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The Efficacy of Gabapentin + Dexamethasone for Postoperative Analgesia Following Septoplasty: A Prospective Randomized Placebo-Controlled Trial

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Abstract

Aims: This study aimed to compare the efficacy of gabapentin, dexamethasone, and gabapentin + dexamethasone for pain control after septoplasty.

Materials and Methods: This prospective randomized trial included 120 patients that underwent septoplasty and were randomly divided into 4 groups: group G (preoperative gabapentin 600 mg p.o.); group D (intraoperative dexamethasone 8 mg i.v.); group GD (preoperative gabapentin 600 mg p.o. + intraoperative dexamethasone 8 mg i.v.); group C (placebo control).

Results: The median VAS score was significantly lower in groups G and GD at 1, 2, 4, 6, 12, and 24 hours postsurgery than in group C ($P < .008$ for all). The median VAS score was significantly lower in group D than in group C at 1, 2, and 4 hours postsurgery ($P < .008$ for all). There weren't any significant differences in the VAS score between groups D, G, and GD at any time point. Groups G, D, and GD had a significantly lower frequency of rescue analgesic use than group C; however, there were no differences between groups G, GD, and C ($P < .001$ and $P = .108$, respectively).

Conclusion: Gabapentin, dexamethasone, and gabapentin + dexamethasone are equally more effective analgesics during the first 4 hours postsurgery than placebo. The addition of dexamethasone to gabapentin does not provide extra analgesia. Both gabapentin and gabapentin + dexamethasone have a more prolonged analgesic effect than dexamethasone alone.

Keywords

gabapentin, dexamethasone, analgesia, postoperative pain, septoplasty

Introduction

Nasal septal deviation is commonly seen in otolaryngology practice and is corrected with septoplasty. Nasal tampons have been used to avoid such associated complications as postoperative bleeding and septal hematoma. Early postoperative pain following septoplasty can be caused by both nasal packing and surgical trauma. The most intense pain is experienced within the first 24 hours of surgery; early postoperative pain control is very important to decrease morbidity and analgesic consumption, and to increase patient satisfaction.[1–3]

Gabapentinoids (pregabalin and gabapentin) were approved for the treatment of neuropathic pain and refractory epilepsy in 2004.[4] They both have anti-hyperalgesic analgesic effects via binding to voltage-gated calcium channels.[5,6] Their use for perioperative management of acute pain has been studied and it was reported that they decrease the severity of pain and use of opioids.[7] Glucocorticoids have analgesic, anti-inflammatory, and antiemetic effects, and they increase the efficacy of analgesia, either as a single-agent or in combination with other drugs[8,9]; however,

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data on the use of gabapentinoids, dexamethasone, or their combination for postoperative pain management after otolaryngologic surgery are lacking. The present study aimed to compare the efficacy of gabapentin, dexamethasone, and gabapentin + dexamethasone for postoperative pain control within 24 hours of septoplasty.

Methods

The study protocol was approved by the Kırıkkale University Ethics Committee (date: 21/07/2014, no. 19/04) and was conducted in accordance with the Declaration of Helsinki.

Design and Participants

This prospective, randomized, double-blind, placebo-controlled study included 120 patients that underwent elective septoplasty at Kırıkkale University, Department of Otorhinolaryngology, and were eligible and agreed to participate. Patients were recruited between July 2014 and December 2014. The patients were randomly divided into four groups of 30 patients each, as follows: group G: preoperative gabapentin 600 mg p.o. (Neurontin, 600 mg, GmbH, Germany); group D: intraoperative dexamethasone 8 mg i.v. (Dekort, 4 mg mL^{-1}, Deva, Istanbul); group GD: preoperative gabapentin 600 mg p.o. and intraoperative dexamethasone 8 mg i.v.; group C: preoperative placebo control p.o. Group randomization was performed using a computer-based randomization list and the patients were unaware of which group they were assigned to. Gabapentin and placebo p.o. were administered 1 hour before surgery by a nurse that was not part of the study. Placebo capsules looked similar to gabapentin capsules.

Exclusion criteria were as follows: age <18 years and >75 years; active infection; significant systemic disease, such as cardiac, hepatic, renal, and pulmonary disease; diabetes mellitus; regular use of certain drugs (NSAIDs, steroids, opioids, antidepressants, and benzodiazepines); allergic reaction to the study drugs; pregnancy or breastfeeding; chronic pain conditions; BMI >40 kg m^{-2}.

