

The effectiveness of gabapentin on post-tonsillectomy pain control

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Abstract Postoperative pain is one of the most troublesome aspects of tonsillectomy for patients. Although various analgesics have been administered for pain control following tonsillectomy, it has still not been effectively controlled. Therefore, this study was conducted to evaluate the effectiveness of premedication using gabapentin on postoperative pain control in patients undergoing tonsillectomy. A total of 58 adult patients were randomly divided into a control group and a gabapentin group. Patients in the control group received an oral placebo preoperatively, whereas those in the gabapentin group received an oral dose of gabapentin preoperatively. All participants were provided with patient-controlled analgesia using fentanyl for 48 h after surgery. The total amount of fentanyl injected and the number of injections of diclofenac sodium (75 mg each) requested by each of the group was then compared. Pain assessment was performed using a visual analog scale during resting periods (rVAS) and during swallowing (sVAS) for 9 days after the operation. The number of diclofenac sodium injections and the total amount of fentanyl injected decreased significantly in the gabapentin group ($P < 0.01$). The sVAS of the gabapentin group was also significantly lower than that of the control group at 2 and 4 h after surgery, but there were no significant differences in the

sVAS observed between the two groups for the remainder of the postoperative period. There were no significant differences in the rVAS observed between the two groups throughout the postoperative period. Thus, premedication with gabapentin decreased post-tonsillectomy pain. So the addition of gabapentin prior to tonsillectomy may have an adjunctive role in pain control.

Keywords Gabapentin · Postoperative pain · Tonsillectomy

Introduction

Tonsillectomy is one of the most common surgical procedures performed in otorhinolaryngology. Postoperative pain following tonsillectomy, which is especially aggravated by swallowing, can lead to various complications, such as impairment of food intake, possible dehydration, sleep disturbance and increased risk of secondary hemorrhage [1]. Therefore, various analgesics and a number of surgical techniques have been suggested to improve pain relief [2–4]. Among them, opioids play a fundamental role in the management of post-tonsillectomy pain control; however, their use is associated with a number of side effects, including nausea, vomiting and respiratory depression. Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) can be used to complement opioids for post-tonsillectomy pain control; however, their use is hampered by an increased incidence of postoperative bleeding due to the nonselective inhibitory action of NSAIDs against cyclooxygenase (COX) [2, 3]. Therefore, it is necessary to develop an effective approach to control post-tonsillectomy pain by combining treatment modalities that can block different pain mechanisms.

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Gabapentin is an antiepileptic drug that has been synthesized to mimic the chemical structure of the neurotransmitter γ -aminobutyric acid (GABA). There have been reports that the use of gabapentin reduced postoperative morphine consumption and movement-related pain after radical mastectomy and hysterectomy [5, 6]. Additionally, Mikkelsen et al. [4] reported that a combination of gabapentin and rofecoxib reduced opioid use after tonsillectomy. Preoperative use of gabapentin can reduce postoperative pain by reducing central neuronal sensitization. However, no reports regarding the effectiveness of premedication with gabapentin at post-tonsillectomy pain control have been conducted. Therefore, this study was conducted to evaluate the effectiveness of gabapentin premedication on postoperative pain control after tonsillectomy.

Materials and methods

Patients older than the age of 15 years, who were scheduled for elective tonsillectomy at our hospital during the period November 2004 to December 2006 were enrolled in this study. Informed consent was obtained from all patients. Prior to surgery, we explained the goal of this study to all patients, who were then educated on the use of the visual analog scale (VAS) chart and the use of the patient-controlled analgesia (PCA) pump. This study was a randomized, double blind and placebo-controlled study that was set up according to a computer-generated block randomization. The night before and 1 h before surgery, each patient received either a 600 mg capsule of gabapentin (Neurontin[®], Pfizer Inc, New York) or a matching placebo capsule orally. Tonsillectomy was performed by the same technique for all patients, using monopolar electrocautery, and bleeding was controlled using simple compression, bipolar electrocautery and covering with hydrogen peroxide (H₂O₂). General anesthesia was induced with intravenous thiopental (5 mg/kg), and tracheal intubation was facilitated with intravenous succinylcholine (1 mg/kg). Anesthesia was maintained with enflurane and 60% nitrous oxide in oxygen. Paralysis was maintained with 4–6 mg of pancuronium and reversed with glycopyrrolate and pyridostigmine at the end of surgery.

As shown in Table 1, there were no significant differences between the two groups in sex, age, height, weight, time of operation and anesthesia, and the amount of bleeding during the operation.

