European Archives of Oto-Rhino-Laryngology (2019) 276:2243–2249
https://doi.org/10.1007/s00405-019-05448-y

RHINOLOGY

Low-dose preoperative pregabalin improves postoperative pain management in septorhinoplasty surgery: a double-blind randomized clinical trial

Pejman Pourfakhr[1] · Mohammad Reza Khajavi[1] · Ali Jalali[1] · Faramarz Memari[2] · Farhad Etezadi[1] · Mehrnoush Momeni Roochi[3] · Reza Shariat Moharari[1] · Atabak Najafi[1]

Received: 8 December 2018 / Accepted: 23 April 2019 / Published online: 4 May 2019

Abstract

Purpose To evaluate the efficacy of single low dose (75 mg) preoperative pregabalin in reducing post-operative pain of septorhinoplasty.

Methods A double blind single center Randomized controlled trial based on block randomization. In the pregabalin group (PG) 34 participants received 75 mg pregabalin orally one hour before anesthesia induction while in control group (CG) 34 participants received a placebo. Pain and sedation were repeatedly measured with Visual Analouge Scale (VAS) and Riker Sedation-Agitation Scale (RSAS) respectively, 0.5, 1, 2, 6, 24 hours postextubation. Cumulative doses of fentanyl and ibuprofen received in both groups were compared.

Results Thirty-two of the participants in PG and 33 of the participants in CG completed the study. The Mean VAS pain score was less in PG versus CG 30 min postoperatively (2.30 ± 1.30 vs. 4.85 ± 1.17), one hour (2.28 ± 0.92 vs. 4.27 ± 0.78), two hours (2.11 ± 0.88 vs. 3.60 ± 0.61) and six hours (1.47 0.62 vs. 2.76 ± 0.91) but not 24-hours postoperatively (0.84 ± 0.62 vs. 1.09 ± 0.92). Participants in the PG were less agitated during early post-extubation period (at 10 min: RSAS 3.93 ± 0.43 vs. 4.42 ± 0.50) and more alert during the first hour post-extubation (at 60 min: RSAS 3.90 ± 0.29 vs. 3.36 ± 0.69). The total dose of rescue fentanyl and ibuprofen was lower in the PG compared to the CG.

Conclusions A single dose of 75 mg pregabalin is very effective for pain control after septorhinoplasty procedure when administered one hour before anesthesia induction. Side effects are rare and opioid sparing was noted.

Trial registration Clinical trial number: IRCT2017043033706N1

Keywords Pregabalin · Pain · Septorhinoplasty · Opioid sparing · Agitation · Remifentanil

Introduction

An essential component of patient management is postoperative pain control. Up to 70% of patients experience pain after surgery [1]. Ineffective perioperative pain management can increase mortality and morbidity [2]. Nasal surgery is usually performed as a common ambulatory procedure. The first 3 days after septoplasty and rhinoplasty surgery is associated with considerable amount of pain and therefore, close attention and analgesic medication control are needed [3]. Use of opioid analgesics in the recovery room is very effective for pain control in these patients [4]. Sedation, respiratory depression, nausea and vomiting are adverse effects of opioid analgesics. Also side effects of opioid analgesics could delay patient's postoperative discharge. Opioid sparing analgesia is crucial in pain management of ambulatory surgeries [5]. Multimodal analgesia is an acceptable approach which is usually used to improve quality of pain control and decrease opioid-associated side effects [6].

Aspirin and non-steroidal anti-inflammatory drugs are commonly prescribed to manage postoperative pain; however, they are not enough to control pain in some cases,

✉ Ali Jalali
a.jalali.md@gmail.com

[1] Department of Anesthesiology, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran

[2] Department of Otology/Neurotology, Erfan Hospital, Tehran, Iran

[3] Department of Oral and Maxillofacial Surgery, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran

especially during the first day of postoperative period [4, 7]. Preoperative administration of gabapentin is successful for pain control in nasal surgery. However, frequent dizziness is a side effect that makes this drug unacceptable in outpatient setting [7].

