

## ORIGINAL RESEARCH

# Comparison of pregabalin with magnesium sulfate in the prevention of remifentanyl-induced hyperalgesia in patients undergoing rhinoplasty: A randomized clinical trial

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**Abstract**

**Objective:** Remifentanyl is usually used for controlled hypotension during rhinoplasty under general anesthesia (G/A). One of the complications of the remifentanyl is postoperative hyperalgesia. In this study, we compare the effectiveness of pregabalin with that of Mg sulfate in postoperative remifentanyl-induced hyperalgesia prevention.

**Methods:** In this prospective, randomized, double-blinded placebo-controlled trial, 105 patients who candidates rhinoplasty with G/A were enrolled and randomly allocated into three groups. Patients in group A received 300 mg pregabalin before anesthesia. They received physiologic saline infusion during the perioperative period. Those in group B received placebo capsules before anesthesia and intravenous Mg sulfate 30 mg/kg during the perioperative period. Those in group C received a placebo capsule before anesthesia and normal intravenous saline during the operation. Then, pain severity, sedation score, postoperative nausea and vomiting (PONV) were assessed and compared.

**Results:** In the Mg sulfate and placebo group, the mean numerical rating scale in the postoperative period was higher compared to the pregabalin group ( $p < .001$ ). The mean total amount of morphine requirement, meanwhile the 24 h post-operation, was significantly decreased in the pregabalin group compared to the other groups ( $p < .001$ ). Participants in the pregabalin group had less PONV compared to those in the pregabalin and placebo groups ( $p = .015$ ).

**Conclusions:** In patients undergoing G/A with remifentanyl for rhinoplasty, preoperative 300 mg pregabalin could effectively prevent not only remifentanyl-induced hyperalgesia but also PONV.

**Level of evidence:** 1b.

**KEYWORDS**

magnesium sulfate, pregabalin, remifentanyl, rhinoplasty

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## 1 | INTRODUCTION

Controlled hypotension is one of the anesthetic strategies in the perioperative period of rhinoplasty used to decrease intraoperative bleeding and surgical difficulties.<sup>1</sup> Currently, several drugs have been experimented with by anesthesiologists to provide a bloodless field during rhinoplasty surgery.<sup>2</sup> One of these drugs is remifentanyl, which is usually used in the perioperative period to reach an acceptable surgical field during rhinoplasty.<sup>3</sup> However, one of the complications of remifentanyl infusion is postoperative hyperalgesia, which makes postoperative pain more difficult to control than usual.<sup>4</sup>

Remifentanyl, as an ultra short-acting opioid, is usually used as a general anesthesia (G/A) supplement during surgery.<sup>5</sup> However, several clinical studies have suggested that remifentanyl infusion in the perioperative period may cause postoperative nociceptive sensitization. This postoperative hyperalgesia may be due to central and peripheral sensitization mechanisms. For peripheral sensitization, events, such as what happens during neuropathic pain, maybe implicated, and for central sensitization, the theory of N-methyl-D-aspartate (NMDA) receptor activation has been proposed.<sup>6-8</sup> Thus, drugs that are usually used to treat neuropathic pain, such as pregabalin, may prevent remifentanyl-induced sensitization and hyperalgesia when administered preemptively.<sup>9</sup> Some clinical studies showed that magnesium sulfate as an NMDA receptor blocker might prevent remifentanyl-induced hyperalgesia.<sup>10,11</sup>

To date, no clinical study has compared the effectiveness of Mg sulfate with that of pregabalin in remifentanyl-induced hyperalgesia prevention. Hence, the present study was designed to find whether pregabalin or Mg sulfate can effectively prevent postoperative remifentanyl-induced hyperalgesia with the least complications.

## 2 | MATERIALS AND METHODS

This randomized, double-blind, parallel clinical trial was approved by the Shiraz Medical School Research Ethics Committee (code: Ir.sums.med.rec.1396.122) and was registered in Iranian IRCT20121204011662N12. This research has been conducted in accordance with all of the ethical standards required by the Declaration of Helsinki issued in 2013. The study's protocol was explained to eligible participants, and written informed consent was obtained from them.

