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The effect of preemptive gabapentin and pregabalin on postoperative pain of septoplasty with and without turbinoplasty: a randomized triple-blind controlled clinical trial

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Abstract

Background Septoplasty is a painful process. Nowadays, opioids and non-opioids are used to control patients' pain, which has different efficacy and consequences. We aimed to assess the effect of preemptive gabapentin and pregabalin on postoperative pain of septoplasty with and without turbinoplasty.

Methods This randomized triple-blind controlled clinical trial was performed on patients over 18 years who were candidates for elective septoplasty in Besat Hospital of Hamadan. In this study, 102 patients were randomly assigned to three equal groups, including pregabalin, gabapentin, and placebo. The pain score (VAS scale), analgesic use, and complications were assessed at the second, sixth, and 16th hours after surgery.

Results Results showed that the mean pain score in the control group was higher than pregabalin and gabapentin at all times after surgery ($P<0.001$). However, there was no significant difference between the pregabalin and gabapentin groups ($P=0.729$). At the second and sixth hours after surgery, the amount of analgesic used in the control group was significantly higher than pregabalin and gabapentin ($P<0.001$). But there was no significant difference between pregabalin and gabapentin groups regarding the used analgesics. Also, at 6 h after surgery, the incidence of complications in the control group was significantly higher than in the pregabalin group ($P=0.006$), but there was no statistically significant difference between the control group and the gabapentin group.

Conclusions Administering gabapentin or pregabalin, 1 h before surgery in patients undergoing septoplasty with or without turbinoplasty, can reduce postoperative pain and complications. Therefore, it is recommended to administer 300 mg oral pregabalin or 600 mg oral gabapentin 1 h before surgery to reduce pain after septoplasty.

Trial registration Iranian Registry of Clinical Trials, IRCT2015112024852N2. Registered on August 28, 2016—retrospectively registered, https://www.irct.ir/trial/20897.

Keywords Gabapentin, Pregabalin, Postoperative pain, Septoplasty, Turbinoplasty

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Background

Septoplasty is one of the most common surgeries in the ear, nose, and throat clinics [1]. Over the past two decades, relieving acute pain after surgery is one of the most important issues for patients and surgeons [2]. It has been suggested to record pain as the fifth pillar of vital signs [3]. The international association for the study of pain described the pain as an unpleasant sensory experience that is associated with actual or potential tissue damage resulting from it [4].

The onset of pain is accompanied by tissue damage and activation of nociceptors [5]. Following tissue damage in uncontrolled pain, sympathetic nerve activity may lead to potentially harmful changes such as increased heart rate, hypertension, hyperglycemia, immunosuppression, regional blood flow or venous stasis, and platelet stimulation in particular, in high-risk patients or patients undergoing high-risk surgery [6].

Nowadays, a variety of medications including opioids, nonsteroidal anti-inflammatory drugs, acetaminophen, regional block, and local anesthesia are used to control postoperative pain [7]. So far, previous studies mentioned promising results regarding the use of gabapentin or pregabalin as a preemptive agent in surgery in other parts of the body [8–12]. Gabapentin, a structural derivative of gamma-aminobutyric acid, was first introduced as an antiepileptic drug and later used to relieve neuropathic pain [13].

On the other hand, pregabalin is a gamma-aminobutyric acid derivative that has anticonvulsant and anxiolytic effects as well as sleep modulating [14]. It is used to relieve neuropathic pain, pain inflammation, tissue sensitivity, neuro-allergy, and fibromyalgia [7]. It also reduces acute pain after surgery and may reduce the need for opioids [11].

Although postoperative pain is typically a nociceptive pain resulting from environmental receptors, it is clear that inflammatory, neurogenic, and visceral mechanisms are also involved. Another suggestive mechanism for pain relief is the modulation of glutamine receptors. Gabapentin reduces pain in both *N*-methyl-D-aspartate (NMDA-dependent) and NMDA-independent ways [15].

Preoperative gabapentin administration has been shown to reduce pain after mastectomy and spinal cord surgery [16–18]. It is noteworthy that few studies have been conducted on the administration of gabapentin in ear, nose, and throat surgeries. To the best of our knowledge, we are the first comprehensive clinical trial that aimed to compare the effects of preemptive gabapentin and pregabalin on postoperative pain of septoplasty with the control group. We hypothesized that administering these preemptive agents could reduce pain considerably.

