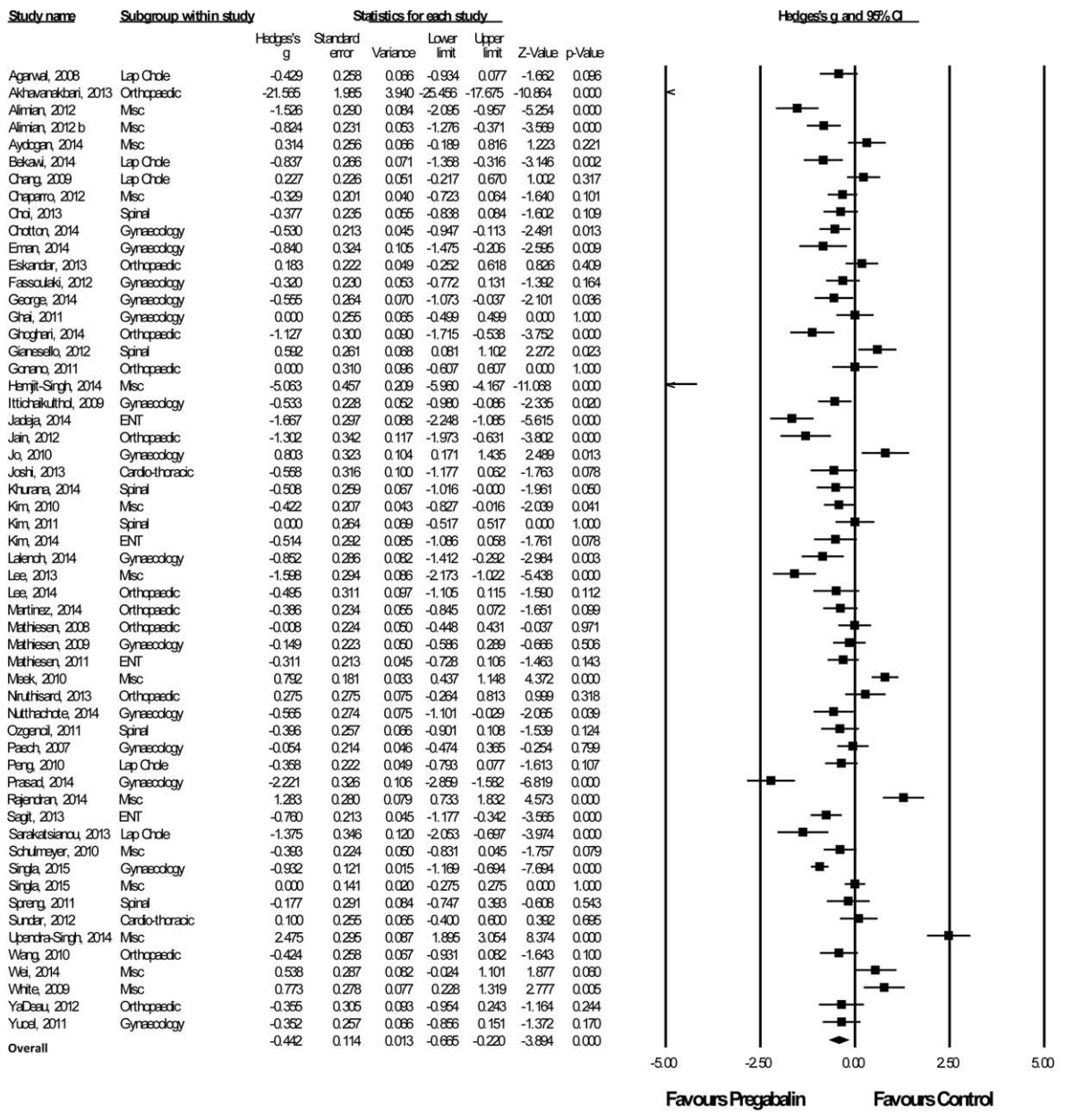


FIGURE 2. Forest plot for 24-hour pain scores.

rest 2 hours postsurgery ($P = 0.001$) and the morphine-equivalent consumption ($P = 0.005$). No significant difference was seen in pain score at rest at 24 hours postsurgery ($P = 0.373$), Figure 9.

Miscellaneous Procedures

There were 20 studies[41,66,70–87] with a total of 1165 patients taking pregabalin and 884 patients on the control treatment in this group. Pregabalin reduced the pain score at rest 2 hours postsurgery ($P < 0.0001$) and the morphine-equivalent consumption ($P = 0.006$). No significant difference was seen in pain score at rest at 24 hours postsurgery ($P = 0.422$), Figure 10.

Common Adverse Effects of Pregabalin

Sedation Effects of Pregabalin

Thirty studies had included data on the sedative effects of pregabalin,[13,14,21,22,25,29,30,32,37,39,43,50–52,55–57,59,60,62,65–69,77,79,82,85,87,88] with a total of 1147 patients taking pregabalin and 1170 patients on the control treatment. Subgroup analysis was performed on studies according to the surgical categories