As a basic analgesic regimen, both groups were given acetoaminophen 325 mg and tramadol 37.5 mg daily for 9 postoperative days. While in the hospital, patients in both groups were supplied with 1% fentanyl that was administered via a PCA device (Abbott Aim PlusTM, Abbott laboratories, IL) with the same parameters (demand

Table 1 Clinical characteristics of the patients

	Control (<i>n</i> = 26)	Gabapentin (<i>n</i> = 32)	<i>P</i>
Male/Female	9/17	18/14	0.10
Age (year)	24.2 ± 6.3	27.7 ± 11.5	0.35
Height (cm)	165.2 ± 6.6	168.4 ± 6.8	0.08
Weight (kg)	59.1 ± 8.4	66.9 ± 14.7	0.06
Operation time (min)	40.8 ± 11.9	46.8 ± 19.8	0.44
Anesthesia time (min)	52.1 ± 9.5	57.9 ± 11.7	0.52
Bleeding (ml)	4.3 ± 4.2	11.0 ± 24.0	0.10

Results are presented as the mean ± standard deviation

dose = 2 ml, lockout time = 10 min, no basal infusion), and the total amount of injected fentanyl was recorded before discharge. Additionally, 75 mg of diclofenac sodium (DCF) was injected intramuscularly at the patients' request, and the number of DCF injections was recorded. The grade of pain was self-assessed by the patients using a 10 cm visual analog scale (VAS), which ranges from 0 (no pain) to 10 (most severe pain). The pain grade during resting periods (rVAS) and during swallowing (sVAS) was assessed at 1, 2, 4, 8, 12, 24, 36 and 48 h postoperatively, and then daily for 7 days after discharge. Each patient was questioned regarding their overall satisfaction with the analgesic effects during the first 24 h after surgery and again 9 days after surgery (0: not satisfied, 10: very satisfied). Possible side effects of the medications, including drowsiness, nausea, dizziness, headache and vomiting were assessed and recorded in the patient's medical chart during the 48 h following tonsillectomy. Results are presented as the mean ± standard deviation. *P* < 0.05 was considered to be statistically significant.

Results

The total amount of PCA fentanyl used by the gabapentin group during admission was significantly lower than that used by the control group. Additionally, the number of DCF injections in the gabapentin group was significantly lower than that of the control group (Table 2). The pain score of both groups during the resting period was highest 2 h after surgery (4.1 ± 2.2 in the gabapentin group and 4.5 ± 2.4 in the control group). After 2 h, the rVAS value decreased gradually, with the lowest value being observed 9 days after surgery (2.1 ± 1.3 in the gabapentin group and 2.5 ± 2.2 in the control group). Throughout the postoperative period, the rVAS value in the gabapentin group was lower than that of the control group, with the exception of the postoperative day 3; however, there were no significant differences observed in the rVAS values of the two groups

Table 2 The amounts of analgesic injected by intravenous patient-controlled analgesia (PCA) and the number of injections of diclofenac sodium (DCF)

	Control (n = 26)	Gabapentin (n = 32)	P
Total amount of fentanyl injected by PCA (mL)	59.7 ± 41.5	28.1 ± 31.5	0.002
Number of DCF injections (75 mg each)	0.8 ± 0.9	0.1 ± 0.3	0.001

Results are presented as mean ± standard deviation. The number of injections of DCF and total amounts of fentanyl injected using PCA for the two groups were significantly different ($P < 0.05$)

PCA patient-controlled analgesia, DCF diclofenac sodium

(Fig. 1). The pain score of the control group during swallowing was highest during the immediate postoperative period (6.8 ± 2.6 at 1 h and 6.8 ± 2.4 at 2 h), after which it gradually decreased to 3.6 ± 2.1 on the ninth postoperative day. In the gabapentin group, the sVAS (5.8 ± 2.0) was highest 8 hours after surgery, after which it gradually decreased to 3.4 ± 1.5 on the postoperative day 9. Throughout the postoperative period, the sVAS in the gabapentin group was lower than that of the control; however, significant differences were only noticed at 2 and 4 h after surgery ($P = 0.04$; $P = 0.04$; Fig. 2). The overall satisfaction score toward pain control assessed at 24 h after surgery was 6.2 ± 2.0 in the gabapentin group and 6.0 ± 1.8 in the control group. On the postoperative day 9, the satisfaction score in the gabapentin group was 6.6 ± 2.0 and in the control group, 6.5 ± 2.1 (Fig. 3). There were no significant differences in the overall patient satisfaction 24 h after surgery and on the postoperative day 9. Drowsiness, nausea and headache were more common in the gabapentin group; however, the occurrence of these symptoms was not significantly different between the two groups. Dizziness was the second most common symptom; however, this occurred in the same proportion (81%) in both groups. In the gabapentin group, 19% of patients experienced vomiting, whereas 35% of the control group experienced vomiting. However, this difference was not statistically significant (Table 3).