Methods

Patients and settings

This is a randomized triple-blind controlled clinical trial that was conducted on patients who were candidates for septoplasty with or without turbinoplasty. The inclusion criteria were 18–60 years of age, lack of a history of sensitivity to gabapentin and pregabalin, kidney disease, behavioral disorders such as depression, alcohol consumption in the last week, and respiratory disease. Patients with hypersensitivity to gabapentin and pregabalin, rhinoplasty and sinus endoscopy, uncontrolled bleeding need, and the use of other measures such as a posterior tampon were not included. Patients were randomly assigned to three therapeutic groups, including gabapentin, pregabalin, and control considering the presence or abscense of turbinoplasty. To randomize patients, the names of each group with separate code numbers (A, B, C) were written on separate sheets, and these sheets were poured into the basket. When assigning a patient to a group of three groups, the sheets were removed from the basket and the patient's group number was determined based on the code recorded on each sheet. The sheets taken out of the basket were returned to the basket after the allocation of the other two patients (random sampling without relocation).

Medication was given to the patient 2 h before the start of the operation in capsule form by a person who was unaware of the contents. Capsules were in the same color and shape. For blindness, all capsules were coded by a pharmacist. The intervention group received 600 mg of gabapentin, and the other group was given 300 mg of pregabalin. The control group was given a placebo capsule containing carboxymethyl cellulose. The anesthesia was performed on all patients based on a single protocol.

Septoplasty straightens the nasal septum through trimming, repositioning, and replacing cartilage or bone. On the other hand, turbinoplasty is an operation performed to reduce the size of turbinates presenting on the side wall of the nasal passageways. In the randomization, we also consider the presence or absence of turbinoplasty to abstain from the probable bias and all groups had similar frequency of this type of surgery. All surgeries were performed by a single surgeon.

For all patients, an anterior tampon was placed after the surgery and was removed during discharge. Then, at the second, sixth, and sixteenth hours after the end of the surgery, the patient's pain was assessed on a visual assessment scale (VAS), and the possible complications of the drug, such as severe diarrhea, diplopia, nausea, and vomiting and the amount of analgesics, were recorded. Through VAS that consists of a 10-cm line, the amount of pain that a patient feels ranges across a continuum from none to an extreme amount of pain

(scored zero to 10). We asked the patient to rate their current level of pain by placing a mark on the line.

Statistical analysis

After collecting the data, statistical analysis was performed by an unaware statistician in IBM SPSS Statistics for Windows, Version 21.0. The normality of quantitative data was assessed using the Kolmogorov–Smirnov test. Non-normally and normally distributed data were analyzed by Kruskal–Wallis and analysis of variance (ANOVA) tests, respectively. Qualitative data were analyzed by chi-square test. A *P* value less than 0.05 indicated statistical significance.

Results

In this study, 102 patients were randomly assigned to be divided into three groups, each consisting of 34 patients (Fig. 1). Results showed no statistically significant difference in terms of age, sex, and being with a turbinoplasty (Table 1).

Based on the results of the Kruskal–Wallis test, a statistically significant difference was observed between the mean score of patients' pain scores in pregabalin, gabapentin, and control groups at the second, sixth, and sixteenth hours after surgery. In the second hour after surgery, the mean pain score in the control group was higher than in the pregabalin and gabapentin groups ($P < 0.001$). However, there was no significant statistical difference between the pregabalin and gabapentin groups