Pregabalin is one of the anticonvulsive drugs which is usually used to control neuropathic and chronic resistance pain. Different doses of pregabalin have been examined for pain control in nasal surgery [8–10]. A recent meta-analysis study showed pregabalin efficacy; however, frequent unfavorable side effects have been reported including dizziness and blurred vision [11]. This meta-analysis included five studies about septoplasty and most of them were performed in the same country. In our opinion, results of this meta-analysis could not be considered definitive and thus, further studies are needed. In another study, the efficacy of single dose of 75-mg and 150-mg pregabalin in septoplasty was evaluated by Sagit in [8]. In contrast to control group, the pain score was lower in patients receiving pregabalin. Evaluation of pain intensity started 1 h postoperatively. Pain control lasted longer when 150-mg pregabalin was administered. Comparing the two groups, patients who received 150-mg pregabalin had lower VAS than patients receiving 75-mg pregabalin, at 12 and 24 h postoperative. However, the group that received 150-mg pregabalin experienced more side effects. The duration of surgery and details of anesthesia management were not recorded in their study; so, this might have effects on pain perception.

Demirhan studied effectiveness of 300-mg preoperative pregabalin and pregabalin + dexamethasone in a multimodal pain control strategy [9]. Pain intensity was measured by NRS which is not as precise as VAS [12–14]. Comparing the pregabalin group with control group, the pain intensity was not significantly different. Side effects, including dizziness and blurred vision, were present in 15% and 30% of patients, respectively. Demirhan concluded that combination of pregabalin 300 mg and dexamethasone 8 mg provided efficient analgesia in postoperative period of septorhinoplasty. Although high doses of pregabalin were used in this study, the dominant pain relief effect seems to be due to dexamethasone [9].

Kim studied the effect of pregabalin 150 mg 1 h before surgery and 12 h after first dose [10]. The pain intensity was evaluated at 6, 12, 24 and 48 h postoperatively. Kim used NRS to measure pain intensity. Pain intensity measured in 6- and 12-h postoperative period was lower in pregabalin group. Nausea and vomiting were similar in both groups (8–13%). Also, sedation reported more prevalent in control group due to more rescue analgesia by opioid injections. They reported that additional dose of pregabalin postoperatively did not improve patients' pain management.

Previous studies used different anesthesia techniques and diverse pregabalin regimens which lead to divergent. In this study, we evaluate the efficacy of simplest method of pregabalin administration in septorhinoplasty surgery. We examined the efficacy of preoperative administration of single low-dose pregabalin in pain control after septorhinoplasty surgery. We used lower pregabalin doses to see if we could achieve same pain control without causing side effects such as blurred vision and sedation.

Materials and methods

Study design/randomization

We designed a randomized double-blind placebo-controlled trial which included 18–50-year-old female/male candidates of elective septorhinoplasty in a tertiary educational academic hospital. Sample size was calculated based on literature. This study was approved by the university's institutional review Board (IRB #25927) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at https://www.irct.ir (IRCT2017043033706N1). Authors have followed the appropriate Enhancing the Quality and Transparency Of Health Research (EQUATOR) guidelines. Consecutive sampling based on block randomization method was done to include 34 participants in each group.

Patients/inclusion/exclusion

During preoperative visit 1 week before surgery, a trial anesthesiologist informed potential cases about the goals and details of study. Participants signed the informed consent before enrollment in the study. Eligibility criteria included: American Society of Anesthesiologist (ASA) score II or I, age 18–50, elective septorhinoplasty. Exclusion criteria were: history of psychiatric disorder/medication; history of drug dependency or abuse; use of benzodiazepines, opioids, corticosteroids, tricyclic antidepressants, non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesic drugs 48 h before surgery; history of antiepileptic drugs; current use of gabapentin or pregabalin; history of allergy to any of the study medications; being pregnant or obese (body mass index > 35 kg/m^2); suffering from cardiac disease, hypertension, pulmonary disease, hepatic disease, renal disease, diabetes mellitus; history of facial trauma and revision surgery.

