Original Article

The effect of pre-emptive gabapentin on anaesthetic and analgesic requirements in patients undergoing rhinoplasty: A prospective randomised study

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ABSTRACT

Background and Aims: Hypotensive anaesthesia is necessary in rhinoplasty for better visualisation of surgical field and reduction of surgery time. Gabapentin is a new generation anticonvulsant with anti-hyperalgesic and anti-nociceptive properties. We aimed to investigate the effect of pre-operative administration of oral gabapentin (1200 mg) on anaesthetic requirements and post-operative analgesic consumption and its role in hypotensive anaesthesia for rhinoplasty. **Methods:** Seventy adult patients undergoing rhinoplasty, were randomly allocated to two groups. Group I (G I) (n = 35) received gabapentin 1.2 g and Group II (G II) (n = 35) received oral placebo capsules 2 h before surgery. General anaesthesia was maintained with sevoflurane in oxygen-nitrous oxide to maintain bispectral index value between 40 and 60, and remifentanil infusion to keep mean arterial pressure (MAP) at 55–60 mmHg. End-tidal sevoflurane concentration, intra-operative remifentanil consumption and time to intended MAP were recorded. Visual analogue scale (VAS) scores, post-operative analgesic requirements and side effects for the first 24 h were recorded. **Results:** G I required significantly lower intra-operative remifentanil (G I = 0.8 ± 0.26 mg and G II = 1.7 ± 0.42 mg; P = 0.001) and end-tidal sevoflurane concentration, with reduced doses of post-operative tramadol and diclofenac sodium. Time to the intended MAP was significantly less in G I than G II (59.1 ± 12.3 vs. 73.6 ± 16.4, respectively, with P = 0.001). **Conclusion:** Pre-operative oral gabapentin significantly reduced intra-operative remifentanil and sevoflurane requirements during hypotensive anaesthesia along with decreased post-operative analgesic requirement.

Key words: Anaesthetic, analgesic, gabapentin, hypotension, rhinoplasty

INTRODUCTION

Hypotensive anaesthesia provides a clear satisfactory view for the surgeon and decreases surgery time in the head-and-neck surgeries. Different pharmacological agents either alone or in combination can be used to induce intra-operative hypotension.[1] Sufentanil and remifentanil provide bloodless field, especially with a high dose of benzodiazepine by augmenting its effect in lowering blood pressure.[2]

Acute post-operative pain management is a challenging clinical problem and if inadequate, may result in increased morbidity, mortality and affect patient's quality of life.[3] However, opioids have several side effects such as respiratory depression, bradycardia, hypotension, nausea and vomiting which raise the need for efficient multimodal analgesic techniques to minimise opioid consumption postoperatively.[4]

Gabapentin is an anticonvulsant that has anti-hyperalgesic and anti-nociceptive properties. It can modulate the peripheral and central response to pain. Gabapentin acts at the level of the spinal cord and dorsal root ganglia.[5] It also inhibits the

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response of C-fibres to painful stimuli by modulating voltage-gated calcium channels and blocking α-amino methyl propionic acid and N-methyl D-aspartate receptors.[6]

In the present study, we hypothesised that the analgesic efficacy of gabapentin would reduce anaesthetic and analgesic requirements and augment deliberate hypotension. Hence, we aimed to investigate the effect of pre-operative administration of oral gabapentin (1200 mg) on anaesthetic requirements and post-operative analgesic consumption and its role in intra-operative hypotension required for rhinoplasty patients.

METHODS

This randomised controlled double-blind trial was conducted in the period between February and September 2017 after ethical committee approval and written informed consent. Seventy patients of age between 18 and 45 years, American Society of Anaesthesiologists (ASA) physical grade I or II, and posted for rhinoplasty were included in this study.

We excluded patients with bleeding disorders, coronary heart diseases, severe renal or hepatic dysfunction, hypertension, known allergy to any of the study drugs and those who refused to give consent for the study.

Patients were randomly allocated using computer-generated numbers into two groups: Group I (G I, the study group) included 35 patients who received oral gabapentin 1.2 g (Pfizer, Neurontine, Gabapentin 400 mg) and Group II (G II, control group) included 35 patients who received oral placebo in the form of identical capsules containing cornstarch 2 h before surgery.

The randomisation was performed by an independent statistician by random allocation software; QuickCalcs (GraphPad Software Inc., La Jolla, CA, USA). Allocation concealment was done by sequentially numbered sealed opaque envelopes. After the written consent was signed, the sealed opaque envelope was opened, and the patient was enrolled in the respective group. All treating staff and outcome assessors were blinded to the treatment groups.