One hundred and five adult male and female patients aged 20–40 years who were scheduled for elective rhinoplasty were enrolled in this study. Patients with a history of heart disease, pulmonary disease, liver disease, kidney disease, allergy to study's drugs (pregabalin, Mg sulfate, remifentanyl, and propofol), alcohol and opioid use, and chronic pain and pain killer use 72 h before anesthesia were excluded from the study. Eligible patients were randomized via simple randomization and classified into three groups, namely, A, B, and C by a resident of anesthesia who did not have any role in this study.

In the operating theater, patients laid down on the operating table and, after the attachment of standard monitors (EKG, noninvasive blood pressures monitor, and pulse oximetry), an angiocatheter

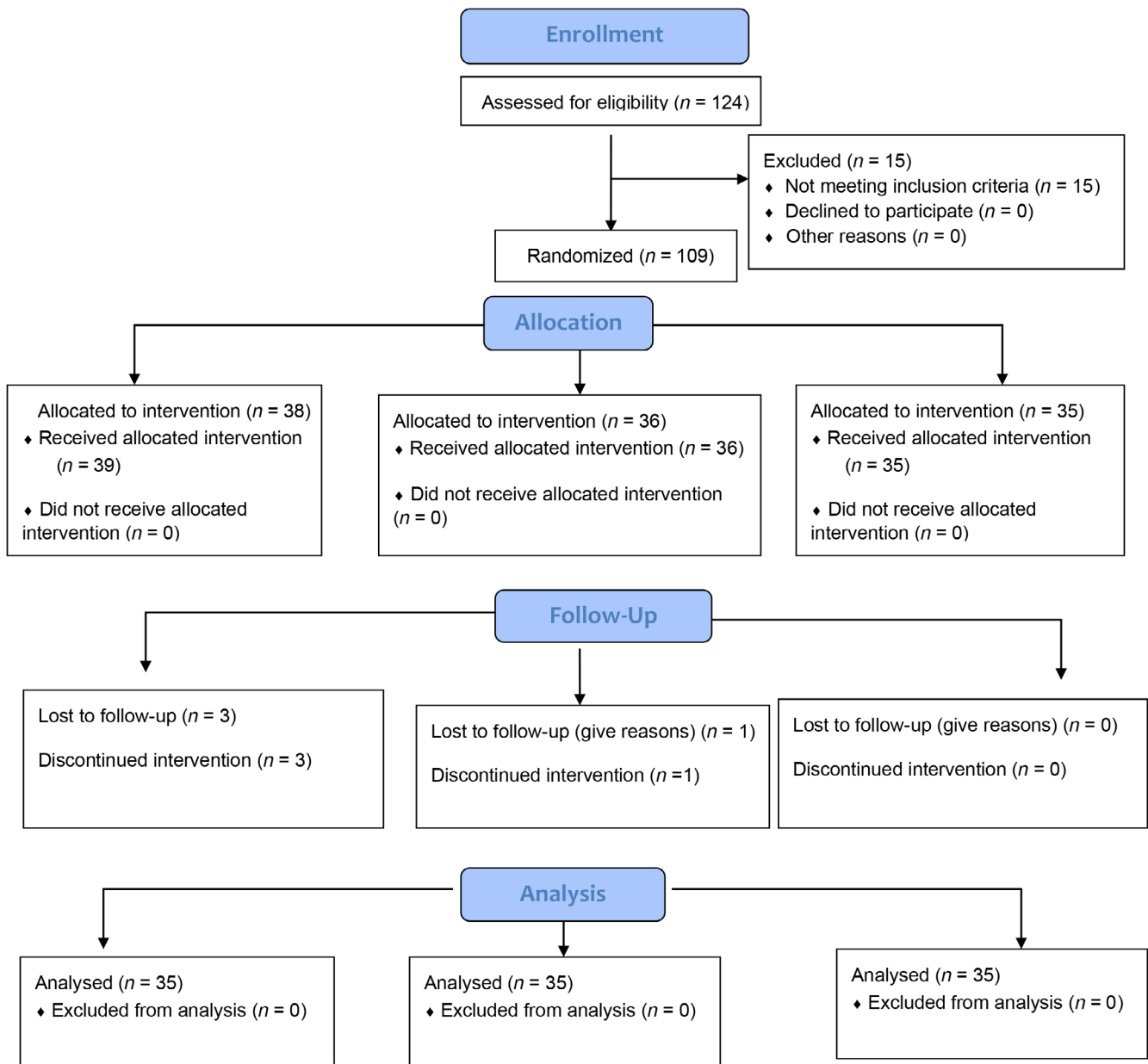
No. 18 was inserted in a suitable vein. The induction of anesthesia with midazolam 0.05 mg/kg, fentanyl 4 mcg/kg, propofol 2 mg/kg, and atracurium 0.6 mg/kg was administered through angiocatheter. Then tracheal intubation was performed with a suitable size tracheal tube. We used isoflurane in a mixture of O<sub>2</sub>/N<sub>2</sub>O (50%/50%) and remifentanyl (0.3 mic/kg/min) to maintain anesthesia with controlled ventilation. Then, patients in group A received physiologic saline through a 50 ml syringe with label A. Those in group B received intravenous Mg sulfate 30 mg/kg through a 50 ml syringe with label B. Those in group C received physiologic saline through a 50 ml syringe with label C during the perioperative period up to the end of anesthesia. We did not use any facial nerve block for patients in the three groups. At the end of anesthesia, when the patient has an adequate train of forth, the muscle relaxant is reversed, and tracheal extubation was done when the patient was completely awake and responded to command. Then, we transferred the patient to the recovery room.

