RHINOLOGY

Single dose of preoperative analgesia with gabapentin (600 mg) is safe and effective in monitored anesthesia care for nasal surgery

Zuleyha Kazak · N. Meltem Mortimer · Sumru Şekerci

Abstract This study was aimed to compare the intraoperative sedative and perioperative analgesic drug requirements and the incidences of postoperative side effects on the patients who received preoperative gabapentin or placebo. Sixty patients undergoing nasal septal or nasal sinus surgery were included. The patients received either 600 mg gabapentin (Group G) or placebo (Group P) orally, 1 h before surgery. The scores for sedation and pain were recorded at 5, 15, 30, 45 and 60 min, intraoperatively and at 30 min, 1, 2, 4, 6, 9, 12, 16, 20, 24 h, postoperatively. Sedation was achieved with an IV bolus of propofol and continuous infusion of remifentanil. There were significant differences between gabapentin and placebo groups with regard to total consumptions of remifentanil (171.42 ± 68 vs. 219.17 ± 95 μg, respectively; $P = 0.033$) and propofol (59.45 ± 36.08 vs. 104.14 ± 54.98 mg, respectively; $P = 0.001$). Group G patients had significantly lower intraoperative VAS scores at all time points ($P < 0.05$). The anxiety score of Group G was better at all times ($P < 0.05$). All postoperative pain scores were lower in the Group G ($P < 0.05$). Time to first request for analgesic was 12.7 ± 2.3 h in Group G, and 7.8 2.1 h in Group P ($P < 0.0001$). Total consumption of lornoxicam was lower in Group G ($P < 0.004$). We concluded that monitored anesthesia care combined with preoperative analgesia with a low dose of (600 mg) oral gabapentin is an efficient option with tolerable side effects for patients undergoing ear, nose and throat ambulatory surgery.

Introduction

In outpatient surgery, analgesia is a very important part of the practice of anesthesia because it effects the duration of hospital stay as well as overall patient satisfaction. Monitorized anesthesia care (MAC) is frequently preferred in ear, nose and throat (ENT) surgery because patients have quick recovery with less nausea and vomiting when compared with general anesthesia.

Nonsteroidal antiinflammatory drugs, α_2 agonists and cyclooxygenase-2 inhibitors as well as opioids are widely used alone or in combinations to provide postoperative analgesia. They can also be used preoperatively to decrease the intra- and postoperative analgesic requirement. However, the contraindications and side effects of these drugs can restrict their use especially in presence of concomitant renal, hepatic or gastrointestinal diseases [1].

Gabapentin had been used preoperatively in sinus surgery and rhinoplasty operations in doses of 1,200 mg. In the study mentioned, gabapentin was reported to decrease analgesic requirement significantly but dizziness, with an incidence as high as 24%, was stated as an important disadvantage. The authors concluded that gabapentin provided a significant analgesic benefit for intra- and postoperative pain relief in patients undergoing ambulatory rhinoplasty or endoscopic sinus surgery; however, dizziness could be a handicap for ambulatory use [2].

The aim of this study was to determine the intra- and postoperative analgesic efficacy of low dose preoperative gabapentin and its effect on opioid requirement during the operation in patients undergoing rhinoplasty or endoscopic

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sinus surgery under monitored anesthesia care. We also aimed to find out if lowering the dose of gabapentin would decrease the incidence of side effects related to gabapentin use.

Methods

Approval of the Ufuk University Medical School Ethical committee (date and number 28.09.07, 07028) and the informed consents of the patients were obtained for this prospective, double-blinded, randomized and placebo-controlled study. Sixty patients, American Society of Anesthesiologists (ASA) physical status grade I and II, of both sexes scheduled for elective nasal septal and nasal sinus surgery were recruited between the dates 1.11.07 and 05.05.07. The patients older than 70 years or younger than 18 years, with known history of hypersensitivity to any drug, with history of drug abuse, with uncontrolled concomitant medical diseases (hypertension, bronchial asthma, diabetes mellitus), with chronic pain conditions, impaired kidney or liver function, with history of bleeding diathesis, and pregnancy were not included in the study.

All patients were visited for preanesthetic assessment, to explain the study protocol and the use of visual analog (VAS; 0 = no pain and 10 = worst pain imaginable) and verbal rating (VRS) scales the day before surgery.