All patients fasted for 8 h before surgery. Baseline heart rate (HR) and mean arterial pressure (MAP) were recorded. In the pre-operative area, all patients received midazolam 0.05 mg/kg intravenous (IV) 30 min before surgery, and an intra-arterial catheter was inserted into the radial artery under local anaesthesia. In the operating room, five lead electrocardiogram, invasive blood pressure monitoring, pulse oximetry, neuromuscular monitoring and bispectral index (BIS) sensor (Aspect Medical System, Norwood, MA) were attached to the patient before induction of anaesthesia.

General anaesthesia was induced in all the patients with propofol 2–3 mg/kg IV, cisatracurium 0.15 mg/kg IV and remifentanil 1 μg/kg IV. The trachea was intubated and lungs ventilated to maintain the end-tidal CO_2 between 32 and 35 mmHg. Anaesthesia was maintained by titrating inhaled sevoflurane from 1.5% to 2.5% and 70% nitrous oxide in oxygen with continuous monitoring of end-tidal sevoflurane concentrations and documentation at 5 min (T_1), 15 min (T_2), 30 min (T_3), 45 min (T4) and 60 min (T_5) after skin incision and at the end of surgery (T_6).

Inspired sevoflurane concentration was adjusted aiming to maintain the BIS level between 40 and 60 and if the MAP was more than 60 mmHg, remifentanil infusion started at 0.25 μg/kg/min and titrated by increasing the dose up to 2 μg/kg/min guided by the MAP (55–60 mmHg). Total intra-operative remifentanil used was calculated. Neuromuscular function was monitored, and 0.02 mg/kg IV cisatracurium bolus was given when one twitch appeared on the train of four (TOF).

At the end of the surgery, tramadol 0.5 mg/kg IV, neostigmine 0.04 mg/kg IV and atropine 0.01 mg/kg IV were given. The trachea was extubated when the patient became conscious, and breathing adequately, with BIS level ≥85 and TOF ratio >90%. The patient was transferred to post-anaesthesia care unit (PACU) and monitored for HR, MAP and oxygen saturation. Pain severity was assessed using visual analogue scale (VAS) (from 0 to 10 while 0 = no pain and 10 = the worst intolerable pain) on arrival to PACU (H0) and then at 1 h (H1), 2 h (H2), 8 h (H3), 16 h (H4) and 24 h (H5) (the study period = 24 h). If VAS scores were at any time more than 4, tramadol 1 mg/kg IV was given as rescue analgesia. However, if VAS scores were ≤4, only intramuscular diclofenac sodium 1 mg/kg was given and time to first analgesic dose was recorded. Patients were monitored for post-operative nausea and vomiting (PONV), persistent nausea for more than 5 min or an episode of vomiting was treated with ondansetron 4 mg IV. Time needed to reach the targeted MAP, estimated intra-operative blood loss, and also total post-operative analgesic consumption were recorded.

The primary outcome was to evaluate the effect of pre-operative administration of oral gabapentin (1200 mg) on anaesthetic requirements including end-tidal sevoflurane concentration and total intra-operative remifentanil required for hypotensive anaesthesia in rhinoplasty patients, and the secondary outcomes were to observe time to achieve the intended MAP and to detect post-operative analgesic requirements.

Based on similar studies,[6,7] a sample size of 35 patients in each group was required to achieve a power of 80% with $\alpha = 0.05$ to detect a difference in intra-operative anaesthetic requirements using effect size of 0.7. The Shapiro–Wilk test was used for testing normal distribution of all data. Data were analysed using SPSS software version 20 (SPSS Inc., Chicago, IL, USA). Quantitative data (total intra-operative remifentanil, end-tidal sevoflurane concentration, total post-operative tramadol and diclofenac, time to first analgesic request, time to intended MAP, estimated blood loss etc.) were expressed as the mean ± standard deviation (SD) and qualitative data (sex, ASA grade) were expressed as a frequency. Independent *t*-test was used for comparison of quantitative data between the two groups and Chi-square test was used for comparison of categorical data (sex, ASA grade) between both groups. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Demographic profile was comparable in both groups [Table 1]. Duration of surgery and anaesthesia, pre-operative HR and MAP were also comparable between the groups [Table 2]. End-tidal sevoflurane concentrations were significantly lower in G I than G II at all times of measurements [Figure 1]. Patients In G I were found to have significantly lower intra-operative remifentanil and lower 24 h post-operative analgesic consumption than G II. Moreover, the time to the first analgesic request was significantly delayed in G I than G II [Table 3]. Time to achieve the intended MAP in seconds was significantly less in G I than G II. VAS scores were significantly lower in G I than in G II except for H0 and H_5 [Figure 2]. The incidence of PONV was significantly lower in G I than G II with a significantly lower use of antiemetic medication in G I [Table 4]. Estimated intra-operative blood loss was significantly lower in G I when compared to G II [Table 2].