Patients in group A received 300 mg pregabalin before anesthesia. During the perioperative period, they received physiologic saline, instead of Mg sulfate infusion, through a 50 ml syringe with label A, up to the end of anesthesia. Patients in group B received two placebo capsules with shape, size, and color similar to those of pregabalin capsule 150 mg. During the perioperative period, they received intravenous Mg sulfate 30 mg/kg through a 50 ml syringe with label B. Patients in group C received two placebo capsules that were similar to pregabalin capsule 150 mg in terms of shape, size, and color. During the perioperative period, they received intravenous physiologic saline through a 50 ml syringe with label C. These syringes and capsules were prepared by a nurse anesthetist who was not participating in the study. The patients and the research assessor were not aware of the contents of either the syringe or the capsules.

The primary outcome of this study was the intensity of postoperative pain that was assessed using the numeric rating scale (NRS), in which zero score represents no pain and 10 represents the most severe pain. If the NRS was >7, we injected 2-mg intravenous morphine for patients every 5 min. If patients had NRS more than four but less than seven, we injected 1-mg intravenous morphine every 5 min up to the time the NRS became <4.

The secondary outcomes were postoperative sedation score and postoperative nausea and vomiting (PONV). The sedation score was assessed using the Ramsay score<sup>12</sup> when patients arrived in the recovery room, and every 15 min was recorded. Ramsay scores are: zero score represents Restlessly, score one represents Calm, score two represents Sleepy, score three represents Drowsy with response to verbal stimuli, Score four represents Drowsy without response to verbal stimuli, and score five represent no response to painful stimuli. The incidence of PONV was evaluated by asking the patients to grade their nausea and vomiting according to the three-point scale<sup>13</sup>: score 0 = no nausea vomiting, score one means nausea only, and score two means retching or/and vomiting.

We used the postoperative pain intensity, which is the primary outcome and measured it by NRS to estimate the sample size. We assumed a two-point decrease in the NRS is a clinical amelioration in



**FIGURE 1** Flowchart of the patients according to the consort guideline

acute pain management following rhinoplasty. Accordingly, we considered preceding research,<sup>14</sup> and 35 patients per group were estimated as a sample size to find a two-score statistical difference in the post-surgical NRS between groups with a standard deviation of two scores to reach a power of 80% and a level of 5%. Furthermore, we considered 10% of participants who will not be allocated to intervention, finally, altogether 109 patients were enrolled for the study.

## 2.1 | Statistical analysis

At first, we used the Shapiro–Wilk test to detect the normal distribution of the data. Then we compared the categorical data with the

chi-square test and Fisher exact test. Furthermore, we compared the normally distributed numerical variable by the Kruskal Wallis test. We compared the variance among the groups by the Levene test and the variables' changes during the study time by repeated analysis. At the end of the survey, we transferred the data into the datasheet of the SPSS for Windows; we used SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) for statistical analysis.

