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REVIEW

Oral pregabalin for acute pain relief after cervicofacial surgery: a systematic review

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Abstract
Objective The objectives of this systematic review were to unify criteria on the effectiveness of oral pregabalin to treat acute post-operative pain after cervicofacial surgery, to establish the most effective dose regimens, and to determine its effect on rescue medicine consumption and its association with adverse effects.
Materials and methods PubMed/Medline (National Library of Medicine, Washington, DC), Scopus, Web of Science, and Cochrane databases were searched for studies in any language published between January 2000 and September 2016. The following question was posed, in accordance with PRISMA guidelines: Is oral pregabalin effective and safe for the relief of acute pain after cervicofacial surgery? The critical reading of the literature utilized a list of questions prepared by the CASPe Network, applying the Jadad scale for evaluation of the methodological quality of trials.
Results Eleven randomized controlled clinical trials were selected. The 11 trials obtained a score ≥ 3, considered as Ib evidence level and high quality. A single oral dose of 75-mg pregabalin before or after cervicofacial surgery alleviates pain and lessens the need for rescue analgesia consumption, while the statistical significance of these effects is higher with a single dose of 150-mg pregabalin, either before or after the surgery.
Conclusion Oral pregabalin appears to significantly alleviate post-operative pain and reduce rescue analgesia consumption, with no severe adverse effects. However, the ideal dose and most effective administration regimen remain controversial issues that need to be addressed in further high-quality clinical trials.
Clinical relevance These findings suggest that pregabalin may be useful for acute pain relief after cervicofacial surgery.

Keywords Pregabalin · Systematic review · Pain · Acute · Cervicofacial

Introduction

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or reported in terms of such damage" [1]. Post-operative pain, i.e., acute pain after surgery, is usually predictable and self-limiting. However, this nociceptive pain is associated with vegetative, psychological, emotional, and behavioral reactions that can become chronic if not correctly treated. There have been important advances in the physiopathology of pain over the past few decades and novel analgesic regimens have been introduced, but post-operative pain remains an unresolved challenge. Thus, out of a random sample of 250 adult surgical patients in the USA, almost 80% experienced pain after surgery, and 86% of these reported extreme, severe, or moderate pain. Control of this pain has been associated with a reduced morbidity-mortality and with fewer post-operative complications such as hypertension, tachycardia, reduced alveolar ventilation, or myocardial ischemia [2].

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Post-operative pain results from nociceptive stimulation caused by direct or indirect aggression due to nerve resection or the release of chemical agents such as ions (H^+ o K^+), neurotransmitters (serotonin or noradrenalin), mediators (bradykinin, prostaglandins, or cytokines), or peptides [3].

According to guidelines published in 2012 by the Spanish Association of Major Outpatient Surgery, four major drug groups can be used against acute post-operative pain: antipyretic and anti-inflammatory analgesics (paracetamol, metamizole, NSAIDs), opioid analgesics (tramadol, codeine), local anesthetics, and analgesic coadjuvants. Coadjuvants are a heterogeneous group of drugs used to enhance the action of conventional analgesics or reduce their adverse effects, including gabapentinoids (gabapentin, pregabalin), α-2 agonists (clonidine), NMDA receptor antagonists (ketamine, dextromethorphan), and glucocorticoids (dexamethasone) [4].

New WHO guidelines encourage research into inexpensive drugs and their administration in the context of the developing world, including proposals for universal access to low-cost opioid analgesics and for the development of techniques that reduce the need for opioids, such as neuromodulation for intractable visceral pain [5].

There are currently two main approaches: "multimodal or balanced analgesia," using a combination of different drugs, anesthetics, and administration pathways; and "preventive analgesia," based on the preoperative administration of local analgesics and/or anesthetics [3]. Three factors should be considered to determine the optimal analgesic for the management of post-operative pain: effectiveness, safety, and cost/effectiveness relationship. The effectiveness of a drug is measured according to the number of patients needed to treat to prevent one additional bad outcome (NNT), which is ideally 1 (i.e., each patient achieves appropriate analgesia) [6]. According to the 2015 Cochrane review [7] on the effectiveness of a single oral analgesic dose to relieve acute post-operative pain, the best (lowest) NNT values were obtained for 120-mg etoricoxib (1.5 NNT), with a mean remedication time of 20 h, and for the combination of 400-mg ibuprofen with 1-g paracetamol (NNT 1.5), with a lower remedication time of slightly more than 8 h.

Pregabalin (CASRN: 148553-50-8) is a structural analogue of gamma-aminobutyric acid (GABA), although it is not functionally related to this inhibitory neurotransmitter. It has anticonvulsant, anxiolytic, and anti-hyperalgesic properties [8] and is used to alleviate pain in diabetic neuropathy [9], postherpetic neuralgia [10], and partial epileptic seizures [11]. Research is under way on its effectiveness against fibromyalgia [12] and generalized anxiety [13, 14]. It is also being investigated as coadjuvant in the multimodal treatment of post-operative analgesia, after reports of its effectiveness against acute pain after minor gynecological surgery [15], laparoscopic cholecystectomy [16, 17], amygdalectomy [18], and third molar surgery [19]. Pregabalin acts by binding to the α2-δ auxiliary subunit of voltage-dependent calcium channels in the central nervous system, potentially displacing [3H]-gabapentin. It is well-known that activation of these receptors is involved not only in partial epileptic seizures but also in pain and hypersensitization phenomena [8, 20, 21].

Therefore, pregabalin reduces excitatory neurotransmitters and blocks hyperalgesia and the sensitization center [22]. Oral pregabalin absorption is fast, with linear pharmacokinetics, 90% bioavailability, and no binding to plasmatic proteins. Its maximum plasma concentration is reached at 1 h, and it has a mean elimination time of 6 h [23]. However, it is also associated with adverse reactions, mainly dizziness or somnolence [24]. Other more rare reactions are as follows: visual disorders, such as blurry vision; speaking disorder; tremor; vertigo; neutropenia; vascular, cardiac, or respiratory disorders; mouth dryness; constipation; and vomiting or urticaria [11]. The oral pregabalin dose for adults in acute pain ranges between 75 and 300 mg/day, with a maximum recommended dose of 600 mg/day [23].