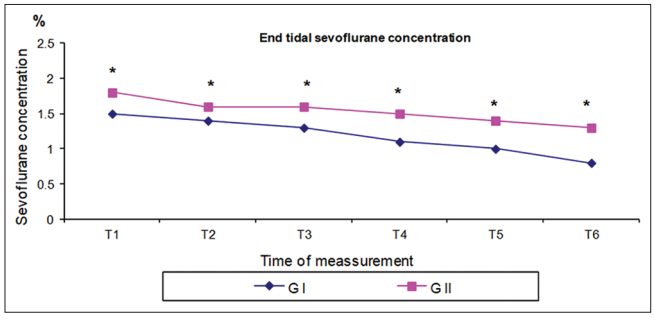

Figure 1: Mean of intra-operative end tidal sevoflurane concentrations in both groups

DISCUSSION

Rhinoplasty can be performed under different modalities of anaesthesia including local anaesthesia, IV sedation and general anaesthesia. Preparation of a clear bloodless surgical field is an important goal in

Table 1: Demographic data

Variable	Group I (*n*=35)	Group II (*n*=35)	*P*
Age (mean±SD)	31.7±5.8	33.2±4.9	0.247
Sex			
Male	11	9	0.597*
Female	24	26	
ASA grade			
I	28	30	0.526*
II	7	5	
Weight (mean±SD)	73.4±9.9	71.7±8.8	0.450
Height (mean±SD)	166.5±15.9	164.2±13.2	0.512

*Chi-square test is used. ASA – American Society of Anaesthesiologists; SD – Standard deviation

Table 2: Operative data in Group I and Group II

Variable	Group I (*n*=35)	Group II (*n*=35)	*P*
Duration of surgery (min)	76.8±10.3	79.1±9.5	0.335
Duration of anaesthesia (min)	85.4±11.9	89.2±10.7	0.165
Pre-operative HR (b/m)	79.9±10.2	81.3±9.8	0.560
Pre-operative MAP (mmHg)	73.5±8.7	75.6±9.4	0.335
Estimated intra-operative blood loss (ml)	81.9±30.8	107.5±34.6	0.002*
Time to intended MAP (s)	59.1±12.3	73.6±16.4	0.001*

*Means significant. HR – Heart rate; MAP – Mean arterial pressure

Table 3: Total intra-operative remifentanil, time to first analgesic request and post-operative analgesic consumption

Variable	Group I (*n*=35)	Group II (*n*=35)	*P*
Total intra-operative remifentanil (mg)	0.8±0.26	1.7±0.42	0.001*
Time to first analgesic request (h)	7.6±5.3	2.8±2.9	0.001*
Total tramadol consumption in 24 h (mg)	81.9±25.3	134.6±32.7	0.001*
Total diclofenac consumption in 24 h (mg)	49.8±22.1	87.3±31.6	0.001*

*Means significant

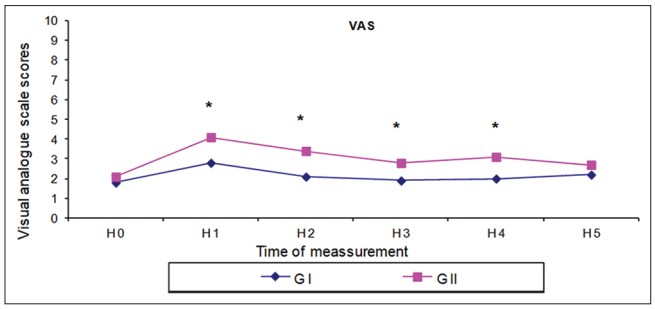

Figure 2: Mean of post-operative visual analogue scale scores in both groups

the anaesthetic management of rhinoplasty patients as it will effectively help the operating team. Hypotensive anaesthesia can optimally achieve such conditions because it reduces the bleeding amount and provides a better view. Various drugs such as nitroglycerine, remifentanil, labetalol and inhaled anaesthetics have been used for this purpose.[2]

