AĞRI 2013;25(4):163-168
doi: 10.5505/agri.2013.98852

Gabapentin premedication for postoperative analgesia and emergence agitation after sevoflurane anesthesia in pediatric patients

Pediyatrik hastalarda ameliyat sonrası analjezi ve sevofluran anestezisi sonrası derlenme ajitasyonu için gabapentin premedikasyonu

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Summary

Objectives: The aim of this study was to investigate the effect of gabapentin premedication on postoperative 24th hour total analgesic consumption and the incidence of emergence agitation after sevoflurane based anesthesia in pediatric patients undergoingtonsillectomyandadenoidectomy.

Methods: 46 healthy, ASA class I or II, aged 3-12 year old children were included into the study. The patients were randomly assigned to one of the control (Group C) or gabapentin group (Group G) consisting of 23 patients in each. Group C received 10 ml of saline, Group G received gabapentin 15 $mg.kg^{-1}$ dissolved in 10 ml of saline orally 30 min. before the induction of anesthesia. After anesthesia induction with 8% sevoflurane in 50% O_2-N_2O. General anesthesia was maintained with 1 MAC sevoflurane in 50% O_2-N_2O. Emergence agitation was assessed with a 5 point scale and recorded every 10 min. of first 30 min. of the postoperative period. Parents were contacted 24 hours after the surgery to evaluate pain, total analgesic consumption, parent satisfactionandanysideeffect.

Results: Agitation scores were significantly lower in group G compared to group C in the postoperative 20th and 30th minutes ($p<0.01$, 0.05 respectively). Total analgesic requirement in postoperative 24 hour was significantly lower in group G ($p<0.01$). Satisfaction scores of parents was also higher in group G ($p<0.05$).

Conclusion: Gabapentin premedication decreases postoperative 24th hour analgesic consumption and attenuates emergence agitation after sevoflurane anesthesia.

Key words: Analgesia; emergence agitation; gabapentin; sevoflurane.

Özet

Amaç: *Bu çalışmanın amacı gabapentin premedikasyonunun tonsillektomi ve adeneidektomiye giden pediyatrik hastalarda ameliyat sonrası 24 saatlik analjezik tüketimi ve sevofluran anerstezisinden sonra derlenme ajitasyonunun insidansı üzerindeki etkisini araştırmaktır.*

Gereç ve Yöntem: *Yaşları 3-12 arasında değişen ASA I-II grubu sağlıklı 46 çocuk çalışmaya dahil edildi. Hastalar randomize olarak her biri 23 hastadan oluşan kontrol (Grup C) ve gabapentin (Grup G) olmak üzere iki gruba ayrıldı.Grup C 10 ml salin ve grup G ise 10 ml salin içinde çözünmüş 15ml.kg^{-1} gabapentini anestezi indüksiyonundan 30 dak. önce oral olarak aldı. %50 O_2-N_2O karışımı içinde %8 sevofluran ile anestezi indüksiyonunu takiben genel anestezi %50 O_2-N_2O karışımı içinde 1 MAC sevofluran ile idame edildi. Derlenme ajitasyonu beş noktalı skala ile değerlendirildi ve postoperatif ilk 30 dak. boyunca 10 dakika arayla kaydedildi. Cerrahiden 24 saat sonra ağrıyı, total analjezik tüketimi, ebeveyn memnuniyetini ve yan etkileri değerlendirmek için ebeveynlerle iletişime geçildi.*

Bulgular: *Ajitasyon skorları grup G'de grup C'ye göre ameliyat sonrası 20. ve 30. dakikalarda anlamlı olarak düşüktü ($p<0.01$, 0.05 sırasıyla). Total analjezik gereksinim postoperatif 24. saatte grup G'de daha düşüktü ($p<0.01$). Ebeveyn memnuniyeti grup G'de daha yüksekti ($p<0.05$).*

Sonuç: *Gabapentin premedikasyonu ameliyat sonrası 24. saatteki analjezik tüketimi ve sevofluran anestezisi sonrası derlenme ajitasyonunu azaltır.*

Anahtar sözcükler: Analjezi; derlenme ajitasyonu; gabapentin; sevofluran.