## 3 | RESULTS

A total of 124 patients were candidates for rhinoplasty under G/A from March 2018 to September 2018; among them, eight patients

were excluded because of the use of pain killers in the last 72 h; two patients, because of the history of chronic pain, and five patients, because of alcohol use; therefore, we recruited a total of 109 patients for this clinical research, and then they assigned into three groups at random. However, three uncooperative patients in group A and one uncooperative patient in group B left the study. Finally, 105 patients completed the study course (Figure 1).

There were no significant differences regarding demographic data between the groups ( $p > .05$ ; Table 1).

Table 2 shows the pain intensity of the patients; the mean NRS in the Mg sulfate and placebo group were significantly higher compared to the pregabalin group meanwhile the 1st-h post-surgery ( $p < .001$ ). Figure 2 shows the mean NRS in the 2nd-h to 24 h post-surgery was significantly higher in the Mg sulfate and placebo groups compared to the pregabalin group ( $p < .001$ ).

Table 3 shows the mean morphine requirement during the 1st-h post-surgery and from the 2nd-h till 24 h post-surgery, which was significantly higher in the Mg sulfate and placebo groups compared to the pregabalin group ( $p < .001$ ) during the 1st-h post-surgery. Moreover, pairwise comparisons revealed that total morphine requirement meanwhile 24 h post-surgery was significantly higher in the placebo group compared to the Mg sulfate group and in the Mg sulfate group was significantly higher compared to the pregabalin group ( $p = .001$ ).

Furthermore, Figure 3 shows the mean morphine requirement during the 2nd-h to 24 h post-surgery was significantly higher in the Mg sulfate and placebo groups compared to the pregabalin group ( $p < .001$ ).

Table 4 shows that participants in the pregabalin group were more cooperative and calm and less drowsy than those in the Mg sulfate and placebo groups ( $p < .001$ ), and those in the placebo group

**TABLE 1** Demographic data of three study groups

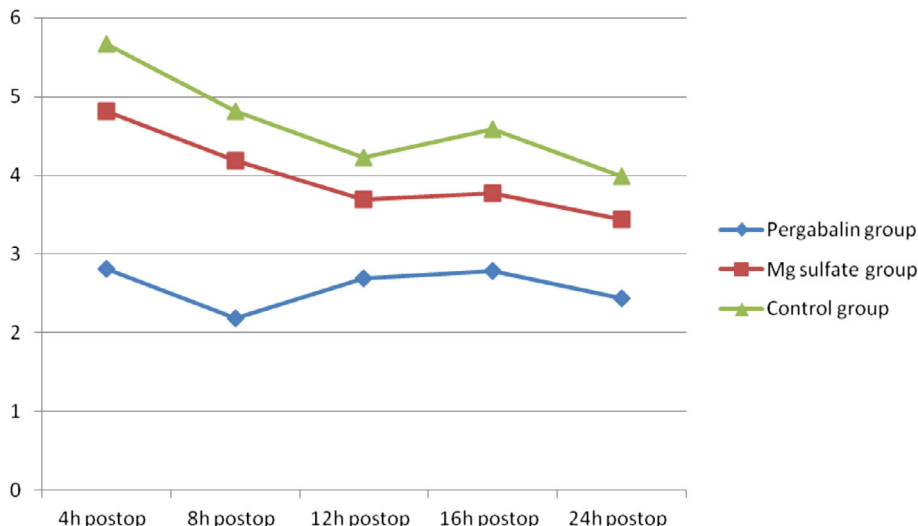
	Pregabalin group (N = 35)	Mg sulfate group (N = 35)	Control group (N = 35)	p-Value
Age (year)	28.12 ± 6.57	29.31 ± 7.94	25.47 ± 4.81	.071
Sex (M/F)	4/31	8/27	12/23	.075
Operation time (min)	176.15 ± 5.28	180.23 ± 4.78	175.98 ± 6.89	.084

Note: All data in mean ± standard deviation.