Using a computer-generated table of random numbers, the patients were randomly assigned into two groups of 30 patients each, to receive either oral gabapentin 600 mg (gabapentin 600 mg, Neurontin®; Pfizer) or placebo, 1 h before surgery. The study drugs were prepared by the pharmacy, and an appropriate code number was assigned. All the patients were premedicated with IM injection of 0.01 mg/kg atropine sulfate and 0.07 mg/kg midazolam 45 min before the operation. Following arrival in the anesthetic room, venous route was established with a 20-gauge IV cannula at the dorsum of left hand and intravenous (IV) injections of 100 mg ranitidine and 10 mg metoclopramide were administered. Continuous monitorization of heart rate (HR), mean arterial blood pressure (MAP), and peripheral oxygen saturation were started.

After local anesthesia (lidocaine 2% with epinephrine) performed by the same surgeon to submucoperichondrial area, sedation was induced by administering an IV bolus of propofol 0.8 mg/kg. Remifentanil infusion was started at the rate of 0.015 µg/kg/h. Remifentanil was given by continuous infusion and the rate was titrated according to patient demand and to maintain a VRS score ≤4. Pain evaluation with VRS is done at 5, 15, 30, 45, and 60 min during the surgery.

Level of sedation was also evaluated at 5, 15, 30, 45, and 60 min during surgery and intermittent IV boluses of propofol 0.8 mg/kg were administered to maintain sedation at level 2–3 on the Ramsay scale. Total remifentanil and propofol consumption for each patient were determined and recorded. Intraoperative pain assessment was made on the basis of the VRS. Current pain intensity was graded on a four-point VRS scale (no pain, mild, moderate or severe pain) and, postoperative pain assessment was made according to VAS. A blinded observer recorded postoperative pain, anxiety score (AS; 1 = panicky, 2 = moaning, 3 = composed, 4 = friendly) and sedation scores at 30 min and 1, 2, 4, 6, 8, 12, 16, 20, and 24 h after completion of surgery. Additional analgesic requirements by each group within 24 h as well as the times to first analgesic request were determined according to VAS; when VAS values were >4, IV lornoxicam 8 mg was administered and recorded. The time to first analgesic request was regarded as the time elapsed between the administration of the study drug and the administration of the first additional analgesic. Patients were followed and evaluated for the occurrence of any side effects such as nausea and vomiting, diarrhea, epigastric discomfort, peripheral edema, somnolence, ataxia, light-headedness, dizziness, visual disturbances or headache in the postanesthesia care unit during the first 2 h of postoperative period and later in the ward every 2 h by an anesthesiology resident who was not involved in the study and all side effects were questioned and recorded.

A power analysis showed that a sample size of 25 patients per group could be sufficient to detect a 40% change in consumption of analgesic (lornoxicam) with a power of 0.8 and $\alpha < 0.05$ [3]. In a pilot study done earlier, the consumption of lornoxicam was found to be 10 ± 5 mg in gabapentin group and 14 ± 5 mg in placebo group. It is calculated that the difference between the two groups was 40% and 26 people per group would be sufficient for $\alpha = 0.05$ and $1 - \beta$ (power) = 0.80. Accordingly, we decided our sample groups to be 30 patients each. Statistical analyses were done by the SPSS 16.0 statistical package program on a IBM computable personnel computer. Descriptive statistics were expressed as mean ± SD unless otherwise stated. All variables were tested for normal distribution by the Shapiro–Wilk's test. Comparison of the means of continuous variables and normally distributed data were made using Student's t test. Not normally distributed variables were compared by Mann–Whitney test. Bonferroni adjustment was made for multiple comparisons at all time points. Variable differences (in hemodynamic variables and in other repeated variables like AS, VAS were evaluated by t test) in groups were evaluated by repeated-measures analysis of variance and post hoc testing was used for multiple comparisons. Categorical data were analyzed with the chi square or Fisher's exact test, as appropriate. A P value of less than 0.05 was considered to be significant.

Table 1 Demographic data, duration of surgery and sedation

	Group G ($n = 30$)	Group P ($n = 30$)	P
Age (year)	37 ± 12	31 ± 12	0.071
Type of operation (rhinoplasty/sinus surgery)	26/4	24/6	0.731
ASA (I/II)	23/7	20/10	0.567
M/F (n)	18/12	17/13	0.793
Weight (kg)	76 ± 15	71 ± 13	0.130
Duration of sedation	53 ± 25	50 ± 23	0.648
Duration of operation	47 ± 25	44 ± 21	0.640

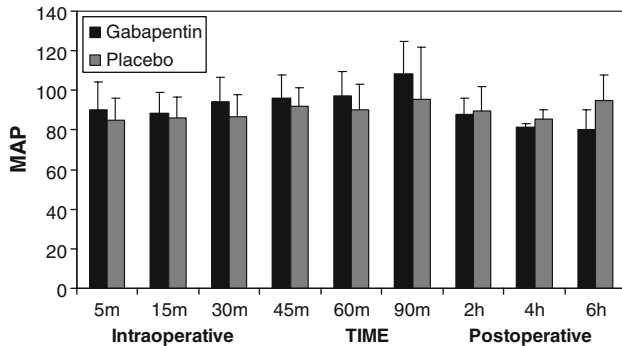No significant difference between the two groups