Intervention/anesthesia process

All participants were fasted 6 h before their anesthesia induction. Participants in control group (CG) received placebo 1 h before anesthesia induction. Patients in pregabalin group (PG) received a capsule of 75-mg pregabalin (Lyrica, Pfizer, Freiburg, Deutschland) 1 h before induction. All patients and

trial anesthesiologists were blinded to the group of treatment (CG vs. PG). The time between induction of anesthesia and extubation was recorded as anesthesia duration.

All participants received identical anesthesia protocol. Premedication and induction included midazolam 0.05 mg/kg; fentanyl 2 μg/kg; lidocaine 0.5 mg/kg; propofol 1–2 mg/kg based on bi-spectral index (BIS), and atracurium 0.5 mg/kg. Maintenance anesthetics include isoflurane 0.8–1.2% in addition to remifentanil infusion. The goal of anesthesia protocol was delivering lowest drug to keep BIS at 40–50. Mean arterial pressure (MAP) was 65–70 mmHg and systolic blood pressure (SBP) was not allowed to go below 75% of patient's baseline. If the patient's anesthesia needed any change in mentioned protocol, patient was excluded from the study to allow them to receive appropriate anesthetics or drugs as needed.

We decreased isoflurane and remifentanil dosage 10 min before end of surgery to keep BIS about 70–75. By the end of the surgery, all anesthetics were ceased. Neostigmine 0.05 mg/kg and atropine 0.02 mg/kg were injected to reverse neuromuscular blockage. Patients were extubated when they reached emergence phase 3 [15]. The total remifentanil infused for each participant was recorded and standardized based on time of remifentanil infusion and patients weight (μg/kg/minute). This enabled us to compare effect of pregabalin administration on remifentanil infusion between the control and intervention groups. The time period between cessation of anesthetics to actual extubation was recorded as "duration of extubation".

Evaluation of outcomes

Each patient was requested to rate their pain based on numeric rating score (NRS) 10 min after extubation. After that pain intensity was measured for each participant based on visual analog scale (VAS)—a horizontal 100-mm line scored 0 for no pain and 10 for maximum imaginable pain—at 30 min and 1, 2, 6 and 24 h post-extubation. The patient's pain level was reported as our primary outcome.

Each patient was observed for 2 h in post-anesthesia care unit (PACU), and then admitted to hospital ward under meticulous observation for the next 24 h. During PACU observation, patient received fentanyl IV 10 μg every 10 min, if they requested for rescue analgesia. The total fentanyl dose, which was injected for each demanding patient, was recorded. Ibuprofen 400 mg IV was injected at participants' request during 24-h postoperative hospital admission and total dose of drug was recorded for each patient. Commonly septorhinoplasty is an outpatient procedure, but in our center, most patients stay at hospital for 24 h after surgery because the hospital is an educational academic center.

Patient's anxiety and consciousness at extubation time were measured based on Riker Sedation–Agitation Scale (RSAS) and Ramsay Sedation Scale (RSS). Also, RSAS was recorded at 30 min and 1, 2, 6 and 24 h after extubation.

Frequency of nausea, vomiting, dizziness and occurrence of blurred vision was recorded during the first 24-h postoperative period.

After the patient was admitted to the hospital ward, he/she received ibuprofen 400 mg IV every 4 h if needed.

Total ibuprofen was injected for each patient during 24-h post-operative ward admission was registered in his/her data file.

Statistical analysis

We used SPSS v.19 to find statistically significant differences or associations. Distribution of numerical variables evaluated for normal distribution and independent *t* test was used to find differences in VAS, NRS, amount of remifentanil infused, the time of remifentanil infusion between CG and PG. Mann–Whitney test was used to compare RSS, RSAS, total fentanyl injected in PACU and total ibuprofen consumed in first 24-h postoperative time between CG and PG. Chi-square test was used to compare frequency of nausea, vomiting and blurred vision.

Two-sided difference was tested and p value of 0.05 was selected as the level of statistical significance.