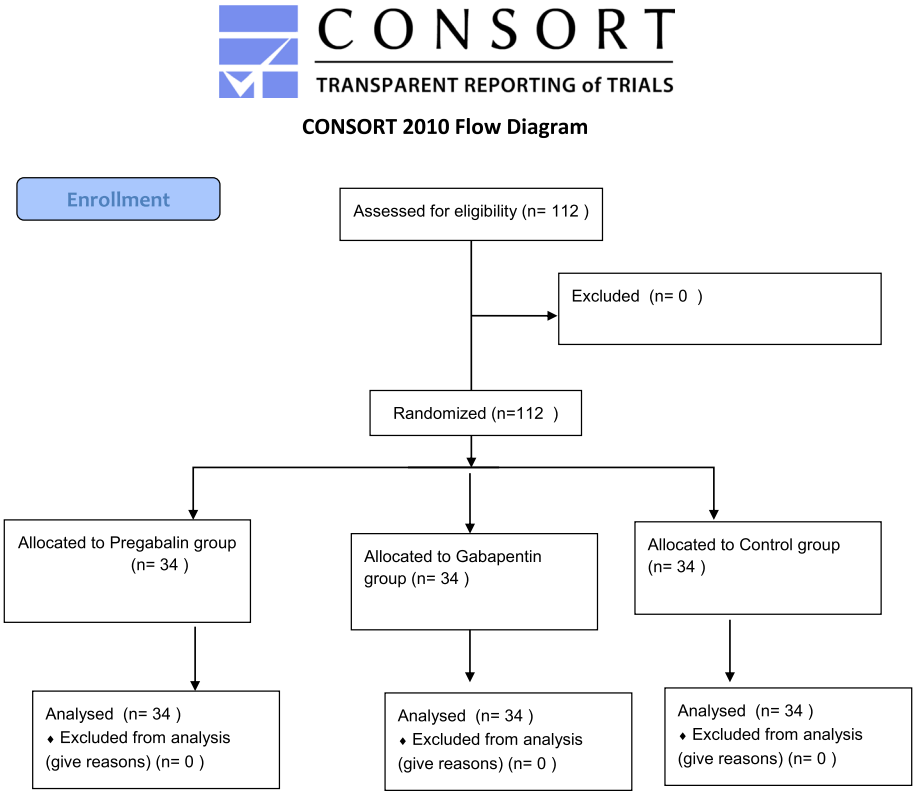

Fig. 1 CONSORT 2010 flow diagram

Table 1 Demographic characteristics and surgery type in groups undergoing septoplasty surgery

Variables	Pregabalin group	Gabapentin group	Control group	*P* value
Age (years) Mean (standard deviation)	35.88 ± 10.69	35.41 ± 11.53	34.14 ± 9.53	0.785
Sex (M/F)	27/7	28/6	25/9	0.751
Concurrent turbinoplasty (%)	38.2	41.2	52.9	0.537

($P=0.729$). Six hours after surgery, the mean pain score was significantly higher in patients in the control group than in the pregabalin and gabapentin groups ($P<0.001$) and the gabapentin group had a higher pain score than in the pregabalin group ($P=0.011$). Although 16 h after surgery, the mean pain score was significantly higher in patients in the control group than in the pregabalin and gabapentin groups ($P<0.001$), no significant difference was noted between the pregabalin and gabapentin groups ($P=1.000$) (Table 2).

In terms of complications, no statistically significant difference was observed between pregabalin, gabapentin, and control groups at the second and 16th hours after surgery. However, based on the results of Fisher's exact test, 6 h after surgery, there was a significant difference between the three groups in terms of the incidence of complications ($P=0.025$). The incidence of postoperative complications in the control group was significantly higher than in the pregabalin group ($P=0.006$). There was no statistically significant difference between the control group with the gabapentin group ($P=0.230$) and the pregabalin group with the gabapentin group ($P=0.197$). In terms of the type of complications, the only common complication was nausea and vomiting (Table 3).

Table 2 Pain score in treatment groups by time

Postoperative evaluation time	Pregabalin group Mean (standard deviation)	Gabapentin group Mean (standard deviation)	Control group Mean (standard deviation)	*P* value
2 h	0.44 (0.503)	0.64 (0.691)	2.14 (0.657)	< 0.001
6 h	0.26 (0.511)	0.79 (0.640)	1.91 (0.753)	< 0.001
16 h	0.29 (0.171)	0.58 (0.238)	0.79 (0.640)	< 0.001

In terms of the mean use of analgesics in the treatment groups of pregabalin, gabapentin, and control group 2 and 6 h after surgery, a statistically significant difference was observed ($P<0.001$). But 16 h after the surgery, there was no statistically significant difference between the three groups. The results of the Tukey post hoc test showed that in the second and sixth hours after surgery, the amount of analgesic used in patients in the control group was significantly higher than in the pregabalin and gabapentin groups ($P<0.001$). But there was no statistically significant difference between the pregabalin and gabapentin groups (Table 4).

Discussion

In septoplasty, manipulation of the soft tissue with bone in an area that is neurologically very rich increases the patient's sense of pain. Also, placing a tampon increases postoperative pain. Using preemptive agents for the prevention of pain neurotransmitter release before the beginning of the surgical trauma is a method to control pain. So far, gabapentin and pregabalin have been studied separately as preemptive agents in surgical procedures in various parts of the body and there is a shortage of evidence on the nasopharyngeal areas. The current study indicated lower pain scores at all times after surgery, a lower amount of analgesics in the second and sixth hours, and a lower incidence of complications at 6 h after surgery in the pregabalin and gabapentin groups compared to the control group.