**TABLE 2** Postoperative pain intensity between three study groups at the 1st-h post-operation

	Pregabalin group (N = 35)	Mg sulfate group (N = 35)	Control group (N = 35)	p-Value
NRS at 0 min	1.00 ± 1.70	6.20 ± 3.10	8.50 ± 3.22	.001
NRS at 15 min	0.40 ± 1.00	5.56 ± 2.13	6.13 ± 2.89	.001
NRS at 30 min	0.28 ± 0.82	5.12 ± 2.1	6.89 ± 3.01	.001
NRS at 45 min	0.20 ± 0.67	4.00 ± 3.1	5.01 ± 1.67	.001
NRS at 60 min	0.17 ± 0.62	4.32 ± 1.78	5.99 ± 2.56	.001

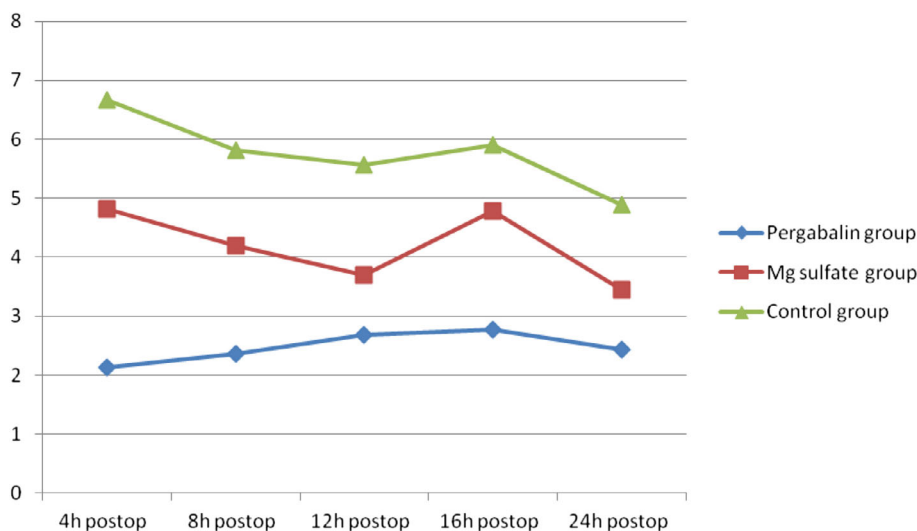
Note: All data in mean ± standard deviation.  
Abbreviation: NRS, numerical rating scale.



**FIGURE 2** Postoperative pain intensity between three study groups after the 1st-h up to 24 h post-operation

**TABLE 3** Mean morphine (mg) consumption during 1st-h post-surgery and from 2nd-h till 24-h post-surgery between three study groups

	Pregabalin group (N = 35)	Mg sulfate group (N = 35)	Control group (N = 35)	p-Value
Morphine consumption at 1st-h post-surgery	2.48 ± 0.78 mg	8.45 ± 1.09 mg	13.05 ± 2.41 mg	.001
Morphine Consumption from 2nd-h till 24-h post-surgery	2.16 ± 0.45 mg	4.05 ± 1.01 mg	6.19 ± 1.45 mg	.001

**FIGURE 3** Postoperative morphine consumption between three study groups from 2nd-h up to 24 h post-operation**TABLE 4** Post-surgery sedation scores among patients of three groups

Ramsay sedation scale	Group A (n = 35)	Group B (n = 35)	Group C (n = 35)	p-Value
Patient was anxious and agitated	1 (2.85%)	5 (n = 14.28%)	16 (n = 45.71%)	.001
Patient cooperative oriented and tranquil	25 (71.42%)	15 (n = 42.85%)	6 (n = 17.14%)	.001
Patient responding to commands only	9 (25.71%)	10 (n = 28.57%)	5 (n = 14.28%)	.001
Patient responding briskly to a light glabellar tap or to verbal stimulus	0 (0.00%)	1 (n = 2.85%)	5 (n = 14.28%)	.001
patient responding sluggishly to a light glabellar tap to verbal stimulus	0 (0.00%)	4 (n = 11.42%)	3 (n = 8.57%)	.001
No response to stimulus	0 (0.00%)	0 (n = 0.00%)	0 (0.00%)	.001

Note: Data presented as n (%), group A: pregabalin group, group B: Mg sulfate group, and group C: placebo group.

were more restless than those in the Mg sulfate and pregabalin groups ( $p < .001$ ).

Furthermore, the incidence of the PONV is 33.30% in the placebo group, 22.20% in the Mg sulfate group, and 0.00% in the pregabalin group during different times of the study. Therefore, there were significant differences between the three groups regarding PONV ( $p = .015$ ).