The first animal study, published in 2000, provided evidence of the anti-nociceptive effect of pregabalin on behavioral responses to visceral pain induced by lipopolysaccharide (LPS) administration [25]. Pregabalin has been used over the past few years as coadjuvant in the multimodal treatment of post-operative pain [26]. Numerous studies on the effectiveness of post-surgical oral pregabalin have yielded highly contradictory results, and no consensus has been established on the optimal dose regimen.

With this background, we conducted a systematic review on the use of oral pregabalin for acute post-operative pain relief after cervicofacial surgery. The objectives were as follows: to unify criteria on the effectiveness of this drug against acute post-operative pain, to establish the optimal dose regimen, and to determine its impact on rescue medication consumption and associated adverse effects.

Material and methods

PICO question

We constructed the following patient intervention comparison outcome (PICO) question based on the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines: "Is oral pregabalin safe and effective for acute post-operative pain relief after cervicofacial surgery?" PI (patients and intervention) = patients undergoing cervicofacial surgery under general or local anesthesia and receiving pregabalin for post-operative pain control; C (comparison) = comparison with a control group (patients not treated with pregabalin); O (outcome) = pain levels, use of rescue analgesic medication, and associated adverse effects.

Eligibility criteria

Inclusion criteria were as follows: (a) clinical trial, (b) randomized or double-blinded, (c) use of control group, and (d) study population undergoing cervicofacial surgery under general or local anesthesia receiving oral pregabalin for postoperative pain. Exclusion criteria: letters to editor, literature reviews, systematic reviews, meta-analyses, case reports, case series, and unpublished articles.

Study search and selection strategy

PubMed/Medline (National Library of Medicine, Washington, DC), Scopus, Web of Science, and Cochrane databases were searched for studies in any language published between January 2000 and September 2016, using the following search strategy: ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("pregabalin"[Supplementary Concept] OR "pregabalin"[All Fields]) AND ("pain"[MeSH Terms] OR "pain"[All Fields]) AND (acute[All Fields] OR post-surgical[All Fields] OR ("post-operative period"[MeSH Terms] OR ("post-operative"[All Fields] AND "period"[All Fields]) OR "post-operative period"[All Fields] OR "post-operative"[All Fields]) OR (("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("surgery"[Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgery"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields]))).

The search was conducted by two independent researchers (SLH, FJMM), who independently evaluated the titles and abstracts (when available) of the retrieved studies to evaluate their fulfillment of the eligibility criteria. When the abstract did not provide sufficient information for this purpose, the entire article was reviewed before a decision was made.

Discrepancies between evaluators were resolved by discussion or, when this was not possible, by consulting a third examiner (MVOG). The Kappa index was used to measure the agreement between these examiners on the inclusion of studies in the review. Search results were cross-checked to remove duplicates. All studies that met eligibility criteria were subjected to validity evaluation and data extraction. Finally, the Kappa value obtained was 0.92.

The baseline search yielded the following results: 96 studies in PubMed, 147 in Scopus, 80 in WOS, and 67 in Cochrane. Finally, 11 studies were selected for analysis and included in the present study, as depicted in the flowchart in Fig. 1.

Evaluation of the methodological quality of studies

The critical reading of the scientific literature was conducted following a list of questions prepared by the CASPe (Critical Appraisal Skills Program *Español*) network [27]. This system is based on 11 short questions; the first three are elimination questions, ruling out articles for which the response is not "yes." The remaining questions explore the methodological quality of the research, generally offering "yes," "no," or "do not know" as possible responses. None of the 11 preselected articles was excluded in this stage (Table 1).

We then applied the widely used Oxford quality score system (Jadad scale) [28] to evaluate the methodological quality of randomized clinical trials (RCTs). The 11 trials obtained a score ≥ 3, considered as Ib evidence level and high quality; hence, all studies were included in the final sample (Table 2).

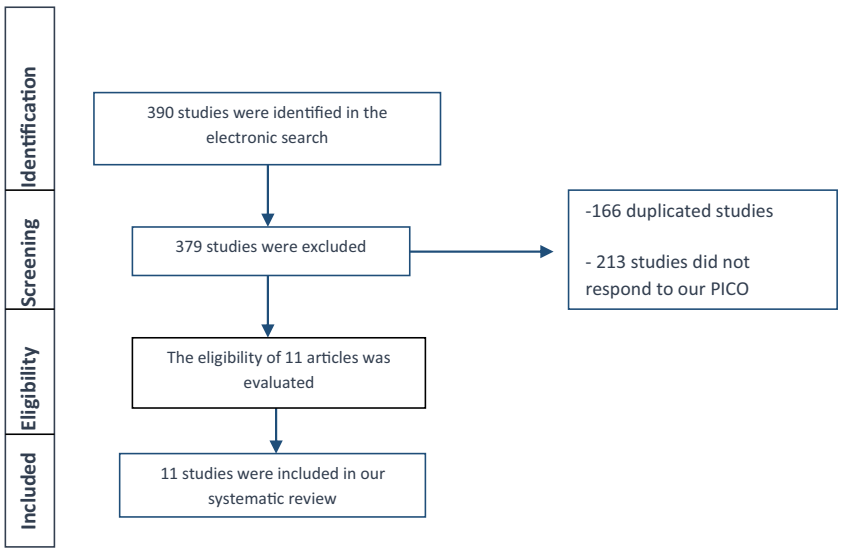

Fig. 1 Flowchart of article selection for the systematic review, according to the PRISMA guidelines

Table 1 Evaluation of study quality, according to the CASPe Critical Reading Program