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Submitted (*Başvuru tarihi)* 08.06.2012 Accepted after revision (*Düzeltme sonrası kabul tarihi)* 22.10.2012

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Introduction

A structural analogue of gamma-amino butyric acid, gabapentin, was developed as an anticonvulsant drug initially.[1] Soon after, it has been used to treat painful neuropathy in patients with diabetes mellitus, post-herpetic neuralgia, and inflammatory injury.[1,2] Moreover, gabapentin belongs to a class of drugs that have anxiolytic properties and is also well-tolerated.[3]

Sevoflurane has gained popularity as an anesthetic for children since it is less pungent and has lower solubility and greater haemodynamic stability than the other potent inhaled anesthetics.[4] However, sevoflurane may be associated with a greater incidence of emergence agitation in pre-school age pediatric patients.[5,6] Genetic predisposition, age, type of the procedure performed, duration of anesthesia, and concurrent medications may be named as possible etiologic factors of emergence agitation.[4] Although this problem has not been associated with significant morbidity, marked emergence agitation may negate the advantages of rapid emergence from general anesthesia.[7] In previous investigations, it has been reported that the prevalence of this adverse effect is between 20%-80%.[8]

The use of gabapentin in the perioperative setting has been evaluated in recent studies.[1-3,9] These studies report promising reduction in postoperative morphine consumption and preoperative administration of gabapentin decreased postoperative pain scores after various types of surgery.[1,2,9] There was only one study involving the use of gabapentin for pediatric patients.[10] Rusy et al demonstrated that preoperative gabapentin 15 $mg.kg^{-1}$ decreased postoperative opioid consumption, but not overall opioid-related side effects in children an adolescents undergoing spinal fusion.

The aim of this study was to test the hypothesis that gabapentin, which has analgesic and anxiolytic properties, reduces the postoperative 24th hour total analgesic consumption and the incidence of emergence agitation after sevoflurane based anesthesia in pediatric patients undergoing adenoidectomy and tonsillectomy.

Materials and Methods

After obtaining approval of the hospital ethical committee, and written informed consent from parents, 46 healthy children 3-12 years old, ASA class I or II, undergoing elective tonsillectomy and adenoidectomy were included in this prospective randomized double blind study. The children with obstructive sleep apnea were excluded from the study.

The patients were randomly assigned to one of the control group (Group C) or gabapentin group (Group G) consisting of 23 patients each, using a randomization list. The patients in Group C received 10 ml of saline 30 min. before the induction of anesthesia, whereas the patients in Group G received gabapentin (Neurontin® Pfizer Goedecke GmbH, Freiburg Germany), 15 $mg.kg^{-1}$ dissolved in 10 ml of saline orally. Drugs were prepared by an investigator who was not involved in the group assignment. The anesthesiologists and data collectors and parents and observers in the recovery room were blinded to treatment group. Standard monitoring included ECG, non-invasive arterial blood pressure, peripheral O_2 saturation, end tidal CO_2. Vital signs were monitored and recorded throughout study. Anesthesia was induced with 8% sevoflurane in 50% O_2-N_2O by a face mask with a fresh gas flow of 5 $L.min^{-1}$ and all patients had a 22 G intravenous cannula placed after induction of anesthesia. Fentanyl at a dose of 1 $mcg.kg^{-1}$ was added. The patients were entubated endotracheally 2 minutes after administration of 0.1 $mg.kg^{-1}$ i.v. vecuronium bromide. All patients were operated by the same surgeon. Similar mechanical ventilation parameters were set in IPPV with volume control mode using the same anesthesia machine. General anesthesia was maintained with 1 MAC sevoflurane delivered in 50% O_2-N_2O that provided stable heart rate, mean arterial blood pressure, and peripheral oxygen saturation throughout surgery. When heamostasis was accomplished, 15 $mg.kg^{-1}$ of metamizol was administered intravenously to all patients. At the end of the procedure, anesthetic gases were discontinued, the circuit was flushed and 100% O_2 was used with a fresh gas flow of 6 $L.min^{-1}$ during emergence. Any residual neuromuscular blockade was antagonized in all patients with 0.01 mg/kg atropine and 0.05 mg/kg neostigmine. Tracheal extubation was