Results

From all of 68 participants, 32 individuals in PG and 33 individuals in CG completed the study (Fig. 1). Both CG and PG were similar in gender, age, weight, duration of operation, and duration of remifentanil infusion. Pain score in PG was (2.40 ± 1.62) based on numeric rating scale (NRS). It was significantly lower than CG (5.39 ± 1.39; $p < 0.001$). Based on VAS of pain, participants of PG had statistically significant ($p < 0.001$) lower score in 0.5, 1, 2 and 6 h post-operative compared to participants in CG (Table 1). Patients in PG received lower fentanyl as rescue medication during 2-h PACU admission (3.75 μg vs. 27.64 μg; $p < 0.001$). Controls needed more ibuprofen during 24 h after surgery (1284.85 mg ± 194 vs. 1012.5 mg ± 226.82 in PG; $p < 0.001$). Ramsay sedation score at extubation was higher in participants of PG (2.62 ± 0.83) vs. participants of CG (1.48 ± 0.56; $p < 0.001$). Riker Sedation–Agitation Score (RSAS) was lower on extubation time in PG (3.90 ± 0.92 vs. to CG (5.33 ± 0.92; $p < 0.001$).

RSAS was similar in both groups when measured 120 min postoperative (Table 1). Five patients (15.6%) in PG had postoperative nausea during 24-h postoperative period versus 13 patients (39.3%) in CG; this was significantly lower in the PG ($p < 0.001$). Occurrence of vomiting was rare and not significantly different in both groups (1/32 in PG vs.