Study	Are the results valid?						What are the results?			Can these results assist us?		
	1	2	3	4	5	6	7	8a	8b	9	10	11
Olmedo-Gaya et al.	Yes	Yes	Yes	No	Yes	Yes	No	$p < 0.05$	$p > 0.05$	Yes	Yes	Yes
Cillo et al.	Yes	Yes	Yes	Yes	Yes	Yes	No	$p < 0.05$	$p < 0.05$	Yes	Yes	Yes
Kim JH et al.	Yes	Yes	Yes	Yes	Yes	Yes	No	$p < 0.05$	$p < 0.05$	Yes	Yes	Yes
Hill et al.	Yes	Yes	Yes	Yes	Yes	Yes	No	–	$p < 0.05$	Yes	Yes	Yes
Cheung et al.	Yes	Yes	Yes	Yes	Yes	Yes	No	$p > 0.05$	$p > 0.05$	Yes	Yes	Yes
Sagit et al.	Yes	Yes	Yes	–	Yes	Yes	No	$p < 0.05$	$p < 0.05$	Yes	Yes	Yes
Kim SY et al.	Yes	Yes	Yes	Yes	Yes	Yes	No	$p < 0.05$	$p < 0.05$	Yes	Yes	Yes
Park et al.	Yes	Yes	Yes	–	Yes	Yes	No	$p < 0.05$	$p > 0.05$	Yes	Yes	Yes
Meek et al.	Yes	Yes	Yes	Yes	Yes	Yes	No	$p < 0.05$	$p > 0.05$	Yes	Yes	Yes
Pakravan et al.	Yes	Yes	Yes	Yes	Yes	Yes	No	$p > 0.05$	$p < 0.05$	Yes	Yes	Yes
Ahiskalioglu et al.	Yes	Yes	Yes	Yes	Yes	Yes	No	$p < 0.05$	$p < 0.05$	Yes	Yes	Yes

1. Does the trial address a clearly defined question?
2. Was patient assignation to treatment randomized?
3. Were all enrolled patients considered appropriately until the end of the study?
4. Was blinding maintained for: —patients. —clinicians. —research team?
5. Were groups similar at the start of the trial?
6. Besides the study intervention, were groups treated equally?
7. Is the treatment effect very large?
8. What is the precision of this effect?
8a: rescue medication consumption
8b: pain relief
9. Can these results be applied in your setting or local population?
10. Were all outcomes of clinical relevance considered?
11. Do the benefits obtained justify the risks and costs?

Results

Characteristics of selected studies

This review finally included 11 RCTs [19, 29–38]. Surgery was conducted under general anesthesia in five studies, under local anesthesia in four, and the anesthesia was not specified in the remaining two. Six studies [19, 29–31] included 12–60 participants, while the remaining five [34–38] enrolled 94–198 participants. The mean age of participants ranged between 18 and 60 years. The control group received a placebo in all RCTs except for two, in which the control group received 4-mg diazepam [33] or no medication or placebo [29] (Table 3).

Ten of the 11 articles included a table summarizing patient characteristics, e.g., age, sex, race, weight, or body mass index (BMI). The study by Olmedo-Gaya et al. [29] gathered data on sex, age, and tobacco consumption, besides surgery predictor variables, including the degree of extraction difficulty and surgical variables that might affect the pain of patients and their rescue medication consumption. The trials by Hill et al. [35] and Cheung et al. [19] also reported surgical variables in a table, including the degree of difficulty or duration of the surgery. In the study by Kim JH et al. [32], a multivariate analysis was conducted to control for the effects of sex and BMI.

Five of the RCTs were oral surgery studies [19, 29–31, 35], and six of them were non-oral surgery studies [32–34, 36–38].

Participants were divided into two groups in eight RCTs [19, 29–34, 38], three groups in two RCTs [36, 37], and four groups in one [35].

Dose regimens

Only one trial used an oral dose of 50-mg oral pregabalin, administered post-operatively in a single dose [35]. Five RCTs used 75-mg oral pregabalin: 1 h before surgery in the study by Sagit et al. [37]; 1 h before and 1 h after surgery in the studies by Cheung et al. [19] and Olmedo-Gaya et al. [29]; 2 h before surgery and every 12 h for 5 days post-surgery in the RCT published by Meek et al. [38]; and post-operatively alone (3× day for 3 days) in the study by Pakravan et al. [36]. Six studies used 150-mg pregabalin: 1 h before surgery in the studies by Cillo et al. [31], Sagit et al. [37], and Ahiskalioglu et al. [30]; 1 h before surgery and 12 h after the first dose in the studies by Kim JH et al. [32] and Kim SY et al. [34]; and the

Table 2 Independent evaluation of study methodological quality according to the Jadad scale

RCT	Quality criteria							
	I	II	III	IV	V	VI	VII	Jadad score
Olmedo-Gaya et al. (2015)	Yes	Yes	Yes	No	No	No	Yes	3
Cillo et al. (2014)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	5
Kim JH et al. (2014)	Yes	No	No	Yes	Yes	Yes	No	3
Hill et al. (2001)	Yes	No	No	Yes	Yes	Yes	Yes	4
Cheung et al. (2012)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	5
Sagit et al. (2013)	Yes	Yes	Yes	No	No	No	Yes	3
Kim SY et al. (2010)	Yes	No	No	Yes	Yes	Yes	Yes	4
Park et al. (2015)	Yes	Yes	Yes	Yes	No	No	Yes	4
Meek et al. (2014)	Yes	No	No	Yes	Yes	Yes	Yes	4
Pakravan et al. (2012)	Yes	Yes	Yes	Yes	Yes	Yes	No	4
Ahiskalioglu et al. (2015)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	5

I: Is the study described as randomized? 1/0

II: Is the method to generate randomization sequence described? 1/0

III: Is the method to generate randomization sequence appropriate? 0/– 1

IV: Is the study described as double blind? 1/0

V: Is the blinding method described? 1/0

VI: Is the blinding method appropriate? 0/– 1

VII: Is there a description of losses to the follow-up and dropouts? 1/0

night before and 1 h before surgery in the study by Park et al. [33]. Only the study by Hill et al. [35] used a dose of 300 mg, administered post-operatively.

Pain scores

Pain levels were lower after pregabalin administration in all trials, but the pain relief was statistically significant in only seven. The scales used to measure pain were as follows: visual analog scale (VAS), verbal rating scale (VRS), patient controlled analgesia (PCA), and palliative prognostic index (PPI).