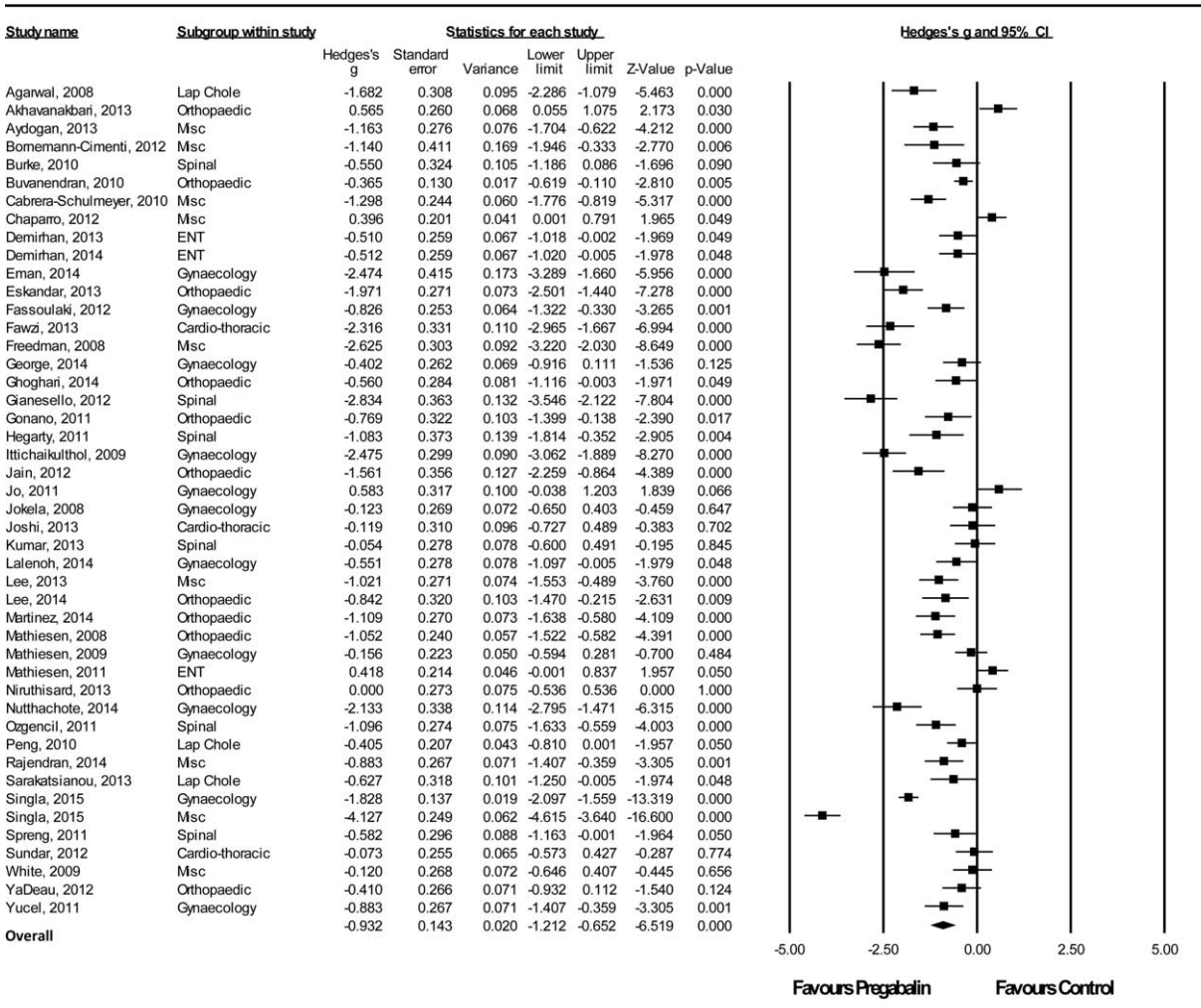


FIGURE 3. Forest plot for 24-hour morphine-equivalent consumption.

(number of studies) under cardiothoracic surgery (2), ENT surgery (3), gynecologic surgery (4), laparoscopic cholecystectomy (2), orthopedic surgery (7), spine surgery (6), and miscellaneous surgery (6). Data from George et al[30] could not be included in the analysis as there was no difference in sedation between the treatment and control group. With the exception of ENT surgery, laparoscopic cholecystectomy and gynecologic surgery, pregabalin was associated with sedation in all other surgical categories (overall OR and 95% CI, 2.144 [1.640–2.803], z score 5.574, $P < 0.0001$), Table 8.

Visual Disturbances

Fifteen studies had included data on incidence of visual disturbance (including blurred vision) after pregabalin administration,[24,34,35,39,46,48,51,62,64,68,77,79,80,85,88] with a total of 491 patients taking pregabalin and 498 patients on control treatment. There were not enough studies under different surgical categories for subgroup analyses to be performed. Overall, pregabalin was found to be associated with an increased incidence of visual disturbances (OR and 95%CI, 6.215 [3.317–11.646], z score 5.702, $P < 0.0001$).

Nausea

Thirty-one studies had included data on nausea prevalence after pregabalin administration,[13,21,24,26,28,30,33,37,44,46,47,50–52,54,56,57,59,60,63–65,67,68,70,71,77,85,86,88] with a total of 1067 patients taking pregabalin and 1038 patients on the control treatment. It was found that there was no difference in nausea incidence in cardiothoracic surgery, ENT surgery, gynecologic surgery, laparoscopic cholecystectomy, and spine surgery between pregabalin and control treatment groups. Pregabalin administration was associated with reduced incidence of nausea in miscellaneous surgery (OR and 95% CI, 0.138 [0.073–0.262], z score −6.085, $P < 0.0001$) and orthopedic surgery (OR and 95% CI, 0.586 [0.377–0.911], z score −2.373, $P < 0.018$). Overall results showed that pregabalin reduced postsurgical nausea (OR and 95% CI, 0.478 [0.365–0.626], z score −5.364, $P < 0.0001$).

Vomiting

A total of 22 studies provided information on vomiting incidence after pregabalin administration,[13,21,23,25,44,46,47,50–52,54,56,59,60,63,65,67,68,70,71,77,85] with 826 patients treated with