Operative Technique

All the patients were American Society of Anesthesiologists (ASA) physical status I-II and underwent surgery by senior surgeons. All participating surgeons were equally allocated to the operations. All patients received a standard general anesthetic protocol of propofol as the induction agent and sevoflurane as the inhalation agent. Intraoperatively, the same quantity local anesthesia (lidocaine 2% and adrenaline) was administered to the subperichondrial plane in all patients. Standard septoplasty via hemitransfixion incision was performed in all patients. Quilting transseptal sutures were used in all patients. Internal silicon nasal splints were used for nasal packing and were removed on postoperative day 3. Tramadol Hcl 50 mg i.v. was administered intraoperatively 30 min before the end of the operation in all patients, followed by non-opioid analgesics postoperatively. No dissolvable packing was used in any of the patients. All the patients underwent septoplasty alone without in combination with sinus or turbinate surgery.

Main Outcome Measures

Patients were kept inpatient 1 day to assess postoperative pain scores. Postoperative pain was assessed using a horizontal Visual Analog Scale (VAS) (0: no pain; 100: unbearable pain) at 1, 2, 4, 6, 12, and 24 h postsurgery by a blinded observer. When the VAS pain score was >40, dexketoprofen trometamol 50 mg i.v. was administered for rescue analgesia and the number of times additional analgesic was required was noted. Patients were followed-up for adverse effects, including postoperative nausea and vomiting, dizziness, aprosexia, constipation, xerostomia, allergic reaction, visual impairment, and postoperative bleeding at the surgical site.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.25.0 (IBM Corp., Armonk, NY, USA) and Microsoft Excel (Microsoft Corp., Redmond, WA, USA). Descriptive analysis was performed, and the normality of the distribution of data was tested using the Kolmogorov-Smirnov normality test and normal distribution parameters. Data are shown as median (range) for non-normally distributed continuous variables, and as frequency and percentage for categorical variables. Categorical variables were compared using the chi-square test and Fisher's exact test for small-sample data ($n < 5$). The Kruskal–Wallis test was used for non-normally distributed independent variables in multiple groups. When significant differences between groups were noted via the Kruskal–Wallis test individual groups were compared using the Mann-Whitney U test. After Bonferroni adjustment applied for multiple comparisons, $P < .05/6 = .0083$ was accepted as statistically significant in pairwise comparisons of groups using the Mann-Whitney U test. One-way ANOVA was used to compare normally distributed parameters in multiple groups. The level of statistical significance was set at $P < .05$; all reported P values are 2-sided.

Results

The study included 120 patients that were randomly divided into four groups of 30 each. There weren't any significant differences in age, sex, duration of surgery, or ASA status between the groups (Table 1). Postoperative VAS pain

Table 1. Demographics and Clinical Parameters.

	Group G	Group D	Group GD	Group C	*P*
Number of patients	30	30	30	30	
Age, median (range)	35 (18-55)	36 (17-56)	35 (18-65)	35.5 (17-61)	.979
Male/Female	22/8	26/4	22/8	23/7	.561
ASA Status, I/II	23/7	25/5	26/4	22/8	.555
Duration of surgery, mean ± SD (min)	41.3 ± 8.1	43.4 ± 10	45.3 ± 7.9	42.5 ± 7.5	.317

Table 2. VAS pain scores according to group and time point.

Hours (h)	Group G, median (range)	Group D, median (range)	Group GD, median (range)	Group C, median (range)	*P**
1	20 (10-80)**	40 (0-100)§	30 (0-70)**	60 (30-80)**,§	<.001
2	20 (0-50)**	30 (0-80)§	20 (0-30)**	40 (10-70)**,§	<.001
4	20 (0-30)**	20 (0-70)§	15 (0-50)**	30 (0-60)**,§	<.001
6	10 (0-30)**	20 (0-50)	10 (0-30)**	30 (0-50)**	.002
12	0 (0-40)**	15 (0-40)	0 (0-30)**	20 (0-70)**	.011
24	0 (0-30)**	0 (0-30)	0 (0-20)**	0 (0-30)**	.010

*Bonferroni adjustment was applied for pairwise comparison of groups. $P < .0083$ was accepted as statistically significant for the pairwise Mann-Whitney *U* test.
**There was a significant difference between group C, and group G and group GD ($P < .008$).
§There was a significant difference between group C and group D ($P < .008$). The difference between group D, and both group G and group GD was not significant at any time point.

scores at all time points in all four groups are shown in Table 2. Group C had a significantly higher VAS pain score than Group G and Group GD at all time points. Group D had a significantly lower VAS pain score than group C at 1, 2, and 4 hours postsurgey. Group D had a lower (not significantly) VAS pain score than group G and group GD at most time points. In addition, the VAS pain score in group G and group GD did not differ significantly at any time point.