Hill et al. [35] found significantly greater pain relief between 2 and 12 h post-surgery and significantly lower pain intensity between 1 and 11 h post-surgery ($p < 0.05$) in the 300-mg pregabalin group versus the ibuprofen group, whereas

Table 3 General characteristics of the studies

Author and year	*N*	Age range (years)	Gender (M/F)	Intervention	Measurement scale
Olmedo-Gaya et al. (2015)	60	18–30	23/37	Impacted lower third molar extractions	Visual analog scale (VAS) Verbal rating scale (VRS)
Cillo et al. (2014)	12	NS	NS	Maxillomandibular advancement surgery	VAS Patient controlled analgesia (PCA)
Kim JH et al. (2014)	47	23–51	38/9	Septoplasty	VRS
Hill et al. (2001)	198	18–54	82/116	Extraction of one or two impacted lower third molars	–
Cheung et al. (2012)	34	20–28	15/19	Bilateral extraction in two stages of impacted third molars	VAS
Sagit et al. (2013)	143	20–45	107/36	Septoplasty	VAS
Kim SY et al. (2010)	94	20–65	89/5	Robot-assisted endoscopic thyroidectomy	VRS
Park et al. (2015)	48	30–36	20/28	Amygdalectomy	VAS PCA
Meek et al. (2014)	130	NS	60/70	Photorefractive keratectomy	VAS Palliative prognostic index (PPI)
Pakravan et al. (2012)	150	19–41	64/86	Photorefractive keratectomy	VAS
Ahiskalioglu et al. (2015)	40	18–45	NS	Double jaw (orthognathic) surgery	VAS PCA

pain relief was similar between the 50-mg pregabalin and placebo groups.

Kim JH et al. [32] reported a mean VRS score of 2.00 for the 150-mg pregabalin group versus 4.57 for the placebo group ($p = 0.015$) at 6 h post-surgery and an even greater difference at 12 h (1.79 vs. 4.48, $p = 0.004$). VRS scores were 2.75 for the pregabalin group versus 4.47 for the placebo group ($p = 0.072$) at 12 to 24 h post-surgery and 1.92 for the pregabalin group versus 2.52 for the placebo group ($p = 1.000$) at 24 to 48 h post-surgery.

Cillo et al. [31] observed significant lower ($p < 0.05$) VAS scores in the experimental (150-mg pregabalin plus 400-mg celecoxib) versus placebo groups during the first week post-surgery with the exception of day 3, when the pain score of the experimental group was higher. Ahiskalioglu et al. [30] also reported a significantly lower ($p < 0.05$) mean VAS score in the 150-mg pregabalin versus placebo groups at 30 min and 1, 2, 4, and 8 h post-surgery.

Sagit et al. [37] found significantly reduced VAS scores in the 75- and 150-mg pregabalin groups than that in the placebo group during the first 24 h post-surgery ($p \leq 0.002$). The reduction was significantly greater in the 150-mg versus 75-mg pregabalin group ($p < 0.05$) between 12 and 24 h but not during the earlier post-operative period.

Kim SY et al. [34] found similar VRS pain scores between groups at the time of surgery but significantly lower scores in the 150-mg pregabalin group versus placebo group at 6 (2 vs. 3, $p = 0.021$), 24 (1 vs. 2, $p = 0.024$), and 48 h (1 vs. 2, $p = 0.001$) post-surgery.

Pakravan et al. [36] reported that VAS scores were highly similar in the 75-mg pregabalin and 300-mg gabapentin groups and always lower than those in the placebo group. The proportion of patients describing severe pain (VAS > 7) was higher in the placebo group, although the difference only reached statistically significance in the first morning post-surgery ($p = 0.043$).

Park et al. [33] reported that VAS pain scores were lower in the 300-mg pregabalin group than that in the 4-mg diazepam group on days 1–4 post-surgery, were similar between the groups on days 5 and 6, and were again lower in the pregabalin group on day 7, although these differences were not statistically significant.

Olmedo-Gaya et al. [29] found no significant differences between pregabalin and control groups in pain intensity or relief (VAS score), although the intensity was lower in the 75-mg pregabalin group from 4 h post-surgery and the pain of this group was more constant, with fewer peaks of intensity.

Cheung et al. [19] found no difference in numerical rating scale (NRS) pain scores between the oral administration of 75-mg pregabalin before and after surgery, while the pain at rest (but not during mouth opening) was lower during the first 24 h in the post-operative group. Finally, Meek et al. [38] observed no significant differences in VAS pain scores between 75-mg pregabalin and placebo groups but reported that the maximum peak of pain was during the morning of day 2 post-surgery for the placebo group but during the night of day 2 for the pregabalin group.

Consumption of rescue analgesics

Numerous studies have evaluated the consumption of rescue analgesics as a measure of post-operative pain control [39]. The utilization of rescue medication was significantly reduced in seven of the 11 RCTs under study. Thus, Ahiskaliolgu et al. [30] reported a significant reduction in fentanyl consumption at 24 h in the 150-mg pregabalin versus placebo groups ($p = 0.004$), and Cillo et al. [31] described a significant ($p < 0.05$) reduction in i.v. morphine during the immediate post-operative period in the 150-mg pregabalin group, whose daily morphine consumption also remained lower during the next 7 days. Likewise, Meek et al. [38] observed a significant decrease in rescue analgesics consumption in the 75-mg pregabalin versus placebo groups on days 1 ($p < 0.03$) and 2 ($p < 0.025$) post-surgery, and Kim JH et al. [32] found a lower consumption during the hospital stay in the 150-mg pregabalin versus placebo groups ($p = 0.042$).

Sagit et al. [37] reported a significantly higher total consumption of rescue analgesics by the placebo group than that by the 75 or 150-mg pregabalin groups ($p < 0.001$), with no difference between the pregabalin groups. In the RCT published by Kim SY et al. [34], significantly fewer patients required additional analgesics in the 150-mg pregabalin group than those in the placebo group during the first 6 (7 vs. 17, respectively, $p = 0.018$) and 24 h (2 vs. 15, $p < 0.001$) post-surgery. Park et al. [33] reported a lower consumption of fentanyl in patients receiving 300-mg pregabalin before surgery than in those receiving 4-mg diazepam after surgery ($p < 0.001$). In the RCT by Olmedo-Gaya et al. [29], the same number of patients required rescue medication in the control and 75-mg pregabalin groups, but fewer pills were consumed by the latter ($p = 0.021$).

Pakravan et al. [36] found the use of rescue medication (acetaminophen-codeine) to be less frequent in the 75-mg pregabalin group than that in the 300-mg gabapentin group, especially during the early post-operative period, although the difference did not reach statistical significance ($p = 0.391$). Cheung et al. [19] found no significant differences in the consumption of rescue analgesics between the administration of 75-mg pregabalin 1 h before or immediately after the surgery. The RCT reported by Hill et al. [35] was interrupted when patients required rescue medication, and the mean duration of the analgesic effect was significantly higher in the 300-mg pregabalin group than that in the 50-mg pregabalin, ibuprofen, and placebo groups.