Discussion

The operative procedure of tonsillectomy results in tissue injury, which stimulates the glossopharyngeal nerve or lesser palatine nerve. Thereafter, afferent nociceptive stimulus arrives in the pain center of the brain and induces central neuronal sensitization [7–9].

One of the neurotransmitters related to central neuronal sensitization is glutamate, which is an excitatory amino acid. The N-methyl-D-aspartate (NMDA) receptor, which is activated by glutamate, transmits a nociceptive stimulus

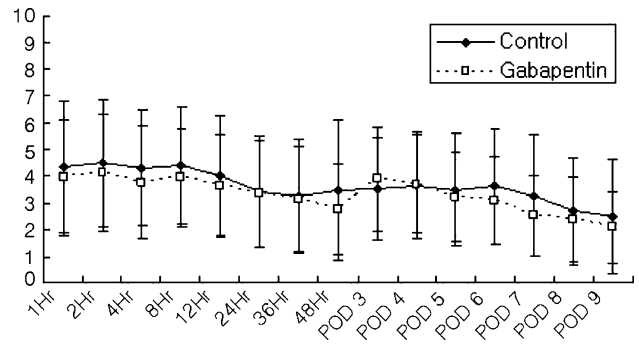


Fig. 1 Visual analog scale during resting periods (rVAS) after tonsillectomy in the control and gabapentin group. Results are expressed as the mean score ± standard deviation (vertical bars represent standard deviation). There were no significant differences in the pain score between the two groups throughout the postoperative period

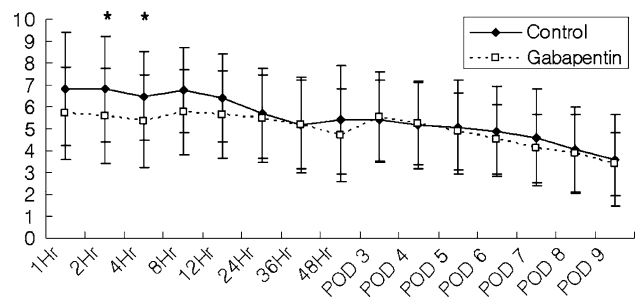


Fig. 2 Visual analog scale during swallowing (sVAS) after tonsillectomy in the control and gabapentin group. Results are expressed as the mean score ± standard deviation (vertical bars represent standard deviation). The sVAS of the gabapentin group was significantly lower than that of the control group 2 and 4 h after tonsillectomy; however, no significant differences in sVAS were observed thereafter. * $P < 0.05$ significantly different compared to the gabapentin group

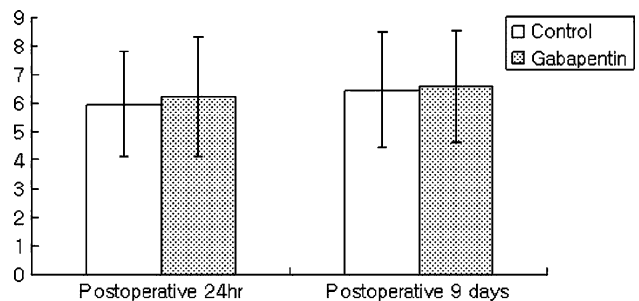


Fig. 3 Satisfaction scores at 24 hours and at 9 days after surgery in the control and gabapentin groups. There were no significant differences observed in the satisfaction score between the two groups 24 hours after tonsillectomy or 9 days after tonsillectomy. Vertical bars represent standard deviation

through the central nervous system and also maintains an unusual neuronal discharge leading to central neuronal sensitization of pain. This unusual hyper-reactivity has a major role in the production of pain in the central nervous system [10, 11].

Table 3 Side effects during the first 48 h following tonsillectomy

		Control (<i>n</i> = 26)	Gabapentin (<i>n</i> = 32)	<i>P</i>
		Number (%)	Number (%)	
Drowsiness	No	4 (15)	1 (3)	0.39
	Moderate	19 (73)	28 (88)	
	Severe	3 (12)	3 (9)	
Nausea	No	9 (35)	8 (25)	0.83
	Moderate	13 (50)	21 (66)	
	Severe	4 (15)	3 (9)	
Dizziness	No	5 (19)	6 (19)	0.94
	Moderate	19 (73)	24 (75)	
	Severe	2 (8)	2 (6)	
Headache	No	14 (54)	14 (44)	0.54
	Moderate	11 (42)	17 (53)	
	Severe	1 (4)	1 (3)	
Vomiting	No	17 (65)	26 (81)	0.19
	Moderate	9 (35)	6 (19)	
	Severe	0 (0)	0 (0)	

There were no differences in the incidence of drug side effects between the two groups ($P > 0.05$)

The exact mechanism of gabapentin is unknown, but its therapeutic action on neuropathic pain is thought to involve voltage-gated N-type calcium ion channels. It is thought to bind to the $\alpha 2\delta$ subunit of the voltage-dependent calcium channel in the central nervous system. This reduces calcium influx into the nerve terminals and decreases the release of neurotransmitters such as glutamate. [12, 13].