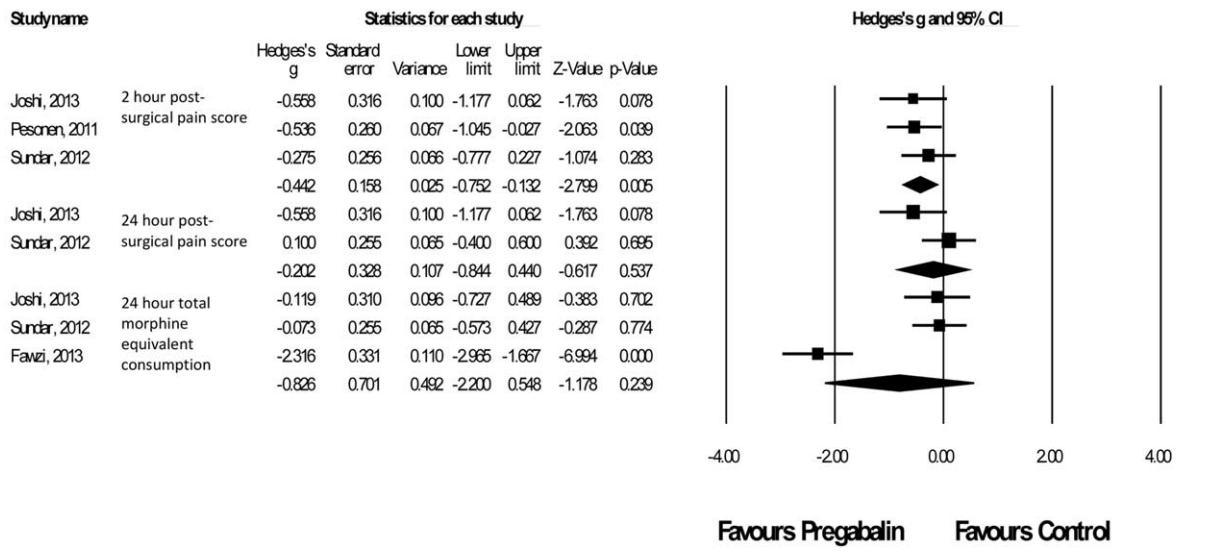


FIGURE 4. Forest plot for primary outcomes of studies under the cardiothoracic surgery category.

pregabalin and 816 on control treatment. The different surgical categories were cardiothoracic surgery (1), ENT surgery (3), laparoscopic cholecystectomy (3), miscellaneous surgery (4), orthopedic surgery (7), and spine surgery (4). In subgroup analysis, pregabalin was associated with reduced vomiting only after miscellaneous procedures (OR and 95% CI, 0.163 [0.073–0.368], z score -4.375, $P < 0.0001$), but pregabalin was found to be associated with reduced postsurgical vomiting in overall analysis (OR and 95% CI, 0.468 [0.328–0.668], z score -4.173, $P < 0.0001$).

Postsurgical Nausea and Vomiting

A total of 20 studies provided data on postsurgical nausea and vomiting (PONV) incidence after pregabalin administration,[12,14,27,31,32,34,35,38,40,42,43,45,62,66,69,73,79,80,82] with 638 patients treated with pregabalin and 644 on control treatment. The different surgical categories were ENT surgery (2), gynecologic surgery (8), laparoscopic cholecystectomy (2), miscellaneous surgery (6), and spine surgery (2). In subgroup analysis, pregabalin was associated with reduced PONV in miscellaneous surgery only (OR and 95% CI, 0.528 [0.309–0.902], z score -2.339, $P < 0.019$) but pregabalin was found to be associated with reduced PONV in overall analysis (OR and 95% CI, 0.592 [0.415–0.845], z score -2.887, $P < 0.004$).

No evidence of publication bias was seen using funnel plot analysis with regard to 2- and 24-hour pain scores and 24-hour morphine-equivalent consumption (Supplementary Figures 2A to C, http://links.lww.com/MD/A495), or with regard to adverse effects (Supplementary Figures 2D to h, http://links.lww.com/MD/A495).

DISCUSSION

This present meta-analysis shows that perioperative administration of pregabalin significantly reduced VAS pain scores at 2 hours postsurgery in all surgical categories, and at 24 hours postsurgery in all surgical categories with the exception of cardiothoracic and spine procedures. Total morphine consumption at 24 hours postsurgery was significantly reduced in all surgical categories with the exception of cardiothoracic and ENT procedures. Adverse effects include significant sedation after pregabalin in cardiothoracic, orthopedic, spine, and miscellaneous procedures. PONV was significantly reduced after pregabalin in all, except miscellaneous procedures. Taken together, results of this meta-analysis show that pregabalin is useful in reducing postsurgical pain as well as reducing morphine consumption, with concomitant reduction in PONV.

It has long been recognized that different surgical procedures require procedure-specific pain management.[89–92] It is evident that the degree of pain experienced by patients after different surgical procedures is not universal, and even some laparoscopic approaches might result in unexpectedly high levels of postsurgical pain.[93,94] Moreover, the analgesic efficacy of different pain medications might also be different in different types of surgery. The analgesic efficacy of paracetamol is 2-fold less in orthopedic compared with dental procedures.[95] It has also been found that the analgesic efficacy between nonsteroidal anti-inflammatory agents and paracetamol depends on the magnitude of the surgical procedure.[96] In addition to differing analgesic effects of the same drug under different conditions, a 50% decrease in pain might have a different clinical relevance depending if it were a reduction from 4 to 2, or 8 to 4 on the VAS pain scale.[97] Therefore, specific recommendations for surgical procedures including abdominal hysterectomy, laparoscopic cholecystectomy, and total knee arthroplasty have been made.[98] It is in recognition that pain management should be procedure-specific that provided the insight to take this approach of subgroup analysis for this current investigation.

A previous meta-analysis of 11 RCTs[10] concluded that presurgical pregabalin administration did reduce 2-hour pain scores and postsurgical opioid requirement. The authors divided the studies under investigation by pregabalin dose, <300 or ≥ 300 mg and found that the higher dose reduced opioid