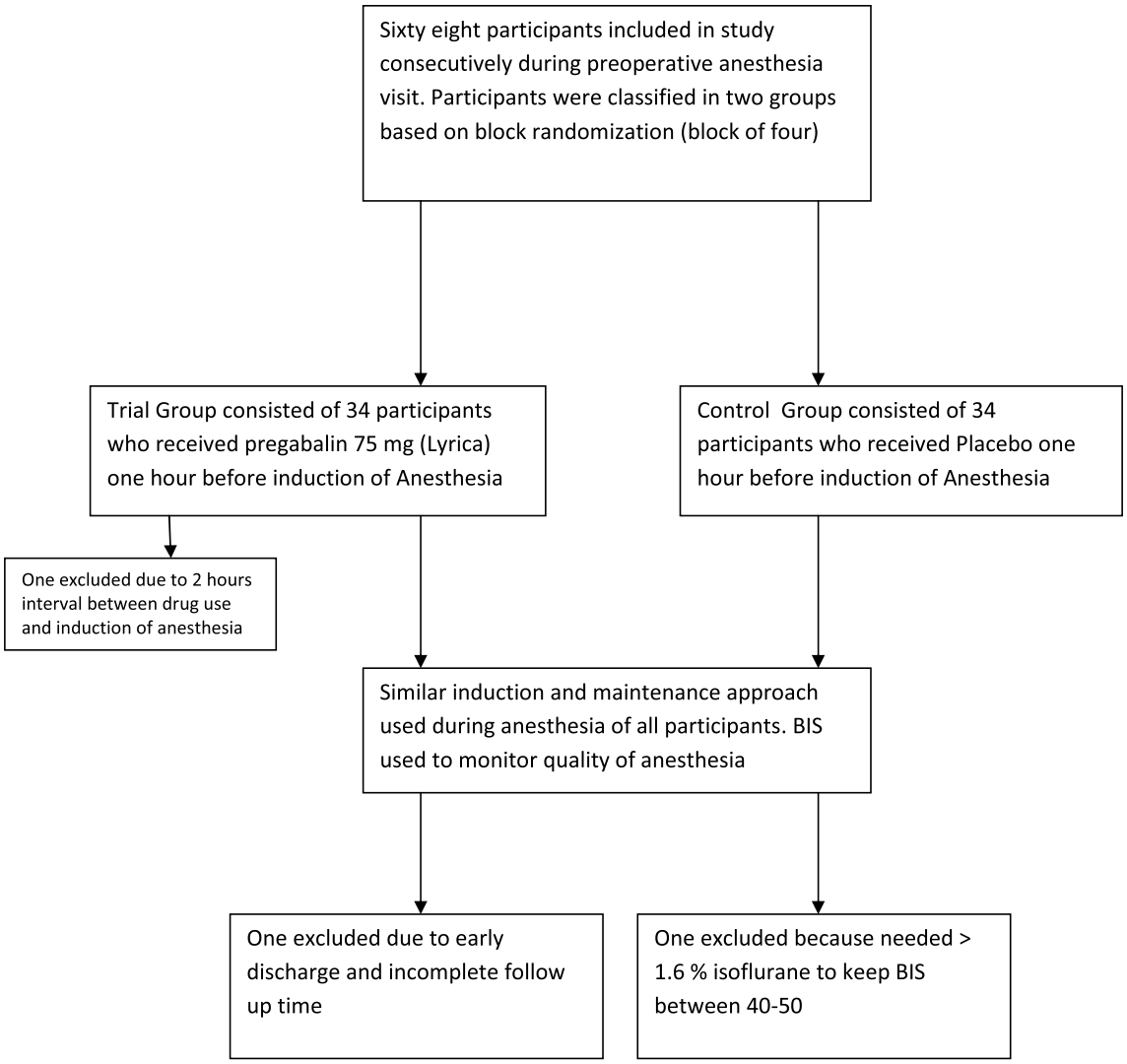

Fig. 1 Flowchart of the study progress

3/33 in CG; $p < 0.613$). In the PG, two patients complained of blurred vision in PACU during 1 h postoperatively. Dizziness during study observation was present in 4 patients of PG and 5 patients of CG, respectively (4/32 vs. 5/33) which was statistically non-significant (Table 1).

Discussion

Several studies evaluated the efficacy of pregabalin on postoperative pain control [5]. In different surgical procedures, effectiveness and side effects of pregabalin were distinctive [5]. Most studies prescribed 150–300 mg of pregabalin preoperatively which was continued for 48 h postoperatively [5, 16]. Pregabalin in doses of 150–300 mg resulted in more side effects, specifically sedation and blurred vision [5, 9, 17].

Based on our knowledge, the current study is the first one to evaluate the effect of pregabalin on sedation and agitation of patients using RSAS and RSS in the early post-extubation period and during post-anesthesia care unit. Patients in PG had lower RSAS scores in contrast to participants in CG. This may be due to better pain control or sedative effect of pregabalin. Being calm and not agitated might lead to easier extubation process. Pregabalin is used for generalized anxiety disorder, although the exact mechanism of effectiveness is not clear [18]. Pregabalin is comparable to benzodiazepines in clinical response [19]. In current study, reduced agitation and anxiety scores during extubation may be the result of anxiolytic effect of pregabalin. However, the efficacy of a single dose of pregabalin in controlling anxiety is not evaluated yet.

Sagit evaluated pregabalin in 75-mg and 150-mg doses. Sagit reported pain scores 57.2 ± 21.9 for intervention group

Table 1 Summarization of demographic data and measured variables in each group

Variable	Pregabalin 75-mg group	Placebo group	*p* value
Gender	F 27 M 5	F 27 M 6	0.783
Age (years old)	28.13 ± 4.80	27.64 ± 5.78	> 0.713
Weight (kg)	59.15 ± 5.78	60.78 ± 7.29	> 0.322
Anesthesia duration (minutes)	167.16 ± 48.76	184.45 ± 46.40	> 0.149
Time to extubation (minutes)	12.56 ± 3.05	10.85 ± 3.57	**< 0.05**
Mean fentanyl injected in PACU (μ)	3.75 ± 7.9	26.67 ± 15.54	**< 0.001**
Ibuprofen injected during 24 h postoperative (mg)	1012.5 ± 226.8	1284.8 ± 193.8	**< 0.001**
Nausea	5 of 32	13 of 33	**< 0.05**
Vomiting	1 of 32	3 of 33	> 0.613
NRS of pain at 10[a]	2.40 ± 1.62	5.39 ± 1.39	**< 0.001**
VAS of pain at 30[a]	2.30 ± 1.30	4.85 ± 1.17	**< 0.001**
VAS of pain at 60[a]	2.28 ± 0.92	4.27 ± 0.78	**< 0.001**
VAS of pain at 120[a]	2.11 ± 0.88	3.60 ± 0.61	**< 0.001**
VAS of pain 6 h	1.47 ± 0.62	2.76 ± 0.91	**< 0.001**
VAS of pain 24 h	0.84 ± 0.62	1.09 ± 0.92	> 0.214
RSS at extubation time	2.62 ± 0.83	1.48 ± 0.56	**< 0.001**
RSAS at extubation time	3.90 ± 0.92	5.33 ± 0.92	**< 0.001**
RSAS 10[a]	3.93 ± 0.43	4.42 ± 0.50	**< 0.001**
RSAS 30[a]	3.84 ± 0.44	2.72 ± 0.83	**< 0.001**
RSAS 60[a]	3.90 ± 0.29	3.36 ± 0.69	**< 0.001**
RSAS 120[a]	4.00 ± 0.0	3.93 ± 0.55	> 0.503