Fig. 1 There was not any statistically significant difference between the MAP (mean $\pm$ SD) among the two groups intra- and postoperatively ($P > 0.05$)
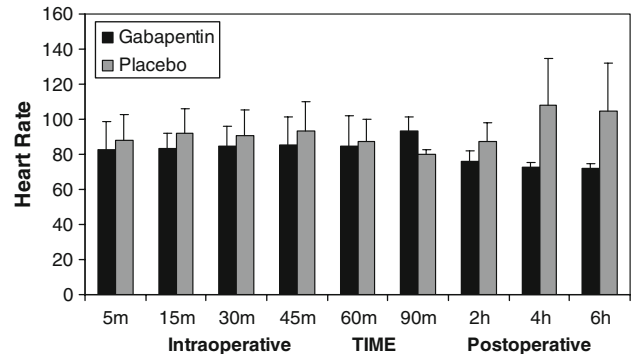

Fig. 2 There was not any statistically significant difference between the HR (mean $\pm$ SD) among the two groups intra- and postoperatively ($P > 0.05$)

Results

There were no differences in age, body weight, gender, ASA classification, type of operation, durations of surgery or sedation between the two groups (Table 1). HR, MAP and SPO_2 in the two groups were similar during and after the surgery ($P > 0.05$) (Figs. 1, 2).

There were significant differences between gabapentin and placebo groups with regard to total consumptions of remifentanil (171.42 ± 68 vs. 219.17 ± 95 µg; $P = 0.033$) and propofol (59.45 ± 36.08 vs. 104.14 ± 54.98 mg; $P = 0.001$).

Patients who received gabapentin 600 mg had significantly lower intraoperative VAS scores at all time points ($P < 0.05$) (Fig. 3). Intraoperative anxiety scores and postoperative anxiety scores were significantly better in the gabapentin group (G) when compared with the placebo group (P) ($P < 0.05$) (Fig. 4).

All subsequent postoperative pain scores were significantly lower in the gabapentin group when compared with the placebo group ($P < 0.05$). Time to first request for analgesic was 12.7 ± 2.3 h in Group G, and 7.8 ± 2.1 h in Group P ($P < 0.01$). Total consumption of lornoxicam was lower in group G compared to Group P ($P < 0.004$). There was also a significant difference in the number of repeated lornoxicam doses (0/1/2) between the two groups (the numbers of repeated doses of lornoxicam was significantly less in Group G compared to Group P) (Table 2).

No patient in any group reported somnolence, ataxia, light-headedness, dizziness, headache or visual disturbances.

Discussion

The aim of this study was to determine the intra- and postoperative analgesic efficacy of low dose gabapentin and its effect on opioid requirement during the operation in monitored anesthesia care of patients undergoing septoplasty or endoscopic sinus surgery. It was also aimed to find out if the incidence of side effects like dizziness related to gabapentin would be lower at the dose of 600 mg. This study was planned to investigate the analgesic efficacy of low dose preoperative gabapentin as well as the incidence of side effects.

The concept of preoperative analgesia, which is an analgesic treatment initiated before rather than after the surgical procedure, was introduced to protect the central nervous system (CNS) from the deleterious effects of noxious stimuli, and the patient from the resulting hyperalgesia, allodynia, and increased pain [4]. Preoperative analgesia, in principal, targets the central sensitization