## 4 | DISCUSSION

The findings of this randomized clinical trial have shown that in patients who were undergoing G/A with remifentanyl for rhinoplasty, 300 mg pregabalin preoperatively is more effective than intraoperative Mg sulfate infusion in preventing remifentanyl-induced hyperalgesia following rhinoplasty.

Controlled hypotension is usually used to reduce bleeding and to make a bloodless operative field during septorhinoplasty.<sup>3</sup> Today, remifentanyl is part of G/A used to induce hypotension during rhinoplasty. However, several studies in the literature have shown that remifentanyl could induce postoperative hyperalgesia through peripheral and central nociceptive sensitization.<sup>15</sup> Many drugs such as NMDA-receptor blocker drugs and gabapentinoids were used to attenuate the nociceptive sensitization of the remifentanyl.<sup>16,17</sup>

Gabapentinoids, including gabapentin and pregabalin, have been used to prevent or attenuate remifentanyl-induced hyperalgesia. Both drugs have the same mechanism they bind to the  $\alpha_2\delta_1$  subunit of voltage-gated calcium channels and inhibiting channel function finally inhibit the release of neurotransmitters that induce nociceptive sensitization such as glutamate, substance P, and serotonin.<sup>18,19</sup> Lee et al. showed that in patients undergoing laparoscopic urologic surgery,

300 mg pregabalin as a single preoperative dose could prevent remifentanyl-induced hyperalgesia.<sup>14</sup> In another study by Jo HR et al., 150 mg pregabalin as a single dose could prevent remifentanyl-induced nociceptive sensitization in patients undergoing total abdominal hysterectomy.<sup>16</sup> In our study, we found the same result, that is, 300 mg pregabalin as a single dose preoperatively could prevent remifentanyl-induced hyperalgesia in patients undergoing septorhinoplasty.

Mg sulfate is another drug that is used to prevent postoperative remifentanyl-induced hyperalgesia, as shown in a clinical study.<sup>20</sup> Mg sulfate blocks ion channels associated with NMDA receptor, and through this mechanism, Mg sulfate could prevent remifentanyl-induced hyperalgesia.<sup>21</sup> Song JW et al. showed that intraoperative Mg sulfate infusion could effectively prevent remifentanyl-induced hyperalgesia.<sup>11</sup> However, Liu Y et al., through a meta-analysis study that included 14 randomized clinical trials, showed that NMDA receptor blocker drugs such as Mg sulfate and ketamine could not prevent remifentanyl-induced hyperalgesia.<sup>22</sup> In our study, intraoperative Mg sulfate in comparison with pregabalin could not prevent postoperative remifentanyl-induced hyperalgesia and tolerance.

According to our study, pregabalin is more effective than Mg sulfate in preventing remifentanyl-induced hyperalgesia. Furthermore, pregabalin is safer than Mg sulfate. Intraoperative Mg sulfate infusion may result in bradycardia, cardiac rhythm disturbance, and myocardial depression and may also potentiate neuromuscular blockage especially at the end of anesthesia. Fortunately, the risk of these adverse effects increases as the dosage of Mg sulfate increases, for example, the dosage usually used in preeclampsia.<sup>23</sup> However, pregabalin is a new antiepileptic drug from the gabapentinoid family, which is effective in preventing different kinds of pain such as neuropathic, incisional, and inflammatory pain, and is safer than gabapentin.<sup>24</sup> Pregabalin also has an anxiolytic effect<sup>25</sup> and provides hemodynamic stability.<sup>26</sup>

Moreover, during the first 24 h after rhinoplasty, besides postoperative pain, PONV usually causes patient discomfort in the treatment.<sup>24</sup> Grant et al., in their meta-analysis study, found that preoperative pregabalin causes a significant reduction of PONV.<sup>27</sup> In our study, 300 mg pregabalin preoperatively is more effective in reducing PONV when compared with Mg sulfate.

This study has some limitations, first of all we should use patient controlled analgesia pump to estimate the exact postoperative morphine consumption and the second is that it was better to follow patients regarding the incidence of chronic pain in patients of three groups.

## 5 | CONCLUSIONS

In patients who are undergoing G/A with remifentanyl for rhinoplasty, preoperative 300 mg pregabalin, as a part of a multimodal approach to pain management, could effectively prevent not only remifentanyl-induced hyperalgesia but also PONV.

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## CONFLICT OF INTEREST

Authors have nothing to disclose.

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