TABLE 8. Summary of Results According to Surgical Type

Surgical type		2 hour VAS	24 hour VAS	24 hour morphine		Sedation	PONV	Evidence to recommend pregabalin
Cardiothoracic	*Hedge's g*	−0.442	−0.202	−0.826	*Odds ratio*	2.34	NA	2 h VAS pain scores reduced, but high incidence of sedation. Use with caution
	95% CI	−0.752 to −0.132	−0.844 to 0.440	−2.200 to 0.548	*95% CI*	1.21 to 4.52		
	z-score	−2.799	−0.617	−1.178	*z-score*	2.525		
	p	0.005	0.54	0.24	*p*	**0.012**		
Ear, nose and throat	*Hedge's g*	−0.684	−0.792	−0.187	*Odds ratio*	1.98	0.72	2 and 24 h VAS pain scores reduced. No reduction in morphine consumption. No higher risk in sedation and PONV. Can consider use
	95% CI	−1.051 to −0.316	−1.328 −0.257	−0.830 to 0.456	*95% CI*	0.28 to 14.17	0.32 to 1.63	
	z-score	−3.647	−2.902	−0.571,	*z-score*	0.677	−0.782	
	p	**0.001**	**0.004**	0.57	*p*	0.50	0.43	
Gynaecological (all)	*Hedge's g*	−0.792	−0.501	−1.085	*Odds ratio*	1.21	0.64	2, 24 h VAS pain scores and morphine consumption all reduced. No increase in sedation and PONV. Can consider use
	95% CI	−1.235 to −0.350	−0.791 to −0.212	−1.582 to −0.441	*95% CI*	0.78 to 1.90	1.56 to −0.98	
	z-score	−3.510	−3.396	−3.473	*z-score*	0.853	0.260	
	p	**0.001**	**0.001**	**0.001**	*p*	0.39	0.33	
Open hysterectomy	*Hedge's g*	−0.816	−0.409	−0.991	*Odds ratio*	NA	NA	2, 24 h VAS pain scores and morphine consumption all reduced. Can consider use
	95% CI	−1.366 to −0.267	−0.681 to −0.138	−1.622 to −0.360	*95% CI*			
	z-score	−2.912	−2.953	−3.077	*z-score*			
	p	**0.004**	**0.003**	**0.002**	*p*			
Laparoscopic cholecystectomy	*Hedge's g*	−0.600	−0.518	−0.886	*Odds ratio*	37.60	0.27	2, 24 h VAS pain scores and morphine consumption all reduced. High incidence of sedation. Use with caution
	95% CI	−0.989 to −0.210	−1.002 to −0.033	−1.652 to −0.120	*95% CI*	144.66 to 2174.91	0.02 to 3.83	
	z-score	−3.016	−2.095	−2.268	*z-score*	1.353	−0.975	
	p	**0.003**	**0.036**	**0.023**	*p*	0.176	0.330	
Orthopaedic	*Hedge's g*	−0.507	−0.838	−0.720	*Odds ratio*	2.80	NA	2, 24 h VAS pain scores and morphine consumption reduced. High incidence of sedation. Use with caution
	95% CI	−0.812 to −0.202	−1.499 to −0.177	−1.118 to −0.323	*95% CI*	1.58 to 4.97		
	z-score	−3.261	−2.485	−3.553	*z-score*	3.514		
	p	**0.001**	**0.013**	**0.001**	*p*	**0.001**		
Spine	*Hedge's g*	−0.972	-0.148	-1.016	*Odds ratio*	3.22	0.64	2 h VAS scores and 24 h morphine consumption reduced. High incidence of sedation. Use with caution
	95% CI	−1.537 to −0.407	−0.473 to 0.177	−1.732 to −0.300	*95% CI*	1.80 to 5.75	0.28 to 1.44	
	z-score	−3.371	−0.891	−2.782	*z-score*	3.952	−1.077	
	p	**0.001**	0.38	**0.005**	*p*	**0.001**	0.28	
Miscellaneous	*Hedge's g*	−1.976	−0.253	−1.329	*Odds ratio*	19.38	0.53	2 h VAS pain scores and 24 h morphine consumption reduced. High incidence of sedation and PONV. Use with caution
	95% CI	−2.654 to −1.297	−0.872 to 0.365	−2.286 to −0.372	*95% CI*	2.72 to 138.39	0.31 to 0.90	
	z-score	−5.704	−0.802	−2.723	*z-score*	2.956	−2.339	
	p	**0.001**	0.42	**0.006**	*p*	**0.003**	**0.019**	

CI = confidence interval, OR = odds ratio, PONV = postsurgical nausea and vomiting, SD = standard deviation, VAS = visual analogue scale.

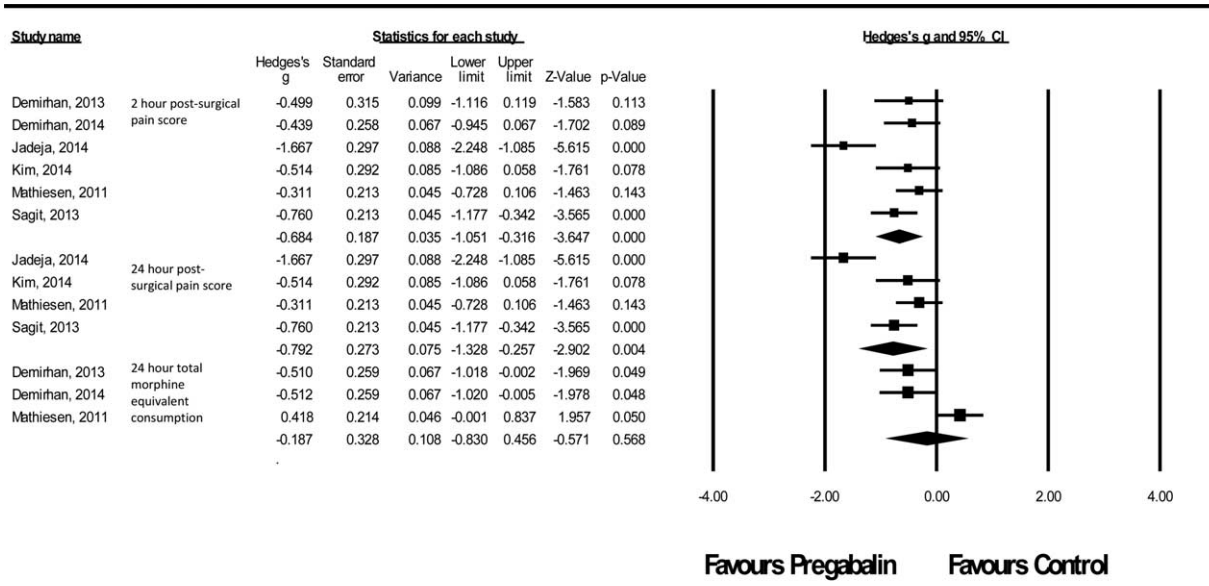


FIGURE 5. Forest plot for primary outcomes of studies under the ear, nose and throat surgery category.

consumption more than the lower dose. Pregabalin also reduced opioid-related adverse effects such as vomiting, but the risk of visual disturbance was greater. Another recently conducted meta-analysis on 55 RCTs[5] concluded that when all doses and administration regimens were combined, pregabalin was associated with a significant reduction in pain scores at rest and during movement and opioid consumption at 24 hours compared with placebo. Pregabalin was also associated with less postsurgical nausea, vomiting, and pruritus, although it was associated with higher incidence of sedation, dizziness, and visual disturbance. These previous meta-analyses have been criticized for not having investigated surgical specific-opioid consumption as different procedures will result in different opioid requirements.[99] Hence, this caveat has been addressed in the present meta-analysis. This meta-analysis is the first study to investigate the efficacy of pregabalin when used under different surgical procedures in acknowledgment that different surgical procedures result in variable pain intensity and different opioid requirements,[94] and that the efficacy of perioperative analgesia varies according to surgical type.[98] By identifying the types of surgery that would benefit from pregabalin, clinicians can improve efficiency in treating acute postsurgical pain and can better allocate resources.