A meta-analysis by Hurley et al. who studied the effects of preoperative gabapentin on pain and postoperative pain in various parts of the body showed that patients' pain scores were significantly lower in the group receiving gabapentin than in the control group [9]. Their results

Table 3 The complications in patients undergoing septoplasty surgery

Postoperative evaluation time	Pregabalin group (%) Number	Gabapentin group (%) Number	Control group (%) Number	*P* value
2 h				0.001
Yes	(0%)0	(0%)0	(0%)0	
No	(100%)34	(100%)34	(100%)34	
Total	(100%)34	(100%)34	(100%)34	
6 h				0.025
Yes	(2.9%)1	(14.7%)5	(26.5%)9	
No	(97.1%)33	(85.3%)29	(73.5%)25	
Total	(100%)34	(100%)34	(100%)34	
16 h				0.121
Yes	(2.9%)1	(0%)0	(11.8%)4	
No	(97.1%)33	(100%)34	(88.2%)30	
Total	(100%)34	(100%)34	(100%)34	

Table 4 The mean amount of analgesics in patients undergoing septoplasty surgery

Postoperative evaluation time	Pregabalin group	Gabapentin group	Control group	*P* value
2 h	0	5.88	61.76	< 0.001
6 h	2.94	11.76	76.47	> 0.001
16 h	0	0	5.88	0.133

were consistent with ours, despite different sample sizes and patients.

Besides, in a previous systematic review, the effectiveness of gabapentin before surgery on various parts of the body was assessed. It was shown that prescribing 1200 mg of gabapentin before surgery significantly reduced postoperative pain [8]. The results of the present study were similar to the findings of Ho et al. [8], except that in our study, 600 mg gabapentin was prescribed.

Consistent with ours, Clivatti et al. reviewed the effect of preoperative gabapentin administration on postoperative pain in various parts of the body. Their study found that the pain score was reduced in 75% of patients who received gabapentin before surgery and 55.6% of patients who received gabapentin before and after surgery [19]. Notably, in the present study, we only prescribed gabapentin once before surgery and none of the patients had pain before the surgery due to the elective septoplasty surgery; however, compared to the control group, gabapentin significantly reduced the patient's pain.

Mohammed et al. compared the effect of gabapentin and placebo on reducing the pain score of patients who underwent sinus endoscopic surgery. Consistent with ours, they found that the severity of pain and the need for postoperative pain control in the gabapentin group were significantly lower than in the control group [11]. Furthermore, Park et al. showed that by prescribing gabapentin after rhinoplasty, the amount of pain in patients taking gabapentin decreased significantly within 24 h after surgery compared to the control group [12].

Regarding the effect of pregabalin on postoperative pain and severity in patients, Youssef et al. compared the analgesic effect of pregabalin, dexamethasone, and placebo in 60 patients under septoplasty. The patient's pain was significantly reduced within 12 h after surgery in the group receiving pregabalin and pregabalin with dexamethasone compared to the control group [14]. In addition, Kim et al. assessed 47 patients under septoplasty and found that patients' pain scores were significantly lower in the pregabalin group than in the control group [10].

Despite the different prescribed medications, Demirhan et al. compared the analgesic effect of pregabalin and placebo and the effect of adding dexamethasone to them in patients with rhinoplasty and septoplasty surgery. They found that adding dexamethasone to pregabalin had a greater pain-reducing effect than placebo and pregabalin alone and reduced opioid use [20]. Sagit et al. compared the effects of placebo and pregabalin with doses of 75 and 150 mg, 1 h before surgery. Their results showed that in both groups, postoperative pain intensity was less than in the control group. Considering the 300 mg dose of pregabalin, the results of our study were consistent with Sagit et al. [21].

In terms of complications, we only observed nausea and vomiting in patients undergoing septoplasty. The incidence of postoperative complications was significantly higher in the control group than in the pregabalin group, but there was no significant difference between the control group with gabapentin group and the pregabalin group with gabapentin group in terms of occurrence of various complications such as vomiting. In the study of Hurley et al., no statistically significant difference was observed between patients receiving gabapentin and the control group in terms of the incidence of complications, such as vomiting and nausea [9]. In the study of Mohammed et al., the incidence of vomiting and nausea in the gabapentin group was lower than in the control group [11]. Although we found that the incidence of nausea and vomiting in the gabapentin group was lower than in the control group, the differences between the two groups were not significant which may be due to the small sample size. It is noteworthy that due to the negative impact of nausea and vomiting on increasing the amount of pain at the surgical site and causing dissatisfaction in patients, it may be clinically valuable to minimize its occurrence.