performed when the patients regained gag or cough reflexes. Thereafter, all patients were transferred to recovery room. Anesthesia duration, and time to eye opening and extubation times were recorded by an observer blinded to the group assignment. Any adverse event was noted. Modified Aldrete scores were recorded during recovery room stay.[11] Children were considered ready for discharge from the recovery room when an Aldrete score of ≥9 was achieved. Emergence agitation was assessed with a 5 point scale described by Cole and recorded every 10 min of first 30 minutes of the postoperative period.[12] Scoring system for emergence agitation was as follows: 1: sleeping; 2: awake, calm; 3: irritable, crying; 4: inconsolable crying; 5: severe restlessness, disorientation.

Postoperative pain was assessed by using OPS (Objective pain scale) recorded at 30 minutes, 2,4,6,12 and 24 hours postoperatively.[13] Paracetamol was prescribed to patients and the parents were asked to give an oral dose of 15 mg.kg-1 only in case of pain with a minimum interval of 4 hours and to keep a record of the dose they gave to their children. Every parent was contacted 24 hours after the surgery to evaluate pain, total analgesic consumption after discharge and parent satisfaction. Any side effect such as vomiting, gait disturbance and dizziness was questioned. Parent satisfaction was scored as: 1: definitely unsatisfied; 2: poorly satisfied; 3: fairly satisfied; 4: definitely satisfied.

Statistical analysis

The number of patients in each group was based on the results of a pilot study of 20 patients that did not receive any gabapentin or placebo. We estimated a standard deviation of agitation scores as 1.2 and we aimed to detect a 25% reduction from a mean score of 4. A two-sided α error of 0.05 and a type II (β) error of 0.2 was considered to be acceptable. Based on these assumptions, a sample size of 23 on each group would be required for a power of 0.80. Obtained data were statistically analysed on a personal computer using the software package SPSS for windows version 10.0.5 (SPSS Inc. Chicago IL) One sample Kolmogorov Smirnov test was used for analyzing distribution of data Mann Whitney U or Independent samples t tests were used where appropriate for comparing data. A p value of <0.05 was considered as statistically significant.

Results

There were no significant differences regarding demographic data, ASA scores between two groups (Table 1). The duration of anesthesia, spontaneous eye opening times and extubation times were also similar in two groups (Table 2).

The incidence of remarkable agitation (Scores of 4 and 5) was 82.6%, 78.2%, 56.5% in the group C and in the group G 65.2%, 47.8% and 30.4% at the 10th, 20th and 30th postoperative minutes re-

Table 1. Demographic data. Values are mean, [median], (range)

Group	Control (n=23)	Gabapentin (n=23)
Age (years)	5.3 [4] (3-11)	5.6 [5] (3-9)
Weight (kg)	21.0 [19] (13-40)	21.7 [22] (13-34)
Sex (Female/Male)	12/11	15/8
ASA (I / II)	23/0	21/2

Table 2. Anesthesia and emergence times. Values are mean±standard deviation

Group	Control (n=23)	Gabapentin (n=23)
Duration of Anesthesia (min)	45.5±20.0	53.6±21.8
Eye opening time (min)	52.3±20.8	59.9±22.6
Extubation time (min)	50.4±19.2	54.9±22.4

Table 3. Preoperative anxiety and postoperative agitation scores Data are Median (range)