Bold indicates statisticallly significant differences between groups

μ microgram, *NRS* numeric rating score, *VAS* visual analog score, *RSS* Ramsay sedation score, *RSAS* Riker sedation agitation scale

[a]Minutes after extubation

and 66.6 ± 28.6 for control group [8]. In our study, the pain intensity is lower (Table 1) due to rescue fentanyl injection during PACU admission. Our study also shows the opioid sparing ability of pregabalin. In our study, pregabalin decreased total rescue fentanyl dose sevenfold. Although in contrast to their study, we had higher female–male ratio, and we observed similar efficacy of pregabalin in female.

Pain control using 75-mg single-dose pregabalin is as effective as 300-mg dose which is used in some studies [5]. Although pain was completely controlled when Demirhan used 300-mg pregabalin [9], frequent side effects such as blurred vision and dizziness were observed which are not acceptable in outpatient setting and for an ambulatory surgery. Also, addition of dexamethasone to pregabalin decreased pain scores more efficiently.

In a study by Demirhan, all patients received 50-mg tramadol intravenously and 75-mg diclofenac intramuscularly before extubation which probably masked pregabalin efficacy in early postoperative time [16]. To be able to clearly measure pregabalin effect, we did not give any analgesic before extubation; instead, we began rescue analgesia by administration of 10-μg fentanyl intravenously immediately post-extubation when rescue analgesia was necessary.

Postoperative pain scores reported by Kim are similar to our results [10]. It is in concordance with the result of a large meta-analysis which evaluated effects of pregabalin in different surgical categories. The meta-analysis reported that there is no difference between single dose preoperative pregabalin and regimens including additional doses during postoperative period [18].

Current study evaluated side effects, measured the pain intensity by VAS and evaluated pain intensity shortly after extubation. VAS is more precise than NRS when used to measure pain intensity [12, 13]. Because patients were unable to score VAS in the early post-extubation period, we used NRS to measure pain at 10 min post-extubation. However, we requested the participants to score pain on VAS after 30 min post-extubation. Not to mask pregabalin efficacy, we did not give analgesic before extubation. However, we immediately administered rescue analgesic for pain control at the request of patient.

Also, we completed VAS and RSAS in early PACU admission to precisely monitor changes in pain and alertness (four times within 120 min). We used BIS to deliver lowest required anesthetic to patients and to make sure that all patients received similar anesthesia. We