Adverse effects

Data on adverse effects were gathered by all authors except for Cillo et al. [31], and the most frequent were dizziness, somnolence, and vomiting or nausea. None of the trials reported severe adverse effects. Olmedo-Gaya et al. [29] reported that adverse effects (somnolence and dizziness) were more frequent and intense in the 75-mg pregabalin group than those in the placebo group ($p < 0.001$). Kim JH et al. [32] found a similar incidence of post-operative nausea and vomiting between the 150-mg pregabalin and placebo groups, with a higher level of sedation in the latter ($p = 0.022$), although it was not possible to control for the consumption of additional analgesics in the multivariate analysis.

Both the incidence and level of sedation were higher in the 150-mg pregabalin group ($p = 0.008$) during the first 6 h post-surgery for Kim SY et al. [34] Sedation scores were recorded on a four-point scale: 0 = awake; 1 = mild sedation; 2 = somnolent but awake; and 3 = very sleepy; given the possible residual effects of anesthetic agents, post-operative sedation was tested at 1 h post-surgery. The incidence of dizziness was higher in the pregabalin group ($p = 0.044$), although it disappeared at 24 h, but there were no differences between groups in nausea, vomiting, headaches, or blurry vision (mild).

In the RCT by Cheung et al. [19], no significant differences in the frequency of adverse effects were found between the 75-mg pregabalin and placebo groups. The most common adverse effects reported by Ahiskaliolgu et al. [30] were nausea and vomiting, which were more frequent in the placebo than in the 150-mg pregabalin group and were associated with higher opiate consumption. However, no between-group differences were observed in the frequency of other adverse effects.

Meek et al. [38] observed no differences in adverse effects reported by patients between the 75-mg pregabalin and placebo groups, and none was severe. Hill et al. [35] found that the intensity of adverse effects was similar among the placebo, ibuprofen, and 50-mg pregabalin groups but higher in the 300-mg pregabalin group. The most frequent adverse effects in pregabalin-treated patients were somnolence, dizziness, and vomiting.

Park et al. [33] found no significant differences in adverse effects between diazepam and 150-mg pregabalin groups: somnolence was the most frequent symptom, followed by dizziness (more frequent in control group), and nausea/vomiting (more frequent in the pregabalin group).

Sagit et al. [37] reported a similar incidence of adverse effects between 75- and 150-mg pregabalin groups; the most frequent were nausea, vomiting, dizziness, somnolence, mouth dryness, concentration difficulties, and constipation. In the RCT by Pakravan et al. [36], mild nausea was observed in three out of 50 patients in the 300-mg gabapentin group, although it did not cause them to abandon their medication.

Discussion

The aim of this systematic review was to contribute to the development of an optimal analgesic therapy protocol after cervicofacial surgery, including oral surgery. All eleven RCTs demonstrated a positive correlation between pregabalin consumption and a reduced post-operative pain score, although the reduction was only statistically significant in seven (63.6%) of them [30–32, 34–37]. The pain relief observed may be attributable to the anxiolytic effect of pregabalin, given reports that an oral dose of 75- or 150-mg pregabalin has a similar effect to that of 5-mg diazepam [40].

According to the results of this review, a single oral dose of 75 mg is sufficient to alleviate acute post-operative pain, although a dose of 150 mg was administered in four out of the seven RCTs that achieved significant pain relief [30–32, 34, 37]. Another trial found a significant difference in post-operative pain between the placebo group and 75- or 150-mg pregabalin groups, with no difference between the latter groups [37]. Out of these seven RCTs, pregabalin was administered in a single preoperative dose in three [30, 31, 37], in two doses (one preoperative and the other at 12 h after the first dose) in two [32, 34], and in a single post-operative dose in the remaining two RCTs [35, 36]. Cheung et al. [19] found no significant difference between the pre- and post-surgical administration of oral pregabalin. Taken together, these results support the administration of a single dose either before or after the surgery.

A statistically significant reduction in rescue analgesia consumption was recorded in eight (72.72%) of the 11 RCTs [29–34, 37, 38]. Three out of the four studies that used 75-mg pregabalin reported a significant reduction in rescue analgesia consumption [29, 37, 38]. Pregabalin was administered both before and after surgery in three of the seven studies reporting a significant effect [32, 34, 38] and before surgery in the other four, in a single dose in three of them [30, 31, 37] and in two doses (night before and 1 h before surgery) in the remaining study [33].

Five of the 11 RCTs in the review obtained a statistically significant reduction in both pain and rescue analgesia consumption, and all five administered an oral dose of 150-mg pregabalin, in a single dose (1 h before surgery) in three of these studies and in two doses in the other two (1 h before surgery and 12 h later). The sample size was large in two of these studies, with more than 90 patients [34, 37], whereas only 12 patients were enrolled in the trial by Cillo et al. [31] Although Ahiskalioglu et al. [30] also reported on a small sample, the significant pain relief obtained with a single preoperative dose of 150 mg is of special interest because the 40 patients underwent orthognathic mandibular advancement surgery, one of the most painful procedures in the cervicofacial area.