The number of times dexketoprofen trometamol i.v. was administered for rescue analgesia within 24 h of surgery is shown in Table 3. Table 3 also shows the frequency of study medication side effects in groups G, D, and GD, and comparisons with group C. In group G and group GD rescue analgesics were required significantly less often than in group C. Group D had fewer analgesic requirement incidents than group C. There wasn't a significant difference in analgesic requirement between group D, and group G and group GD ($P = .108$). Postoperative nausea, dizziness, and xerostomia were the most common side effects of the study medications. Group D had significantly fewer patients with nausea than the other groups. The number of patients with nausea in groups G and GD were similar to that in group C ($P = 0.425$ and $P = .052$, respectively).

Discussion

Septoplasty is a commonly used procedure in routine ENT practice. In addition to surgical trauma, nasal tampons and splints can also induce postoperative pain.[10] The first 24 hours postsurgery is a critical period for pain management, as the most intense pain is experienced during this time.[1,3] Gabapentinoids (pregabalin and gabapentin) are gamma-aminobutyric acid (GABA) analogues and α_2-δ ligands.[4] They exert their effect by binding to α_2-δ subunits in presynaptic voltage-gated calcium channels, thusly inhibiting calcium influx and release of excitatory neurotransmitters in the brain and spinal cord.[6] Gabapentinoids have been used to treat epilepsy and neuropathic pain for nearly 2 decades.[4] Their use as a postoperative analgesic, with and without dexamethasone, for various ENT surgeries, such as tonsillectomy, endoscopic sinus surgery, septoplasty, and rhinoplasty, has been studied.[8,10–14]

A unique aspect of the present study is the use of a single intraoperative dose of dexamethasone (group D) in addition to gabapentin, gabapentin + dexamethasone, and placebo, and comparison of the four groups. Pregabalin is approximately five-fold more potent than gabapentin.[15] Reported doses of gabapentinoid agents after nasal surgery vary. Pregabalin 75 mg, 150 mg, and 300 mg, and gabapentin 600 mg and 1200 mg have been used to study their efficacy and side effects.[8,10–12,16,17] The present study used gabapentin 600 mg in septoplasty patients, as this dose is reported to be safe and effective.[11]

The present findings show that gabapentin and gabapentin + dexamethasone decreased VAS pain scores within 24 hours of septoplasty, as compared to placebo.

Table 3. The frequency of rescue analgesic use and side effects of the study medications.

	Group G, median (range)	Group D, median (range)	Group GD, median (range)	Group C, median (range)	*P*
Number of times dexketoprofen trometamol administered within 24 h of surgery	0 (0-1)**,§	0 (0-2)**,§	0 (0-1)**,§	1 (0-3)**	<.001*
Side effects, yes/no					
Nausea	10/20[a]	1/29[a,b]	6/24	13/17[b]	0.002
Vomiting	6/24	1/29	2/28	5/25	.139
Dizziness	10/20	7/23	7/23	7/23	.759
Aprosexia	6/24	2/28	5/25	6/24	.442
Constipation	0/30	1/29	0/30	0/30	.388
Xerostomia	18/12	19/11	12/18	17/13	.272
Allergic reaction	0/30	0/30	0/30	0/30	N/A
Blurred vision	3/27	2/28	4/26	0/30	.240
Postoperative bleeding	3/27	3/27	5/25	6/24	.604

*Bonferroni adjustment was applied for pairwise comparisons of groups. $P < .0083$ was accepted as statistically significant for the pairwise Mann-Whitney *U* test.
**Group C had higher rescue analgesic use than group G, group D, and group GD ($P < 0.001$).
§There wasn't a difference between group D, and group G and group GD ($P = .108$).
[a]There was a significant difference between group D and group G ($P = .005$).
[b]There was a significant difference between group D and group C ($P < .001$).