Recently, several reports have indicated that gabapentin may be useful for the management of postoperative pain [4, 5, 14]. Dirks et al. [5] observed a decrease in pain during movement at 2 and 4 h postoperatively, but not during the remainder of the follow-up period, following a single dose of gabapentin administered during breast surgery. Additionally, Fassolulaki et al. [14] investigated the analgesic efficacy of gabapentin in 75 patients who had undergone breast cancer surgery. In this study, patients provided with 1,200 mg of gabapentin daily for 10 days exhibited a significantly reduced amount of codeine use as well as significantly decreased pain scores during resting periods and during movement. Mikkelsen et al. [4] also reported the effect of gabapentin on post-tonsillectomy pain control. In their study, the treatment group received a combination of gabapentin and rofecoxib and the control group received only rofecoxib for 5 days after surgery. The gabapentin–rofecoxib group showed a significantly reduced opioid requirement during the first 24 h after surgery when compared with the rofecoxib group.

In our study, patients received 600 mg of gabapentin twice before tonsillectomy. Treatment with gabapentin

decreased the requirement of fentanyl and additional use of analgesics (DCF injection) significantly ($P = 0.002$; $P = 0.001$), which is concordant with the findings of other studies [4, 5, 14] that have reported diminished opioid intake when gabapentin was used. This suggests that pre-medication with gabapentin may have an effective role in the control of pain following tonsillectomy.

We were unable to demonstrate any remarkable decrease in pain scores during resting periods in the gabapentin group; however the mean pain scores observed during swallowing were lower in the gabapentin group for the first 12 h after tonsillectomy, with statistically significant differences being observed 2 and 4 h after surgery ($P = 0.04$; $P = 0.04$; Fig. 2).

The side effects of gabapentin are are sedation, nausea, dizziness, headache, vomiting and so on. Mikkelsen et al. [4] reported that a significant preponderance of dizziness, vomiting, and gait disturbance was seen in the gabapentin group compared with the placebo group. They suggested that this side effect was probably caused by 5 days of continuous ingestion of gabapentin at relatively high doses (1,800 mg/day). In a study by Gilron et al. [15], which consisted of 110 hysterectomized patients who received either placebo, gabapentin (1,800 mg/day), rofecoxib (50 mg/day) or a gabapentin–rofecoxib combination (1,800/50 mg/day) starting 1 h preoperatively for 72 h, sedation was the only side effect noted in the gabapentin group when compared with the other group.

Compared to the studies of Mikkelsen et al. [4] and Gilron et al. [15], a relatively small dose (1,200 mg) of gabapentin was used in our study. However, 97% (31/32) of patients in the gabapentin group and 85% (22/26) in the control group felt drowsy for 48 h postoperatively. Both groups showed far higher incidence of drowsiness than is usually reported for gabapentin. We think that this high incidence of drowsiness was caused by the combined action of gabapentin and fentanyl, which is one of the main analgesics we used in intravenous PCA. There were no significant differences between the two groups with respect to the frequency of drowsiness and other side effects (Table 3).

However, the adequate dosage and medication method of gabapentin has not yet been defined. In a study by Dirks et al. [5], patients received an oral dose of 1,200 mg of gabapentin 1 h before mastectomy, whereas Dierking et al. [6] administered oral gabapentin 1,200 mg 1 h before hysterectomy, followed by oral gabapentin 600 mg 8, 16 and 24 h after the initial dose. Further, in a study by Fassolulaki et al. [14], patients received 1,200 mg/day of gabapentin for 10 days following breast surgery. In our study, we used an oral dose of 600 mg of gabapentin the night before and again 1 h before tonsillectomy. In spite of the relatively small dosage of gabapentin used in this study, the total amount of fentanyl demanded and the frequency of the

need for additional analgesics were decreased in the gabapentin group, which indicates that gabapentin had a significant analgesic effect on post-tonsillectomy pain. The effective dosage and medication mode of gabapentin have not yet been defined and research is needed to reduce its side effects and increase its efficacy. Comparative studies of its combination with other drugs (such as pregabalin) are needed.

Conclusion

Preoperative administration of gabapentin reduced the number of diclofenac sodium injections and the total amount of fentanyl injected without increasing adverse effects. Therefore, we suggest that the addition of gabapentin prior to tonsillectomy may have an adjunctive role in pain control.

Conflict of interest We have no financial relationship with the organization that sponsored the research.

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