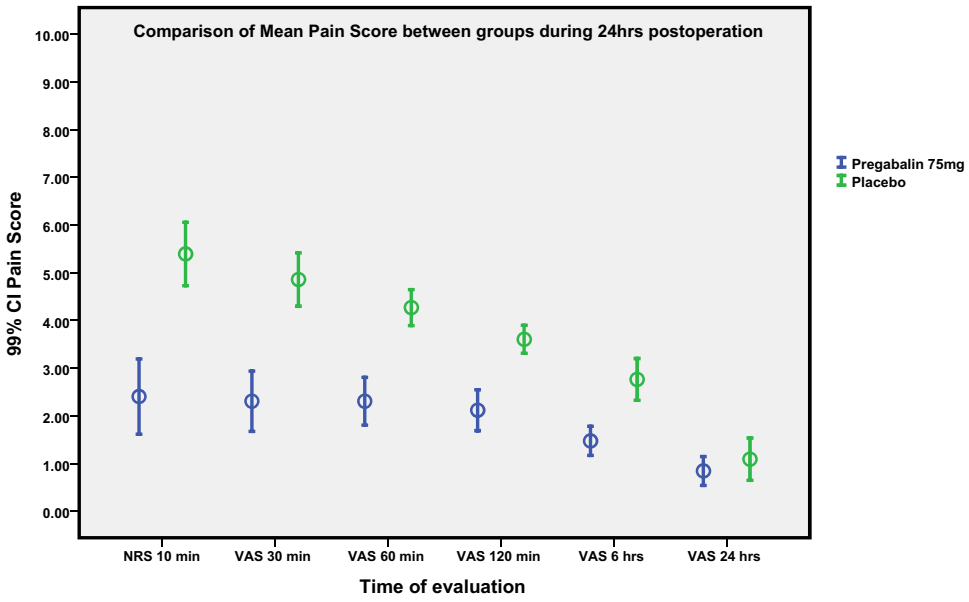

Fig. 2 Changes in pain score measured by NSR and VAS during 24-h postoperative period. *NSR* numeric rating score, *VAS* visual analog scale

administered remifentanil to avoid using any long-acting opioid during anesthesia, which might have interfered with pain assessment of patients postoperatively.

Figure 2 shows significantly different pain scores in patients who received pregabalin compared with patients receiving placebo up to 6 h post-extubation. Half-life of pregabalin is about 6.3 h [20, 21]. The average duration of operation was 2–3 h. In addition, it took 1 h between pregabalin intake and anesthesia induction. Thus, the total time between pregabalin intakes to the end of surgery was less than half-life of pregabalin (6.3 h). The efficacy of pregabalin will be reduced after 12 h (Fig. 2).

Limitations

One limitation of our study was not using patient-controlled analgesia pump. We did not have access to Patient-Controlled Analgesia (PCA) pump but we tried to solve this problem by administering frequent small doses of fentanyl during 2-h PACU admission. Use of PCA pump might have increased precision of opioid use measurement for pain control. However, PCA pump is not used for pain management in ambulatory surgery. Another limitation is the long duration between fourth and last pain measurement. Since most surgeries ended in the afternoon, if we were to measure pain between 6 and 24 h postoperatively, we should have to interrupt patients' sleep which was not ethical.

Conclusion

Efficacy of single dose of 75-mg pregabalin in postoperative pain control in septorhinoplasty procedure is similar to multiple-dose regimen and high-dose regimens in early postoperative period, while having lower side effects such as blurred vision or dizziness. In addition, pregabalin improved safety and comfort of patients during extubation and transfer from operating bed to recovery. In contrast to high doses used in some studies, we recommend use of single low-dose regimen in cases of septorhinoplasty ambulatory surgery.

Acknowledgements Authors would like to thank research development Center of Sina Hospital for their kind support.