It should be noted that the effectiveness of gabapentin in the treatment of complications depends on its dose. Ho et al. reported that prescribing less than 1200 mg of gabapentin in various surgeries reduced the risk of complications such as vomiting and postoperative itching [8]. Also, blurred vision is a common complication of gabapentin [12]. However, in our study, none of the patients in the gabapentin and pregabalin groups had blurred vision.

Demirhan et al. and Youssef et al., who assessed patients under rhinoplasty and septoplasty, found that postoperative nausea and vomiting were significantly lower than the control group [14, 20, 22]. Meanwhile, Demirhan et al. reported an increased blurred vision in patients receiving pregabalin and pregabalin with dexamethasone [20, 22]. Contrary to ours, Kim et al. mentioned no significant difference between the pregabalin and the control groups in terms of the incidence of vomiting and nausea [10], which may be due to the sample size difference.

Regarding the higher effectiveness of pregabalin on postoperative pain relief, a previous study suggested that

adding dexamethasone to pregabalin may increase its effectiveness in relieving pain [7]. But in another study, adding dexamethasone to pain relief after septoplasty did not help. Therefore, the researchers recommended administering pregabalin alone to relieve pain after septoplasty [20].

Also, the effectiveness of pregabalin in relieving pain after surgery is dose-dependent. The results of a review study showed that a dose of 150 mg was more effective than 75 mg [7]. In our study, 300 mg was chosen, which did not cause hazardous complications. In 2019, Pourfakhr et al. estimated the effect of 75 mg of pregabalin on patients' postoperative pain one hour before septorhinoplasty surgery. Their results showed that the VAS pain scores in the pregabalin group were lower than the placebo group at 0.5, 1, 2, and 6 h after the surgery, but they did not differ from each other in the 24 h after the operation [23]. Moreover, Morgan et al. evaluated the effect of multidrug, including acetaminophen, celecoxib, and gabapentin, in patients under septoplasty. They reported that postoperative pain, the need for opioids, and discharge time from the hospital were significantly reduced [24]. Obviously, in multidrug therapy, the effective drug cannot be indicated.

This study had some strengths and limitations. To the best of our knowledge, we compared the effect of gabapentin and pregabalin with the control group for the first time and groups were assessed for 24 h which was a longer duration compared to previous studies. However, we had a limited sample size, therefore, it seems that further controlled clinical trials with a larger sample size can be recommended.

Conclusion

In patients undergoing septoplasty surgery with or without turbinoplasty, the administration of gabapentin or pregabalin, 1 h before surgery as a preemptive agent and before releasing of pain neurotransmitters due to surgical trauma, significantly reduced postoperative pain and the need for analgesics compared to the control group. Therefore, it is recommended to administer 300 mg oral pregabalin or 600 mg oral gabapentin 1 h before surgery to reduce pain after septoplasty.