Dexamethasone only also decreased VAS pain scores within 4 hours of surgery, as compared to placebo. Gabapentin and gabapentin + dexamethasone had a longer effect than dexamethasone only; however, despite the fact that group D had slightly higher VAS pain scores than groups G and GD, the difference was not significant. This may indicate that gabapentin and gabapentin + dexamethasone exhibit an analgesic effect similar to that of dexamethasone only in the early postoperative period; however, a longer analgesic affect during the first 24 hours postsurgery can be guaranteed by using gabapentin. Gabapentin + dexamethasone did not provide a significantly better analgesic effect than gabapentin only. A 2016 meta-analysis by Park et al.[18] that included 602 nasal surgery patients (septoplasty, rhinoplasty, and sinus surgery) from nine randomized controlled trials showed that preoperative gabapentinoid p.o. led to significantly lower postoperative pain scores at 2, 4, 8, 12, and 24 hours postsurgery, and less use of analgesics than in the control group, which is comparable to the present findings. Moreover, they also reported that the gabapentinoid group had a significantly lower frequency of postoperative nausea and vomiting, but a higher incidence of blurred vision. The present findings do not confirm those results; however, in the present study a single intraoperative dose of dexamethasone i.v. (group D) was associated with a significantly lower incidence of postoperative nausea than in groups G, GD, and C. Other adverse effects did not differ significantly between the present study's four groups.

A 2018 review by Nguyen et al.[19] that included studies on the post-septoplasty and post-rhinoplasty efficacy of perioperative analgesia methods reported that gabapentinoids were effective analgesics associated with lower VAS pain scores in six of seven studies. Only Farzi et al.[20] did not observe a significant difference in mean VAS pain scores between their gabapentin and control groups. Moreover, a meta-analysis of the efficacy of gabapentin use for postoperative analgesia after various otolaryngologic procedures reported that gabapentin had a significant beneficial effect on perioperative pain relief and analgesic consumption[21]; however, a meta-analysis by Fabritius et al.[5] that included randomized clinical trials and 7201 adult surgical patients reported that preoperative pregabalin had a minimal opioid-sparing effect and increased the risk of adverse effects.[5] Additionally, the quality of their evidence is insufficient to recommend routine use of pregabalin for postoperative pain treatment. Furthermore, their analysis focused only on pregabalin use and included patients that underwent various surgical procedures other than otolaryngologic surgery. These two factors make it difficult to confidently interpret their findings.

The side effects of gabapentinoids should be taken into consideration when planning postoperative analgesia. These adverse effects of gabapentinoids can roughly be classified as mild and serious. A meta-analysis by Fabritius et al.[5] reported that there were 55 serious adverse effects reported in 7201 patients, including re-admission to hospital, prolonged hospital stay, allergic reaction, stroke, pulmonary embolism, myocardial infarction, and acute kidney injury, with a relative risk of 2.9-fold. On the other hand, it was reported that there also might be an increased risk (2.1-3.2 fold) of some milder adverse effects, such as dizziness and visual disturbances, but a lower incidence of postoperative nausea and vomiting.[5,18] Visual disturbances are well tolerated and usually disappear within 1 hour postsurgery; therefore, it would be appropriate to inform patients beforehand.[8,10]

The analgesic efficacy of dexamethasone has been reported.[9,22] Although in the present study the median VAS pain score in group D was higher than in group GD, the difference was not significant. The frequency of rescue analgesic use was also similar in groups D, G, and, GD; however, these three groups had lower incidences than group C. These findings indicate that gabapentin + dexamethasone did not provide extra analgesia. Moreover, dexamethasone alone provided analgesia as efficiently as gabapentin + dexamethasone at 1, 2, and 4 hours postsurgery, which is a unique finding. Prolonged analgesia can be achieved using gabapentin and gabapentin + dexamethasone. In addition, the incidence of nausea in group D was lower than in group G and group C. Demirhan et al.[10] also reported that dexamethasone + pregabalin was not beneficial in terms of pain control after septoplasty; however, Koç et al.[23] reported that gabapentin + dexamethasone provided better postoperative analgesia than administration of gabapentin or dexamethasone alone.

The present study has several limitations. The study population was small and larger prospective randomized trials would be required to generalize similar findings. The pain assessment method used was based on subjective VAS scores, which we think was partially counterbalanced by the objective non-steroid rescue analgesic drug use rates. In addition, VAS pain scores after 24 hours postsurgery were not measured, so the prolonged effects of the study drugs remain unknown. Additional larger scale research is warranted to further elucidate the efficacy of dexamethasone as a postoperative single-agent analgesic after septoplasty.

Conclusion

Gabapentin, dexamethasone, and gabapentin + dexamethasone are equally more effective analgesics within 4 hours of septoplasty than placebo. The addition of dexamethasone to gabapentin does not provide extra analgesia. Both gabapentin and gabapentin + dexamethasone have a more prolonged analgesic effect than dexamethasone alone (up to 24 hours post septoplasty).

Declaration of Conflicting Interests

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