This present meta-analysis is the first to show that the analgesic effect of perioperative pregabalin is procedure specific. With regard to the cardiothoracic procedure category, pain at 2 hours postsurgery was significantly lower in the pregabalin group, but no difference was seen at 24 hours postsurgery. It should be noted that only 2 studies showed data for 24-hour VAS pain scores, therefore there are insufficient data to draw definitive conclusions, and the only study showing reduction in morphine consumption after pregabalin did not show either 2-, or 24-hour VAS pain scores. No data on PONV were given and significant sedation was seen after pregabalin, so although overall, pregabalin appears to be efficacious for acute postsurgical pain in cardiothoracic procedures, caution should be exercised when deciding to use pregabalin.

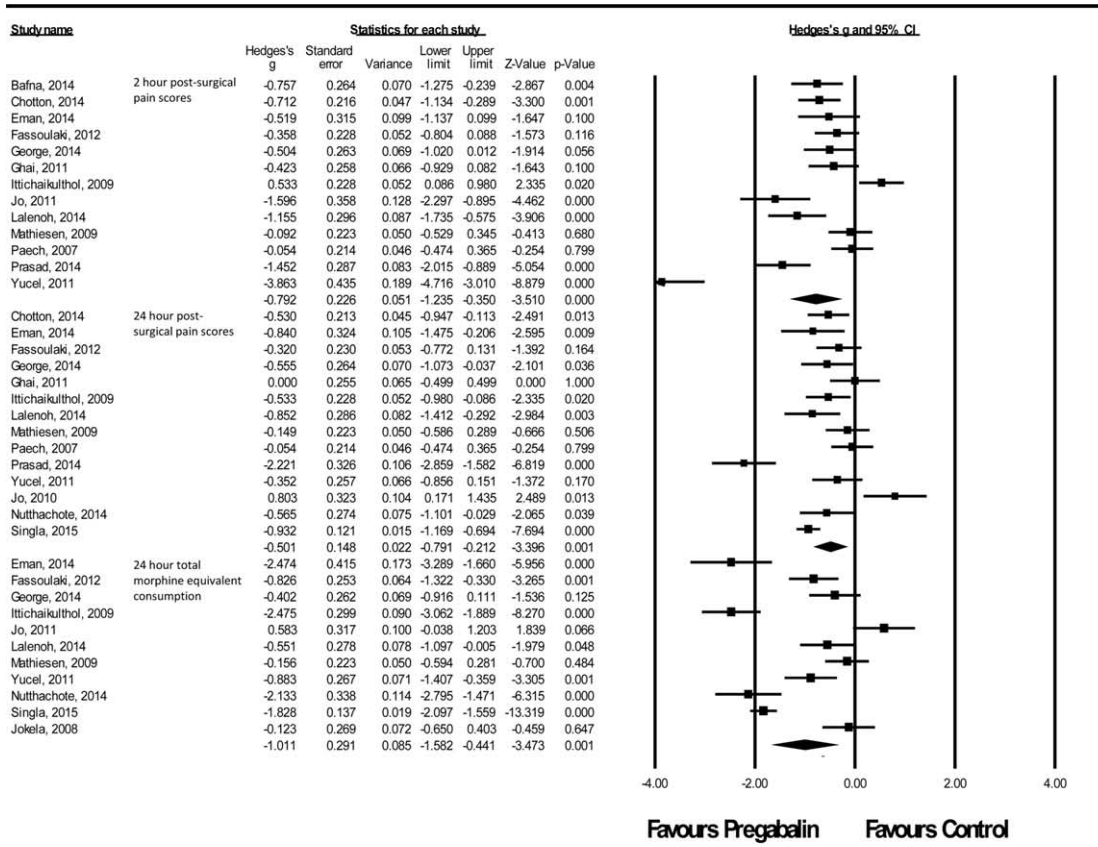
In the ENT category, although both 2- and 24-hour postsurgical pain was shown to be reduced in the pregabalin group, there was no difference in total morphine-equivalent consumption at 24 hours between pregabalin and the control group. PONV is more common in patients undergoing ENT, compared with other procedures,[100] and as no difference was seen in either sedation or PONV, pregabalin can be recommended for use in ENT procedures.

There is strong evidence to recommend the use of pregabalin in gynecologic procedures, due to the large effects sizes with regard to pain reduction, and no evidence of increased sedation and PONV.

With regard to laparoscopic cholecystectomy, caution should be exercised when considering pregabalin, as although pain scores at 2 and 24 hours, and morphine-equivalent consumption are reduced, the OR seen for sedation was extremely high, even though, due to the heterogeneity of the studies, this was not statistically significant. Pain scores tend to be low after laparoscopic cholecystectomy procedures (not >5 on the VAS at 2 hours postsurgery according to the studies included here), and as pain reduction at 24 hours postsurgery and total morphine-equivalent consumption is modest in terms of effect-size, the risk–benefit ratio should be carefully considered.

Although pain scores at 2 and 24 hours, and morphine-equivalent consumption are reduced in orthopedic surgery, the reduction of pain scores at 2 hours is modest and sedation was significantly increased in the pregabalin group. The increased risk of sedation might be preferable when weighed with the significantly decreased morphine-equivalent consumed. Considering that many orthopedic procedures are performed in the elderly[101] the risk of sedation might outweigh the benefit of modest decrease in pain scores.