Table 4 Pregabalin regimens: outcomes and adverse effects

Author and year	Study groups	Pregabalin dose regimen	Additional pharmacotherapy	Outcomes	Adverse effects	Conclusion
Olmedo-Gaya et al. (2015)	Group 1 (n = 30): 75-mg pregabalin Group 2 (n = 30): no pregabalin	75-mg pregabalin 1 h before and 1 h after surgery	650-mg paracetamol 1/8 h (2 days); 875/125-mg amoxicillin/clavulanic acid or 300-mg clindamycin 1 × 8 h (for 7 days); 600-mg ibuprofen when needed	No significant pain relief ($p > 0.05$) Reduced rescue medication ($p < 0.05$)	More frequent somnolence and dizziness in pregabalin group (< 0.001)	Pregabalin reduces the requirement of rescue medication and is associated with a more constant pain level with fewer intensity peaks after third molar extraction
Cillo et al. (2014)	Group 1 (n = 6): 150-mg pregabalin and celecoxib Group 2 (n = 6): placebo	150-mg pregabalin + 400-mg celecoxib 1 h before surgery	3-g ampicillin + sulbactam or 600-mg clindamycin pre-surgery; 325-mg paracetamol 5-mg oxycodone and morphine i.v. by PCA	Pain relief ($p < 0.05$) Reduced rescue medication ($p < 0.05$)	Not specified	Pregabalin and celecoxib before mandibular advancement surgery significantly reduced post-operative pain and consumption of intravenous morphine
Kim JH et al. (2014)	Group 1 (n = 24): 150 -mg pregabalin Group 2 (n = 23): placebo	150-mg pregabalin 1 h before surgery and 12 h after the first dose	650-mg paracetamol 1 × 8 h	Pain relief ($p < 0.05$) Reduced rescue medication ($p < 0.05$)	Nausea and vomiting similar in the two groups; more frequent sedation in placebo group ($p = 0.022$)	The administration of pregabalin before and after septoplasty is effective and safe to reduce pain in early post-operative period
Hill et al. (2001)	Group 1 (n = 50): placebo Group 2 (n = 49): 50-mg pregabalin Group 3 (n = 50): 300 -mg pregabalin Group 4 (n = 49): 400 -mg ibuprofen	Post-operative administration of the study medication in a single dose (1 h after surgery)	Not specified	Pain relief ($p < 0.05$) in 300-mg pregabalin group No significant change in rescue medication ($p > 0.05$)	More frequent dizziness, somnolence, and vomiting in 300-mg pregabalin group	Pregabalin has significant analgesic properties in third molar extraction
Cheung et al. (2012)	Group 1 (n = 16): 75-mg pregabalin 1 h pre-surgery and placebo 1 h post-surgery Group 2 (n = 18): placebo 1 h pre-surgery and 75-mg pregabalin 1 h post-surgery	75-mg pregabalin 1 h before or 1 h after surgery	320-mg paracetamol and 32.5 -mg dextropropoxyphene 1 × 8 h maximum	No significant pain relief ($p > 0.05$) No significant change in rescue medication ($p > 0.05$)	Similar frequency of dizziness in the two groups	The post-operative administration of 75-mg pregabalin appears to improve analgesic effectiveness after third molar extraction under local anesthesia
Sagit et al. (2013)	Group 1 (n = 50): 75 -mg pregabalin Group 2 (n = 46): 150 mg pregabalin Group 3 (n = 47): placebo	Preoperative (1 h before surgery)	75-mg sodium diclofenac i.m.	Pain relief ($p < 0.05$) in 75- and 150-mg pregabalin groups Reduced rescue medication ($p < 0.05$) in 75- and 150-mg pregabalin groups Pain relief ($p < 0.05$)	Similar frequency of nausea, vomiting, dizziness, and mouth dryness in all groups	A single dose of 75- or 150-mg pregabalin before septoplasty is effective to reduce post-operative pain and analgesic consumption

Table 4 (continued)

Author and year	Study groups	Pregabalin dose regimen	Additional pharmacotherapy	Outcomes	Adverse effects	Conclusion
Kim JY et al. (2010)	Group 1 (n = 47): 150 -mg pregabalin Group 2 (n = 47): placebo	150-mg pregabalin 1 h before surgery and 12 h after first dose	30-mg ketorolac and 4-mg ondansetron at wound closing and 200-mg ibuprofen 1 × 12 h	Reduced rescue medication ($p < 0.05$)	More frequent sedation ($p = 0.008$) and dizziness ($p = 0.044$) in pregabalin group	Pregabalin before and after thyroidectomy (150-mg 2× day) is effective to reduce pain in early post-operative period
Park et al. (2015)	Group 1 (n = 23): 150 -mg pregabalin Group 2 (n = 25): 4-mg diazepam	150-mg pregabalin the night before and 150-mg 1 h before surgery	1% fentanyl by PCA, 30-mg ketorolac or- tromethamine i.m. on demand, 650-mg paracetamol 3 v/d 8 days	No significant pain relief ($p > 0.05$) Reduced rescue medication ($p < 0.05$)	Similar frequency of somnolence, nausea, vomiting, dizziness, and headache between groups	150-mg pregabalin before amygdalectomy reduces fentanyl consumption without increasing the incidence of adverse effects
Meek et al. (2014)	Group 1 (n = 67): 75-mg pregabalin Group 2 (n = 63): placebo	75-mg pregabalin 2 h before surgery and for 5 days after surgery 1 × 12 h	5-mg oxycodone, 500-mg paracetamol, 0.5% tetracaine drops, 25-mg promethazine, 0.5% moxifloxacin (all on demand); 0.1% fluorometholone acetate 4 v/d. Ibuprofen when necessary	No significant pain relief ($p > 0.05$) Reduced rescue medication ($p < 0.05$)	Higher frequency of somnolence, dizziness in pregabalin group	75-mg pregabalin is an effective option for pain relief after photorefractive keratectomy
Pakravan et al. (2012)	Group 1 (n = 50): 75-mg pregabalin Group 2 (n = 50): 300 -mg gabapentin Group 3 (n = 50): placebo	3× day for 3 days (first dose 2 h post-surgery)	0.5% chloramphenicol drops for 1 week, 0.1% betamethasone drops for 2 weeks, 0.1% fluorometholone. 300/ 10-mg paracetamol-codeine 4 v/d on demand	Pain relief ($p < 0.05$) in 75-mg pregabalin and 300-mg gabapentin groups No significant change in rescue medication ($p > 0.05$)	Nausea higher in the gabapentin group	Both 75-mg pregabalin and 300-mg gabapentin appear effective to relieve pain after photorefractive keratectomy; however, pregabalin is associated with a greater reduction in rescue medication consumption and fewer adverse effects
Ahiskalioglu et al. (2015)	Group 1 (n = 20): 150 -mg pregabalin Group 2 (n = 20): placebo	150-mg pregabalin 1 h before surgery	50-mg dexketoprofen-trometamol i.v. 1 × 12 h; fentanyl by PCA when needed	Pain relief ($p < 0.05$) Reduced rescue medication ($p < 0.05$)	Nausea and vomiting higher in the pregabalin group	A single dose of 150-mg pregabalin before double jaw surgery reduces opioid consumption during the first 24 h post-surgery

PCA, patient controlled analgesia; i.v., intravenous; i.m., intramuscular; administration was oral if not otherwise specified

Contradictory results were obtained in the two published studies on pregabalin administration for more than 1 day. In one RCT [36], 75-mg oral pregabalin was administered for 3 days, significantly reducing pain but not rescue medication consumption. In the other, it was prescribed for 5 days [38], obtaining a significant reduction in rescue medication consumption but not pain. Hence, there appears to be no clear evidence supporting the administration of pregabalin for more than one day after surgery.