Fig. 3 Intra- and postoperative pain scores: presented as mean ± SD. Intraoperative pain scores were significantly lower (P < 0.05) and all postoperative pain scores were significantly lower in the gabapentin group (G) when compared with the placebo group (P) (P < 0.05). VAS visual analog scale, VRS verbal rating scale, *P < 0.05
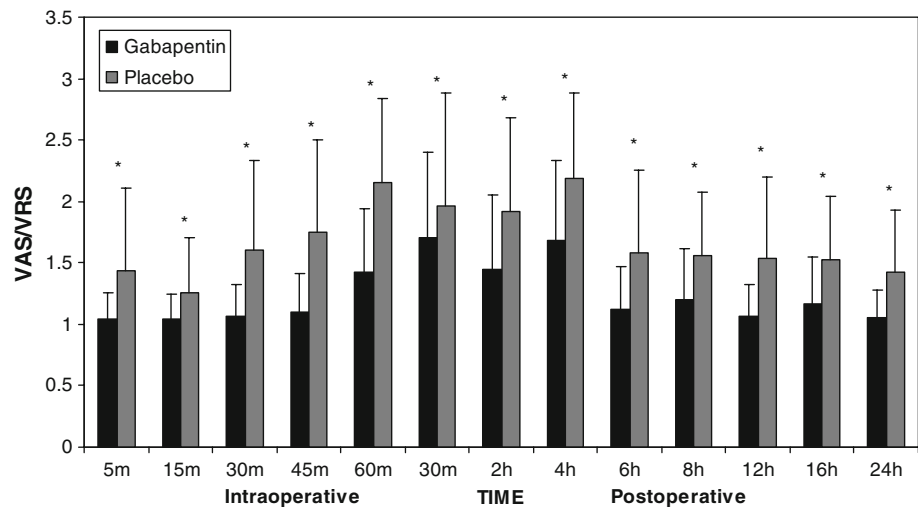
Fig. 4 Intra- and postoperative anxiety scores: significantly better in the gabapentin group (G) when compared with the placebo group (P) (P < 0.05). AS anxiety score, *P < 0.05
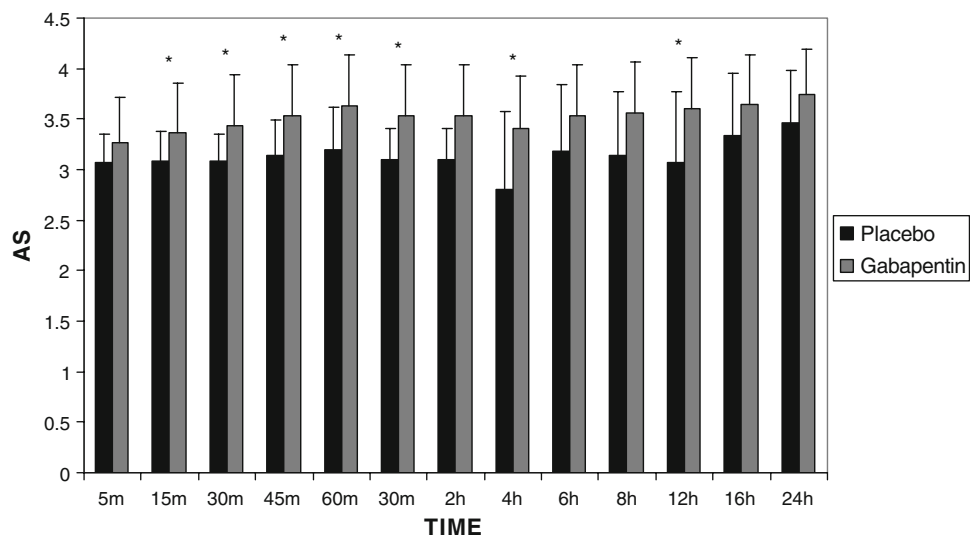
Table 2 Remifentanil, propofol, and lornoxicam consumption; first analgesic requirement time

	Group G	Group P	P
Total remifentanil consumption (μg)	171.42 ± 68	219.17 ± 95	0.033
Total propofol consumption (mg)	59.45 ± 36	104.14 ± 54	0.001
First analgesic requirement time (h)	12.7 ± 2.3	7.8 ± 2.1	0.0001
Number of lornoxicam applications (0/1/2)	20/9/1	14/9/7	0.047
Total lornoxicam consumption (mg)	9.33 ± 30	17.78 ± 5.33	0.004

process against painful stimuli. The aim is to block any noxious stimulus to reach CNS.

The search for new drugs that can decrease the analgesic requirement is still going on and one of the drugs under investigation for this purpose is gabapentin. Gabapentin is a structural analog of gamma-amino butyric acid and has been used as an anticonvulsant and antinociceptive drug but its mode of action is not well understood [5]. In preclinical and clinical studies, gabapentin has been found to be an effective, potent antihyperalgesic that does not affect acute nociception [6, 7]. Experimental studies also demonstrated that gabapentin suppresses experimentally induced hyperalgesia and, when administered intrathecally, reduces tactile allodynia and mechanical hyperalgesia in a rat model of postoperative pain [8]. In human volunteers, gabapentin has been demonstrated to inhibit the development and establishment of secondary allodynia and hyperalgesia resulting from skin sensitization with heat and capsaicin [9]. Gabapentin was introduced as an antiepileptic drug in 1993. It was subsequently reported to possess

antihyperalgesic and antiallodynic properties in a wide range of animal models [10] and to be effective in randomized clinical trials of neuropathic pain [11, 12]. Recently, several reports have also indicated that gabapentin may have a place in the treatment of postoperative pain [2, 13–15]. Finally, suggestions are made both by Gilron and Turan [2, 16] for further research within the field of preoperative analgesia by gabapentin for surgical patients.