Compliance with ethical standards

Conflict of interest No conflict exists: Pejman Pourfakhr declares that he has no conflict of interest. Mohamadreza Khajavi declares that he has no conflict of interest. Ali Jalali declares that he has no conflict of interest. Faramarz Memari declares that he has no conflict of interest. Farhad Etezadi declares that he has no conflict of interest. Mehrnoush Momeni Roochi declares that she has no conflict of interest. Reza Shariat Moharrari declares that he has no conflict of interest. Atabak Najafi declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. de Leon-Casasola OA (1996) New concepts in postoperative pain management: is there more beyond pain control? J Fla Med Assoc 83(10):695–700
2. Vanderah TW, Suenaga NM, Ossipov MH, Malan TPJ, Lai J, Porreca F (2001) Tonic descending facilitation from the rostral ventromedial medulla mediates opioid-induced abnormal pain and antinociceptive tolerance. J Neurosci 21(1):279–286
3. Szychta P, Antoszewski B (2010) Assessment of early postoperative pain following septorhinoplasty. J Laryngol Otol 124(11):1194–1199. https://doi.org/10.1017/S0022215110001519
4. Wittekindt D, Wittekindt C, Schneider G, Meissner W, Guntinas-Lichius O (2012) Postoperative pain assessment after septorhinoplasty. Eur Arch Otorhinolaryngol 269(6):1613–1621. https://doi.org/10.1007/s00405-011-1854-x
5. Lam DMH, Choi S-W, Wong SSC, Irwin MG, Cheung C-W (2015) Efficacy of pregabalin in acute postoperative pain under different surgical categories: a meta-analysis. Medicine (Baltimore) 94(46):e1944. https://doi.org/10.1097/MD.0000000000001944
6. Kehlet H, Dahl JB (1993) The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg 77(5):1048–1056
7. Turan A, Memis D, Karamanlioglu B, Yagiz R, Pamukcu Z, Yavuz E (2004) The analgesic effects of gabapentin in monitored anesthesia care for ear–nose–throat surgery. Anesth Analg 99(2):375–378. https://doi.org/10.1213/01.ANE.0000136646.11737.7B
8. 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. https://doi.org/10.1097/SCS.0b013e31827fece5
9. Demirhan A, Akkaya A, Tekelioglu UY et al (2014) Effect of pregabalin and dexamethasone on postoperative analgesia after septoplasty. Pain Res Treat. https://doi.org/10.1155/2014/850794
10. Kim JH, Seo MY, Hong SD et al (2014) The efficacy of preemptive analgesia with pregabalin in septoplasty. Clin Exp Otorhinolaryngol 7(2):102–105. https://doi.org/10.3342/ceo.2014.7.2.102
11. 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. https://doi.org/10.1002/lary.25951
12. Akad K, Solmaz D, Sari I, Onen F, Akkoc N, Akar S (2013) Performance of response scales of activity and functional measures of ankylosing spondylitis: numerical rating scale versus visual analog scale. Rheumatol Int 10:2617–2623. https://doi.org/10.1007/s00296-013-2789-x
13. Myrvik MP, Drendel AL, Brandow AM, Yan K, Hoffmann RG, Panepinto JA (2015) A comparison of pain assessment measures in pediatric sickle cell disease: visual analog scale versus numeric rating scale. J Pediatr Hematol Oncol 37(3):190–194. https://doi.org/10.1097/MPH.0000000000000306
14. Ahlers SJGM, van Gulik L, van der Veen AM et al (2008) Comparison of different pain scoring systems in critically ill patients in a general ICU. Crit Care 12(1):R15. https://doi.org/10.1186/cc6789
15. Brown EN, Lydic R, Schiff ND (2010) General anesthesia, sleep, and coma. N Engl J Med 363(27):2638–2650. https://doi.org/10.1056/NEJMra0808281
16. Demirhan A, Tekelioglu UY, Akkaya A et al (2013) Effect of pregabalin and dexamethasone addition to multimodal analgesia on postoperative analgesia following rhinoplasty surgery. Aesthet Plast Surg 37(6):1100–1106. https://doi.org/10.1007/s00266-013-0207-0 **(Epub 2013 Sep 21)**
17. White PF, Tufanogullari B, Taylor J, Klein K (2009) The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. Anesth Analg 108(4):1140–1145. https://doi.org/10.1213/ane.0b013e31818d40ce
18. Lauria-Horner BA, Pohl RB (2003) Pregabalin: a new anxiolytic. Expert Opin Investig Drugs 12(4):663–672
19. Generoso MB, Trevizol AP, Kasper S, Cho HJ (2017) Pregabalin for generalized anxiety disorder: an updated systematic review and meta-analysis. Int Clin Psychopharmacol 32(1):49–55
20. Ben-Menachem E (2004) Pregabalin pharmacology and its relevance to clinical practice. Epilepsia 45(Suppl 6):13–18. https://doi.org/10.1111/j.0013-9580.2004.455003.x
21. Bockbrader HN, Radulovic LL, Posvar EL et al (2010) Clinical pharmacokinetics of pregabalin in healthy volunteers. J Clin Pharmacol 50(8):941–950. https://doi.org/10.1177/0091270009352087