No severe adverse effects were found that suggest the need to avoid the use of pregabalin. The absence of statistically significant differences in adverse effects between pregabalin-treated individuals and controls, as reported in most studies, may be attributable to the higher rescue medication consumption of the latter.

We also searched the literature on pregabalin for acute post-operative pain after surgery at any site. In 2008, Agarwal et al. [41] concluded that a single dose of 150-mg pregabalin before laparoscopic cholecystectomy significantly reduced post-operative pain and fentanyl consumption. Bekawi et al. [42] and Balaban et al. [43] also supported the effectiveness and safety of pregabalin for this surgery. In contrast, questions were raised about the usefulness of pregabalin to alleviate acute visceral pain in the RCTs by Yadeau et al. [44], Paech et al. [15], and Mathisen et al. [18] The RCT by Buvanendran et al. [46] in 2010 found that perioperative pregabalin administration for total knee arthroplasty reduced post-operative opioid consumption and the frequency of chronic pain and improved the mobility of patients during rehabilitation. According to the Cochrane review in 2009 [45], there was insufficient evidence to support the administration of pregabalin for acute pain and further clinical trials were required; it was based on six studies with population samples that were too heterogeneous for grouped analysis.

According to the meta-analyses by Engelman et al. [47] and Zhang et al. [48] in 2011 and by Yu et al. [49] in 2013, oral pregabalin administration reduces post-operative analgesic consumption. A meta-analysis by Mirshriky et al. [50] in 2015 reported that the pre- or post-operative administration of pregabalin significantly reduced pain scores and opioid consumption, with no differences between single and multiple doses.

Limitations of the present review include differences among the 11 selected RCTs in surgical procedure, anesthesia technique, oral pregabalin dose regimen, and coadjuvant analgesic therapy. There was also a wide heterogeneity in the surgical approach, with only a small number of studies on each procedure, leading us to group together the studies on cervicofacial surgeries. Hence, although oral pregabalin proved to be safe and effective to treat acute post-operative pain, further clinical trials are required in large samples of patients undergoing specific surgical procedures in order to establish optimal dose regimens (Table 4).

In conclusion, oral pregabalin can significantly reduce post-operative pain and the consumption of rescue analgesia, with no severe adverse effects. Although the optimal treatment dose and the most effective treatment regimen remain controversial, a single oral dose of 75-mg pregabalin before or after cervicofacial surgery appears adequate to alleviate pain and lessen the need for rescue analgesia consumption, while the statistical significance of these effects is higher with a single dose of 150-mg pregabalin, either before or after the surgery.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals carried out by any of the authors.

Informed consent For this type of study, formal consent is not required.

References

1. Macintyre PE, Schug SA, Scott DA, Visser EJ, Walker SM (2010) Acute pain management: scientific evidence, 3rd edn. ANZCA & FPM, Melbourne
2. Apfelbaum JL, Gan TJ, Chen C (2003) Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 97:534–540
3. Rosa-Díaz J, Navarrete-Zuazo V, Díaz-Mendiondo M (2014) Aspectos básicos del dolor postoperatorio y la analgesia multimodal preventive. Rev Mex Anestesiol 37:18–26
4. López Álvarez S, Agustí Martínez-Arcos S, Bustos Molina F et al (2012) Manejo del dolor agudo postoperatorio en cirugía ambulatoria. In: 2° ed. España, Inspira Network
5. Kumar N (2007) WHO normative guidelines on pain management. World Health Organization, Geneva
6. Cook RJ, Sackett DL (1995) The number needed to treat: a clinically useful measure of treatment effect. BMJ 310:452–454
7. Ra M, Derry S, Aldington D, Pj W (2015) Single dose oral analgesics for acute postoperative pain in adults—an overview of Cochrane reviews. Cochrane Db Syst Rev. https://doi.org/10.1002/14651858
8. Tro A, Quartey GK, Schmelz M et al (2007) Effects of oral pregabalin and aprepitant on pain and central sensitization in the electrical hyperalgesia model in human. Br J Anaesth 98:246–254
9. Richter RW, Portenoy R, Sharma U et al (2005) Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. J Pain 6:253–260
10. Cherry DA, Jacquot F, Sabatowski R et al (2004) Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. J Pain 109:26–35
11. Rose MA, Kam PCA (2002) Gabapentin : pharmacology and its use in pain management. Anaesthesia 57:451–462