With regard to spinal, and also miscellaneous surgeries, a large decrease in pain at 2 hours and total morphine



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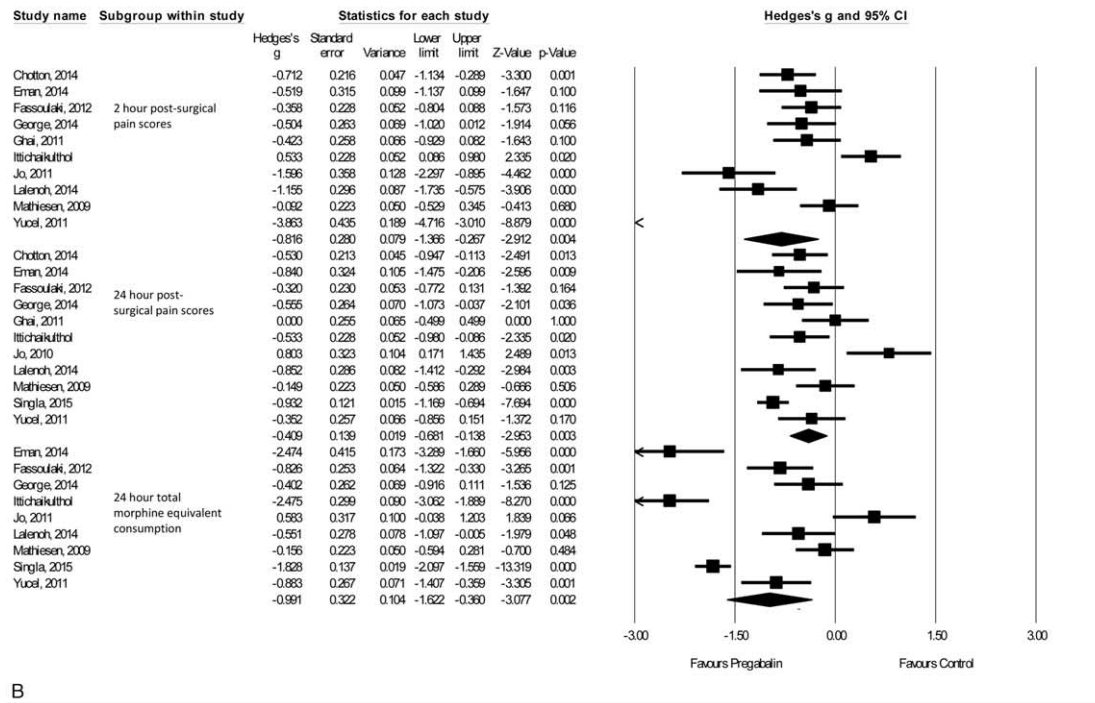

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FIGURE 6. A,B Forest plot for primary outcomes of studies under the gynecologic surgery category.

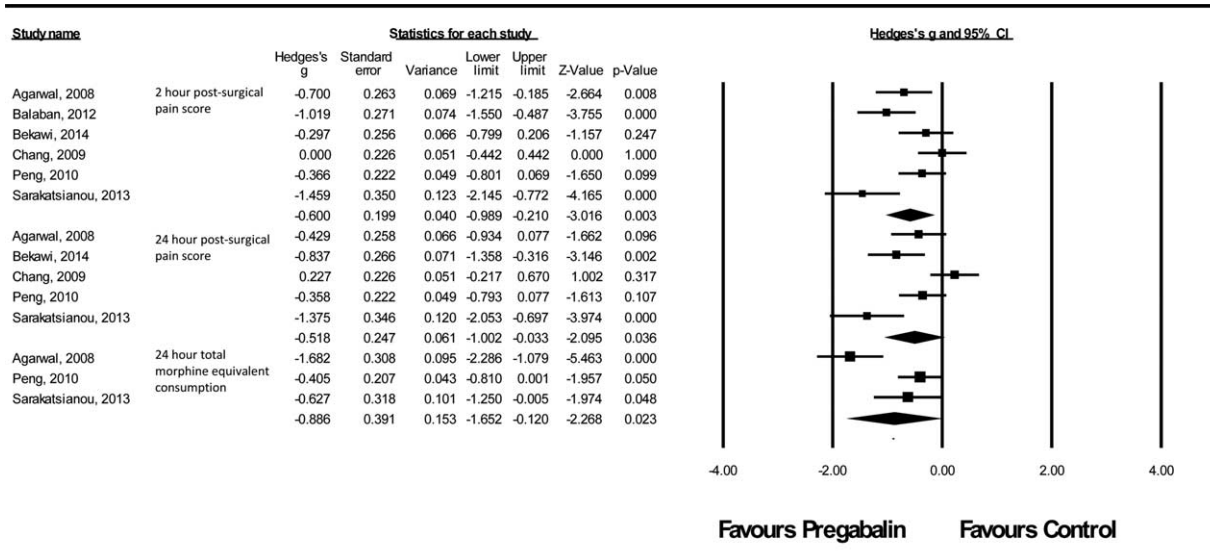

FIGURE 7. Forest plot for primary outcomes of studies under the laparoscopic cholecystectomy category.

consumption was seen, although there was no reduction in pain at 24 hours postsurgery. Considering the high incidence of sedation, in both spinal and miscellaneous surgical procedures, pregabalin should be used with caution.

It should be noted that although statistically significant reductions in the pain scores were noted in all surgical procedures in this meta-analysis, the magnitude of effect is relatively small. For example, in Bafna et al,[26] Balaban et al,[44] Aydogan et al,[72] Eskandar and Ebeid,[51] and Lee et al,[55] statistically significant decreases in pain scores at 2 hours postsurgery were reported, although the standard difference in mean pain scores between pregabalin and the control group was only