The current study revealed that pre-operative gabapentin, as a single dose of 1.2 g given 2 h preoperatively, decreased intra-operative remifentanil consumption and end-tidal sevoflurane concentrations required to achieve the induced hypotension in rhinoplasty patients. Gabapentin significantly decreased the time needed to achieve intended MAP and estimated intra-operative blood loss. Postoperatively, opioid requirements were reduced by about 40% with significantly less total diclofenac sodium used during the first 24 h in gabapentin group. Meanwhile, VAS scores were significantly lower at all times except H0 and H5 together with significantly delayed time to the first analgesic request in G I than G II. Furthermore, PONV was significantly less in gabapentin group. Our results confirmed the hypothesis that pre-operative gabapentin reduce anaesthetic and analgesic requirements and augment deliberate hypotension and were in agreement with previous studies.[8-10] Moreover, a systematic review and meta-analysis concluded that pre-operative administration of gabapentin effectively reduced post-operative opioid requirements, post-operative pain scores and PONV in women undergoing abdominal hysterectomy.[11]

Gabapentin was reported to significantly reduce propofol requirements for induction and maintenance of anaesthesia. Furthermore, lower VAS scores at 30 min, 1 h and 2 h postoperatively with significantly less cumulative morphine consumption were noticed in patients who received gabapentin in comparison to placebo.[12]

Table 4: Incidence of post-operative nausea and vomiting

Variable	Group I (*n*=35), *n* (%)	Group II (*n*=35), *n* (%)	*P*
Nausea	2 (5.7)	8 (22.9)	0.040*
Vomiting	1 (2.9)	6 (17.1)	0.046*
Use of ondansetron	1 (2.9)	8 (22.9)	0.012*

*Means significant

A significant decrease in fentanyl consumption was reported in patients receiving gabapentin before ear, nose and throat surgery compared to placebo.[13]

The choice to administer gabapentin approximately 2 h before surgery seems rational to achieve maximum plasma concentration at the time of surgical stimulus. Pre-emptive single dose gabapentin inhibited hyperalgesia development for 2 days in an animal study for post-operative pain, however when administered 1 h after the intervention, it decreased symptoms only for 3 h.[7] In this study, we chose gabapentin dose of 1.2 g, which is within the limit of single daily dose, as that used for neuropathic pain treatment ranging from 900 to 1200 mg three times a day and after reviewing the doses used in previous studies.[14-16]

Pre-operative gabapentin has analgesic efficacy that is dose-dependent and this was reported by many studies.[15,17,18] To the best of our knowledge, this prospective randomised controlled double-blind study is the first to report that pre-emptive gabapentin significantly reduced intra-operative remifentanil consumption and end-tidal sevoflurane concentrations to achieve the intended intra-operative hypotensive anaesthesia with less post-operative opioid needs, better analgesic qualities, lower pain scores and reduced side effects that may negatively affect the patient's health in rhinoplasty patients.

Pre-operative anxiolysis caused by pre-emptive gabapentin may also help to reduce opioid requirements because there is a possible relationship between post-operative pain and pre-operative anxiety.[7] Moreover, gabapentin was proved to have a synergistic action with opioids in both humans and experimental studies.[19]

In contrast to our study, gabapentin was found to have no effect with regard to the intra-operative fentanyl consumption and this was explained by the use of fentanyl 2 μg/kg at the time of induction with nitrous oxide 65% in oxygen during maintenance, so only low additional doses of fentanyl were needed.[12]

Furthermore, in another study, there was no difference in intra-operative propofol consumption between gabapentin group and control group.[20] This discrepancy between the findings in our study and others may be due to different doses of gabapentin, type of surgery or methodology.

Limitations of the study include the relatively small number of patients studied. However, the sample size was estimated to achieve a power of 80% which is sufficient to support our results. Second, we were unable to assess dizziness and drowsiness that may accompany gabapentin administration because all patients received pre-operative sedation in the form of midazolam and received post-operative tramadol before tracheal extubation. Third, we studied only a single dose of gabapentin. Since it produces dose-dependent inhibition of N-methyl D-aspartate receptor, this may be a point for a further investigation to compare different doses of gabapentin.

CONCLUSION

Pre-operative oral gabapentin reduced intra-operative remifentanil and sevoflurane requirements and augmented intra-operative hypotension in rhinoplasty patients along with decreased post-operative pain, post-operative analgesic requirements.

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Conflicts of interest
There are no conflicts of interest.

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