12. Crofford LJ, Rowbotham MC, Mease PJ et al (2005) Pregabalin for the treatment of fibromyalgia syndrome. Arthritis Rheum 52: 1264–1273
13. Feltner DE, Liu-dumaw M, Schweizer E, Bielski R (2011) Efficacy of pregabalin in generalized social anxiety disorder: results of a double-blind, placebo-controlled, fixed-dose study. Int Clin Psychopharm 26:213–220
14. Zimbroff DL, Bielski RJ, Tobias K, Brock JD (2005) Pregabalin for treatment of generalized anxiety disorder. Arch Gen Psychiatry 62: 1022–1030
15. Paech MJ, Goy R, Chua S et al (2007) A randomized, placebo-controlled trial of preoperative oral pregabalin for postoperative pain relief after minor gynecological surgery. Anesth Analg 105: 1449–1453
16. Chang SH, Lee HW, Kim HK, Kim SH, Kim DK (2009) An evaluation of perioperative pregabalin for prevention and attenuation of postoperative shoulder pain after. Anesth Analg 109:1284–1286
17. Peng PWH, Li C, Farcas E et al (2010) Use of low-dose pregabalin in patients undergoing laparoscopic cholecystectomy. Br J Anaesth 105:155–161
18. Mathiesen O, Rasmussen ML, Dierking G et al (2009) Pregabalin and dexamethasone in combination with paracetamol for postoperative pain control after abdominal hysterectomy. A randomized clinical trial. Acta Anaesthesiol Scand 53:227–235
19. Cheung CW, Choi WS, Leung YY et al (2012) A double-blind randomized crossover study to evaluate the timing of pregabalin for third molar surgery under local anesthesia. J Oral Maxillofac Surg 70:25–30
20. Ha K, Carragee E, Cheng I, Kwon S, Kim Y (2011) Pregabalin as a neuroprotector after spinal cord injury in rats: biochemical analysis and effect on glial cells. J Korean Med Sci 26:404–411
21. Stahl SM (2004) Mechanism of action of α 2 δ ligands: voltage sensitive calcium channel (VSCC) modulators. J Clin Psychiatry 65:1033–1034
22. Shneker BF, McAuley JW (2005) Pregabalin: a new neuromodulator with broad therapeutic indications. Ann Pharmacother 39:2029–2037
23. Bockbrader HN, Radulovic LL, Posvar EL et al (2010) Clinical pharmacokinetics of pregabalin in healthy volunteers. J Clin Pharmacol 50:941–950
24. Kavoussi R (2006) Pregabalin: from molecule to medicine. J Euroneuro 16(Suppl 2):S128–S133
25. Eutamene H, Coelho M, Theodorou V et al (2000) Antinociceptive effect of pregabalin in septic shock-induced rectal hypersensitivity in rats. J Pharmacol Exp Ther 295:162–167
26. Gilron I (2007) Gabapentin and pregabalin for chronic neuropathic and early postsurgical pain: current evidence and future directions. Curr Opin Anaesthesiol 20:456–472
27. Cabello JB (2005) Plantilla para ayudarte a entender un Ensayo Clínico.CASPe. Guías CASPe de Lectura Crítica de la Literatura Médica. Alicante: CASPe. Cuaderno I. p5–8
28. Jadad AR, Moore RA, Carroll D et al (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17:1–12
29. Olmedo-Gaya MV, Manzano-Moreno FJ, Galvez-Mateos R et al (2016) Oral pregabalin for postoperative pain relief after third molar extraction: a randomized controlled clinical trial. Clin Oral Invest. https://doi.org/10.1007/s00784-015-1657-3
30. Ahiskalioglu A, İnce İ, Aksoy M, et al (2015) Effects of a single-dose of pre-emptive pregabalin on postoperative pain and opioid consumption after double-jaw surgery: a randomized controlled trial. J Oral Maxillofac Surg 74:53.e1–53
31. Cillo JE, Dattilo DJ (2014) Pre-emptive analgesia with pregabalin and celecoxib decreases postsurgical pain following maxillomandibular advancement surgery: a randomized controlled clinical trial. J Oral Maxillofac Surg 72:1909–1914
32. Kim JH, Seo MY, Hong SD et al (2014) The efficacy of preemptive analgesia with pregabalin in septoplasty. Clin Exp Otorhinolaryngol 7:102–105
33. Park SS, Kim D-H, Nam I-C, Lee I-H, Hwang J-W (2015) The effectiveness of pregabalin for post-tonsillectomy pain control: a randomized controlled trial. PLoS One 10:e0117161
34. Kim SY, Jeong JJ, Chung WY et al (2010) Perioperative administration of pregabalin for pain after robot-assisted endoscopic thyroidectomy: a randomized clinical trial. Surg Endosc Other Interv Tech 24:2776–2781
35. Hill CM, Balkenohl M, Thomas DW et al (2001) Pregabalin in patients with postoperative dental pain. Eur J Pain 5:119–124
36. Pakravan M, Roshani M, Yazdani S, Faramazi A, Yaseri M (2012) Pregabalin and gabapentin for post-photorefractive keratectomy pain: a randomized controlled trial. Eur J Ophthalmol 22(Suppl 7):106–113
37. Sagit M, Yalcin S, Polat H et al (2013) Efficacy of a single preoperative dose of pregabalin for postoperative pain after septoplasty. J Craniofac Surg 24:373–375
38. Meek JM, Rosbolt MB, Taylor KR et al (2014) Pregabalin versus placebo in postoperative pain relief of patients' status post photorefractive keratectomy: a double-masked, randomized, prospective study. J Ocul Pharmacol Ther 30:527–532
39. Mcquay HJ, Poon KH, Derry S, Moore RA (2008) Acute pain: combination treatments and how we measure their efficacy. Br J Anaesth 101:69–76
40. Korttila K, Jokela R, Ahonen J, Tallgren M, Haanpa M (2008) Premedication with pregabalin 75 or 150 mg with ibuprofen to control pain after day-case gynaecological laparoscopic surgery. Br J Anaesth 100:834–840
41. Agarwal A, Gautam S, Gupta D et al (2008) Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. Br J Anaesth 101:700–704
42. Bekawi MS, El Wakeel LM, Al Taher WMA, Mageed WMA (2014) Clinical study evaluating pregabalin efficacy and tolerability for pain management in patients undergoing laparoscopic cholecystectomy. Clin J Pain 30:944–952
43. Balaban F, Yağar S, Özgök A, Koç M, Güllapoğlu H (2012) A randomized, placebo-controlled study of pregabalin for postoperative pain intensity after laparoscopic cholecystectomy. J Clin Anesth 24:175–178
44. Yadeau JT, Paroli L, Kahn RL et al (2012) Addition of pregabalin to multimodal analgesic therapy following ankle surgery: a randomized double-blind, placebo-controlled trial. Reg Anesth Pain Med 37:302–307
45. Ra M, Straube S, Pj W, Derry S, Hj M (2010) Pregabalin for acute and chronic pain in adults. Cochrane Db Syst Rev DOI. https://doi.org/10.1002/14651858
46. Buvanendran A, Kroin JS, Della Valle CJ et al (2010) Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. Anesth Analg 110:199–207
47. Engelman E, Cateloy F (2011) Efficacy and safety of perioperative pregabalin for post-operative pain: a meta-analysis of randomized-controlled trials. Acta Anaesthesiol Scand 55:927–943
48. Zhang J, Ho K-Y, Wang Y (2011) Efficacy of pregabalin in acute postoperative pain: a meta-analysis. Br J Anaesth 106:454–462
49. Yu L, Ran B, Li M, Shi Z (2013) Gabapentin and pregabalin in the management of postoperative pain after lumber spinal surgery: a systematic review and meta-analysis. Spine 38:1947–1952
50. Mishriky BM, Waldron NH, Habib AS (2015) Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. Br J Anaesth 114:10–31