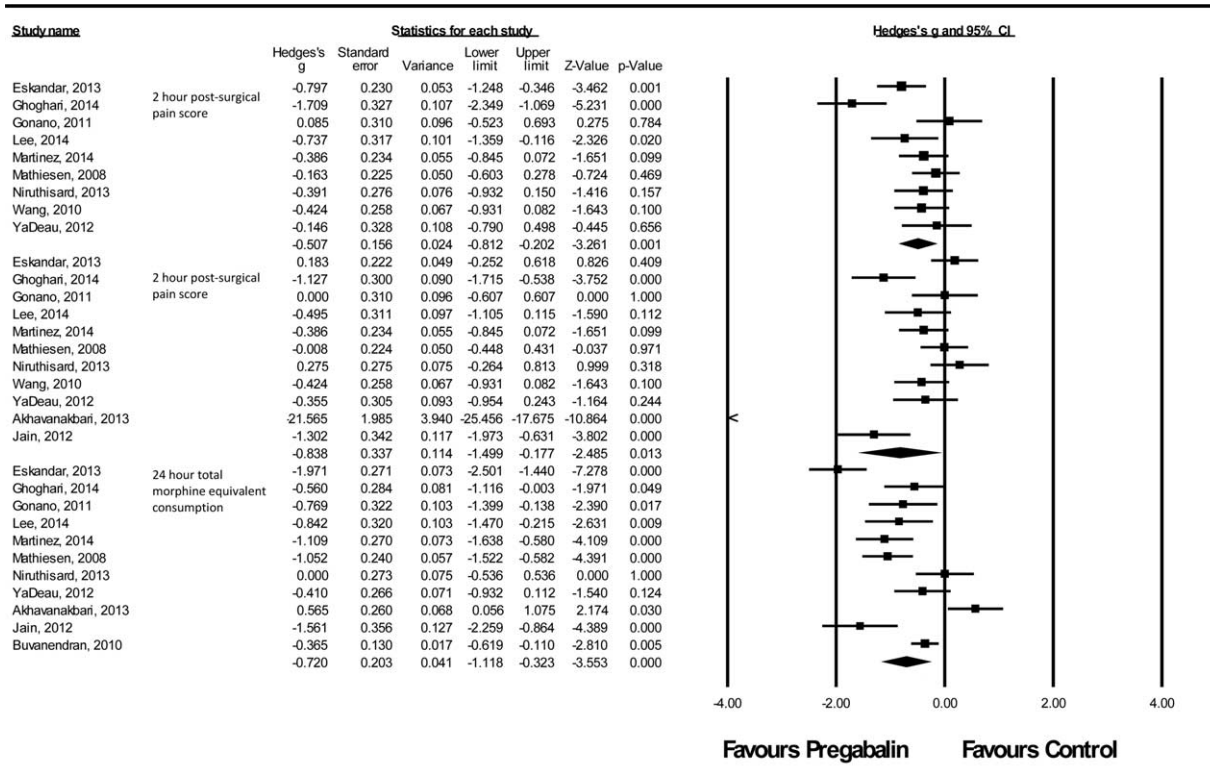

FIGURE 8. Forest plot for primary outcomes of studies under the orthopedic surgery category.

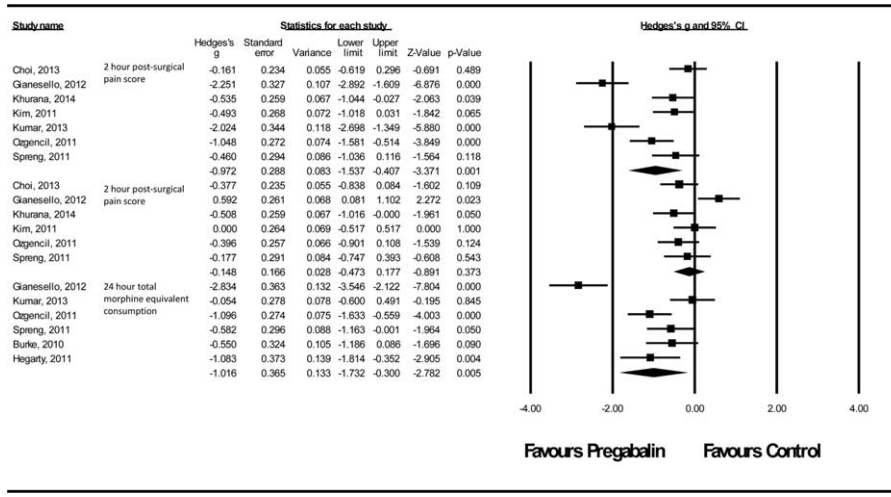

FIGURE 9. Forest plot for primary outcomes of studies under the spine surgery category.

<1 point on the VAS pain score. Studies on clinically significant decreases in VAS/NRS pain scores have demonstrated that an average decrease in pain score of at least 1.80 points on NRS scores or 1.3 to 2.8 points on VAS pain scores are required for the decrease to be considered clinically meaningful.[102,103] The reduction in pain scores demonstrated in the studies included in this meta-analysis may reach statistical significance, but might be too small to be considered of clinical significance.

An interesting finding from study by Mishriky et al[5] was that a single preoperative dose was as effective as multiple doses, and that smaller doses (≤75 mg) were as effective as larger (300 mg) doses in terms of reducing opioid consumption. It was beyond the scope of this present meta-analysis to subdivide the studies according to surgical-type as well as dosages and dosing regimens, although an analysis of single versus multiple doses did not reveal any differences in efficacy regarding 2-hour postsurgical pain. Subgroup analyses performed in this present meta-analysis according to whether single or multiple doses of pregabalin were used showed a statistically significant reduction in 24-hour postsurgical pain for both single and multiple dose, contrary to previous studies.[10] In particular, with regard to the gynecologic category, it was noted, that 8 out of 13 studies showed significant reduction in 24-hour postsurgical pain score, of which, 6 studies used a single-dose of pregabalin and 2 used multiple dose. The dose of pregabalin used included low dose (≤75 mg), intermediate dose (100–150 mg), and high dose (>150 mg). Sensitivity analysis data from this present meta-analysis do not show that higher

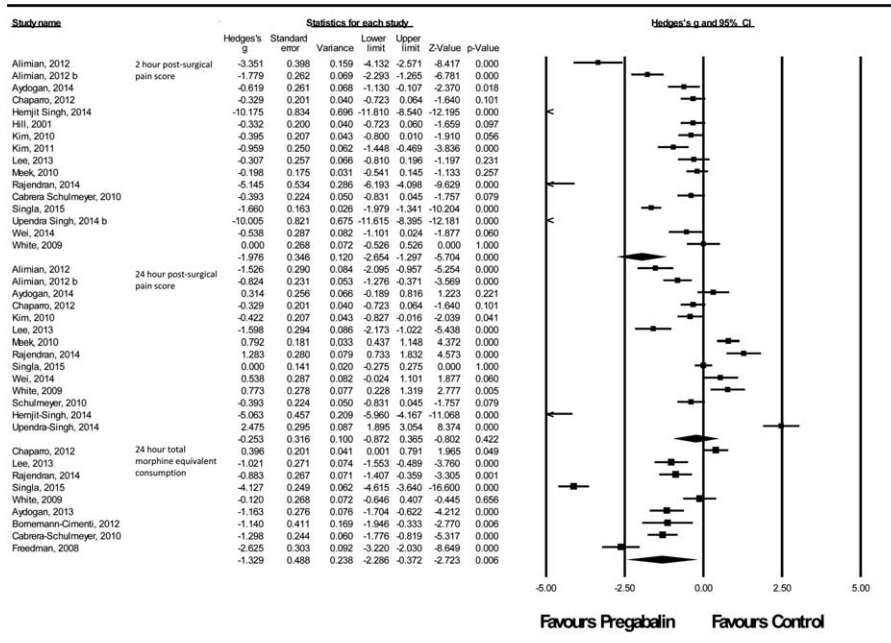

FIGURE 10. Forest plot for primary outcomes of studies under the miscellaneous surgery category.