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Authors' contributions
RA and FH have made a substantial contribution to the concept or design of the article. RA, FH, MSA, JJ, EKH, AK, and AM contributed to the acquisition, analysis, or interpretation of the data for the article. MSA, JJ, EKH, AK, and AM drafted the article or revised it critically for important intellectual content. All authors approved the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The written informed consent letter was obtained from the patients. This study was approved by the Ethics Committee of the Hamadan University of Medical Sciences (code: IR.UMSHA.REC.1394.328). This study was registered in the Iranian Registry of Clinical Trials (code: IRCT2015112024852N2).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. Kotisalmi I, Hytönen M, Mäkitie AA, Lilja M (2022) Septoplasty with and without additional sinonasal surgery: postoperative sequelae and the use of prophylactic antibiotics. Eur Arch Otorhinolaryngol 279(7):3449–3458
2. Rawal N (2016) Current issues in postoperative pain management. Eur J Anaesthesiol 33(3):160–171
3. Martins Novais AC, Simãozinho de Matos N, Ferreira de Almeida C (2023) Management of chronic pain: the importance of improving patient quality of life. Acta Med Port 36(1):65
4. Malik NA (2020) Revised definition of pain by 'International Association for the Study of Pain': Concepts, challenges and compromises. Anaesth Pain Intensive Care 24(5):481–483
5. Baral P, Udit S, Chiu IM (2019) Pain and immunity: implications for host defence. Nat Rev Immunol 19(7):433–447
6. Small C, Laycock HJ (2020) Acute postoperative pain management. J Bri Surg 107(2):e70-80
7. Chen N, Soneru C, Kacker A (2018) Does a single dose of pregabalin help with postoperative pain after septoplasty? Laryngoscope 128(5):1023–1024
8. Ho KY, Gan TJ, Habib AS (2006) Gabapentin and postoperative pain–a systematic review of randomized controlled trials. Pain 126(1–3):91–101
9. Hurley RW, Cohen SP, Williams KA, Rowlingson AJ, Wu CL (2006) The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. Reg Anesth Pain Med 31(3):237–247
10. Kim JH, Seo MY, Hong SD, Lee J, Chung SK, Kim HY et al (2014) The efficacy of preemptive analgesia with pregabalin in septoplasty. Clin Exp Otorhinolaryngol 7(2):102–105
11. Mohammed MH, Fahmy AM, Hakim KYK (2012) Preoperative gabapentin augments intraoperative hypotension and reduces postoperative opioid requirements with functional endoscopic sinus surgery. Egypt J Anaesth 28(3):189–192
12. Park IJ, Kim G, Ko G, Lee YJ, Hwang SH (2016) Does preoperative administration of gabapentin/pregabalin improve postoperative nasal surgery pain? Laryngoscope 126(10):2232–2241

13. Masri S, Kenney AE, Scigliano D, Juba KM (2022) Gabapentin-induced overflow urinary incontinence: a case report and review of the literature. J Pain Palliat Care Pharmacother 16:1–6
14. Youssef S, Yehia S, Kadah S, Khaled O (2013) Effect of pregabalin and dexamethasone on early postseptoplasty clinical outcome. Ain-Shams J Anaesthesiol 6(3):236–242
15. Stoicea N, Russell D, Weidner G, Durda M, Joseph NC, Yu J, Bergese SD (2015) Opioid-induced hyperalgesia in chronic pain patients and the mitigating effects of gabapentin. Front Pharmacol 27(6):104
16. Dahl JB, Mathiesen O, Møiniche S (2004) 'Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post-operative pain. Acta Anaesthesiol Scand 48(9):1130–1136
17. Fassoulaki A, Patris K, Sarantopoulos C, Hogan Q (2002) The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. Anesth Analg 95(4):985–991
18. Turan A, Memiş D, Karamanlioğlu B, Yağiz R, Pamukçu Z, Yavuz E (2004) The analgesic effects of gabapentin in monitored anesthesia care for ear-nose-throat surgery. Anesth Analg 99(2):375–378
19. Clivatti J, Sakata RK, Issy AM (2009) Review of the use of gabapentin in the control of postoperative pain. Rev Bras Anestesiol 59(1):87–98
20. Demirhan A, Akkaya A, Tekelioglu UY, Apuhan T, Bilgi M, Yurttas V et al (2014) Effect of pregabalin and dexamethasone on postoperative analgesia after septoplasty. Pain Res Treat 2014:850794
21. Sagit M, Yalcin S, Polat H, Korkmaz F, Cetinkaya S, Somdas MA (2013) Efficacy of a single preoperative dose of pregabalin for postoperative pain after septoplasty. J Craniofac Surg 24(2):373–375
22. Demirhan A, Tekelioglu UY, Akkaya A, Bilgi M, Apuhan T, Karabekmez FE et al (2013) Effect of pregabalin and dexamethasone addition to multimodal analgesia on postoperative analgesia following rhinoplasty surgery. Aesthetic Plast Surg 37(6):1100–1106
23. Pourfakhr P, Khajavi MR, Jalali A, Memari F, Etezadi F, Momeni Roochi M et al (2019) Low-dose preoperative pregabalin improves postoperative pain management in septorhinoplasty surgery: a double-blind randomized clinical trial. Eur Arch Otorhinolaryngol 276(8):2243–2249
24. Morgan B, Stanik-Hutt J (2015) Utilization of a preemptive, multimodal analgesic regimen in adult ambulatory septoplasty patients: a quality improvement project. ORL Head Neck Nurs 33(4):6–13

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