Preoperative gabapentin has been shown to provide significant postoperative analgesia after laparoscopic cholecystectomy [15], total abdominal hysterectomy [14, 17], and lumbar discectomy [13]. The most common side effects of gabapentin are dizziness and drowsiness [12, 16], either of which can delay emergence from general anesthesia or prolong postoperative recovery. Turan et al. [2] observed considerable dizziness (24%) when gabapentin 1,200 mg was given 1 h before outpatient surgery. Therefore, they stated that it might limit gabapentin's use as a "coanalgesic" in routine anesthesia care.

A recent dose–response study defined gabapentin 600 mg as the optimal preoperative dose for postoperative pain relief after lumbar discectomy. Increasing the dose beyond 600 mg did not improve analgesia, but did increase the incidence of side effects [18]. Patients receiving gabapentin 900 and 1,200 mg had more complaints about light-headedness, feeling on a "high" (feeling of sitting on a "high"), and lack of concentration. Thus in his study, Adam et al. [19] empirically chose 800 mg of gabapentin as a reasonable compromise between efficacy and toxicity in their study on patients undergoing shoulder arthroscopy. In their patients, 800 mg of gabapentin did not provoke dizziness or other apparent side effects (headedness, visual disturbance, and headache), suggesting that this dose of gabapentin can be used in ambulatory patients without fear of excessive side effects.

In the light of the two studies that are mentioned above, it can be assumed that when used for preoperative analgesia purposes, gabapentin can be considered to have optimum efficacy with minimum incidence of side effects in the dose interval of 600–800 mg. This assumption needs more evidence. Therefore, in the present study, 600 mg gabapentin was chosen for preoperative analgesia of the patients undergoing MAC for outpatient rhinoplasty or endoscopic sinus surgery; the efficacy and the incidence of side effects were investigated. In this study, the preoperative use of 600 mg gabapentin decreased the amount of remifentanil and propofol needed intraoperatively during MAC. The time to first analgesic request was longer and the postoperative lornoxicam consumption was less in gabapentin group. In group G, VAS and AS measurements were more favorable at all times both intra- and postoperatively.

All the patients were premedicated with IM injection of 0.07 mg/kg midazolam 45 min before the operation. In these doses, VAS and VRS assessment are not expected to be affected significantly [2]. Though it is wise to state that atropine is useful in facilitating surgery by decreasing mucosal secretions, it is also useful for decreasing cardiac inhibitory effects of anesthetic agents such as remifentanyl.

Similar to the results of Turan et al. where they used 1,200 mg gabapentin preoperatively, we found in the current study that the preoperative administration of a 600 mg single oral dose of gabapentin provided a significant analgesic benefit for intra- and postoperative pain relief in patients undergoing ambulatory rhinoplasty or endoscopic sinus surgery. However, while 1,200 mg gabapentin was associated with a high incidence of dizziness, in our study we did not observe dizziness or any other side effects with 600 mg gabapentin.

The increasing costs of long hospitalization, the busy life style of patients and the cost of absence from work are reasons for why ambulatory surgery is becoming increasingly more popular. Another factor is the availability of short-acting drugs, which make early discharge from the hospital possible. In these cases, MAC is preferred because it requires shorter hospital stay. However, there is one problem that has to be overcome.

Perioperative analgesia has traditionally been provided by opioid analgesics. However, extensive use of opioids is associated with a variety of perioperative side effects. In addition, intraoperative use of large bolus doses or continuous infusions of potent opioid analgesics may actually increase postoperative pain as a result of their rapid elimination and/or the development of acute tolerance [20]. So gabapentin administration gives us an opportunity to decrease incidence of these side effects.

The opioids used for perioperative analgesia must be titrated well that they would not cause respiratory depression or delayed discharge. On the other hand, the postoperative analgesia should be sufficient to allow the patient leave the hospital without considerable pain. Preoperative analgesia with an agent like gabapentin seems to be the answer to both questions. It decreases not only the intraoperative need for opioids but also the postoperative need for analgesics.

For further study, we believe the efficacy of even lower doses of gabapentin should be studied in combination with MAC in ENT or other operations. Also comparison of pregabalin with gabapentin should be considered.

Conclusion

We concluded that MAC combined with preoperative analgesia with a low dose of (600 mg) oral gabapentin is an

efficient option with tolerable side effects for patients undergoing ENT ambulatory surgery.

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

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