doses were more effective at reducing pain scores when compared with lower doses (data not shown). There is no evidence from this current meta-analysis to recommend multiple dosing, or dosages >75 mg, in any of the surgical procedures that has investigated dosing.

Well established adverse effects of pregabalin are sedation, dizziness, and headache, and so pregabalin should be used with caution in an ambulatory setting.[104] As shown in previous meta-analyses, pregabalin is associated with increased incidence of visual disturbances and sedation; but reduced incidence of PONV.[5,10] Of the 15 studies included in this analysis that showed such an association, only 4 provided information on morphine-equivalent consumption. Two of these 4 studies showed a pregabalin-associated reduction in morphine-equivalent consumption, whereas the remaining 2 showed no reduction. Due to the limited data available, it is not possible to ascertain whether the reduction in incidence of PONV is due to a direct effect of pregabalin or a result of reduced opioid consumption. Opioids are considered the primary analgesic therapy in postsurgical pain, but are associated with many dose-related adverse effects such as sedation, respiratory depression, postsurgical nausea and vomiting, urinary retention, ileus, and constipation.[105] This meta-analysis shows that administration of pregabalin reduced morphine-equivalent consumption in most surgical categories, and looking at the effect size data show that there is up to 30% reduction. These data indicate pregabalin is useful to reduce opioid induced adverse effects, as seen by the reduced incidence of nausea and vomiting.

Meta-analyses have been conducted to assess the effects of perioperative gabapentin on postoperative pain,[106–108] and although all the studies concluded that perioperative gabapentin was able to reduce postsurgical pain and 24-hour morphine consumption, a recent meta-regression on RCTs of perioperative gabapentin that included 133 trials, found that these effects of gabapentin might have been overestimated by statistically significant small study effects.[109] Small study effects may also explain the difference in findings between our current meta-analysis and previously published work on pregabalin.

A problem inherent with meta-analyses using the random-effects model is the assumption that the effects underlying different studies are drawn from a normal distribution.[110] This is seldom true, especially in the case of pain scores, which commonly show a skewed distribution. Much data used in this present meta-analysis were drawn from median, rather than the mean values required. Efforts were made to reduce the impact of clinical heterogeneity by analyzing data according to the type of surgery. Some studies are heterogeneous in themselves in that the investigators had included different surgical types in their own analysis.[84] Methodologic heterogeneity also exists in the assessment of pain and sedation. In addition to the commonly used VAS pain scores and NRS pain scores, which have been shown to correlate well,[7] Roger Pain Scale was used in 1 study.[76] Similarly, with regard to assessing sedation, both the Ramsay Sedation Scale and Richmond Agitation Sedation Scale were used. Although these scales have been shown to correlate well,[111] some studies have neither stated with which method they have assessed sedation, nor at which time postsurgery, was the assessment carried out. Some studies have instead reported on either presence or absence of somnolence and these data were excluded in the analysis for sedation effects. It is noted here although that none of the studies included in this present meta-analysis were powered to assess pregabalin-associated adverse effects, as these were secondary outcomes of the studies.

In the setting of an ideal RCT, subjects are placed in a closely monitored environment, where their pain intensity is regularly assessed. Analgesia is provided on demand by the nursing staff in the form of nursing-controlled analgesia or delivered by the subjects themselves using patient-controlled analgesia (PCA). The pain intensity of both control and treatment group should therefore be titrated to similar levels, although total opioid consumption and time to first analgesic would differ between the 2 groups based on the effectiveness of the treatment. Limitations certainly exist for both nursing-controlled analgesia and PCA in providing adequate analgesia. For the former, inadequacy of nursing staff can result in delay in delivering analgesics; for the latter, malfunctioning, poor initial titration, or incorrect setup of the PCA instruments can also prevent timely delivery of analgesics. Such limitations, however, would apply to both control and treatment group in a well-conducted trial and the pain scores of both control and treatment group will therefore be similar. It is proposed here that pain scores should only be 1 of the primary outcomes in such trials, whereas the more pertinent parameters would be changes in analgesic consumption and in time to first analgesic requirement.

Pain is not only affected by gender, age, and psychologic well-being, but also by polygenetic elements. The current list of genetic polymorphisms that may affect the action of analgesics is growing rapidly, but 1 of the enzyme systems of high relevance to opioids is the cytochrome P450 system.[112] As it has been shown that polymorphisms that affect opioid metabolism are found in up to 30% of the general population,[112] future clinical trials utilizing opioid consumption as an outcome could take genetic variability into consideration. The fact that none of the studies included here have factored in the genetic variability in opioid metabolism brings in another layer of heterogeneity, especially when an increase in opioid requirement in 1 or 2 patients can have substantial impact in the overall results.

Out of the 74 studies assessed in this meta-analysis, only 12 investigated the effects of pregabalin on chronic (≥3 months) postsurgical pain.[19,21,29,30,33,41,61,63,65,76,79] Chronic postsurgical pain is an underexplored area and more studies are required to assess the efficacy of pregabalin in this regard.

CONCLUSIONS

In conclusion, the analgesic efficacy and adverse effects of pregabalin might not be similar under all surgical categories. Although sedation may be increased, especially in cardiothoracic, spinal, and miscellaneous procedures, this was not seen in ENT, gynecologic, or laparoscopic cholecystectomy procedures. Two-hour VAS scores were reduced in all procedures, but effect sizes varied greatly. Taken together, this meta-analysis shows strong evidence that consideration for the use of pregabalin in postsurgical pain should be procedure-specific.

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