	Preoperative	Postoperative 10 min	Postoperative 20 min	Postoperative 30 min
Control	2 (2-4)	5 (3-5)	4 (2-5)	4 (2-5)
Gabapentin	2 (2-4)	4 (1-5)	3 (1-5)*	2 (2-5)†
p	0.527	0.053	0.009	0.036

*p<0.01 compared to control group; †p<0.05 compared to control group.

spectively. Preoperative agitation scores were similar between groups. Agitation scores were significantly lower in group G compared to group C in the postoperative 20th and 30th minutes (p<0.01, 0.05 respectively) (Table 3). Total analgesic requirement in postoperative 24 hour was significantly lower in group G (p<0.01) (Table 4). Satisfaction scores of parents was also significantly higher in group G (p<0.05) (Table 5). Gait disturbance and dizziness was not stated at all after discharge from the hospital by parents. Home readiness was not different between groups.

Discussion

To our knowledge this is the first study documenting the use of gabapentin in pediatric ambulatory patients undergoing tonsillectomy and adenoidectomy. The result of this study indicate that gabapentin premedication at a dose of 15 mg/kg orally, reduces postoperative 24 hour total analgesic consumption in children undergoing adenoidectomy and tonsillectomy and the incidence of emergence agitation following sevoflurane anesthesia.

Table 4. Analgesic consumption. The count of required paracetamol dose (15 $mg.kg^{-1}$) in the postoperative 24 hours. Values are mean, [median], (range)

	n	Paracetamol consumption
Control	23	3.29 [3], (0-6)
Gabapentin	23	1.68 [2], (0-4)*

*p<0.01 compared to control group.

Table 5. Parent satisfaction scores. Data are mean, [median], (range)

	n	Satisfaction scores
Control	23	2.91 [3] (1-4)
Gabapentin	23	3.70 [4] (3-4)

*p<0.05 compared to control group.

Postoperative pain following tonsillectomy includes injury induced inflammation at the surgical wound and sensitization of peripheral nociceptive nerve terminals and central neurons.[14] The analgesic effects of gabapentin result from an action at the alpha $_2$ delta $_1$ subunits of the voltage dependent Ca^{+2} channels for which it has substential affinity. These are upregulated in the dorsal root ganglia and spinal cord after peripheral nerve injury produced by surgical incision. Gabapentin may produce analgesia by binding to and inhibiting presynaptic voltage dependent Ca^{+2} channels, decreasing calcium influx and inhibiting the release of neurotransmitters including glutamate from the primary affarent nerve fibers that synapse on and activate pain responsive neurons in the spinal cord.[1,14,15] Recently several studies have demonstrated that gabapentin may have a place in postoperative pain in adult surgical patients in a single dose design as well as when continued for 1 week after surgery.[3,10,16] Mikkelsen et al showed firstly that gabapentin reduced opioid requirements in the first 24 hour after tonsillectomy in adult patients but the benefits of reduced opioid intake seem to be overshadowed by the drawbacks of side effects during 5 days after tonsillectomy in adult patients, but in this study very high dose of gabapentin was chosen.[14]

Sevoflurane is a popular anesthetic for children because it is less pungent and has a more rapid onset and offset due to its lower solubility in blood, a relative lack of airway agitation and greater heamodynamic stability than other potent inhaled anesthetic

agents.[17] However, a number of studies report that sevoflurane is associated with a relatively high incidence of emergence agitation in children.[17-20]

Age, preoperative behaviour and anxiety, premedication, rapid awakening in a hostile environment, parental presence upon awakening, pain, surgery type and used anesthetic and adjuvants are the factors that affect emergence agitation.[18] Although there is no clinical evidence that this event affects long term outcome, it is a cause of dissatisfaction for parents. Drugs such as analgesics, opioids, benzodiazepines, clonidine, remifentanil and dexmedetomidine have been used either prophylactically or as treatment of emergence agitation with variable success.[17,18,20-24]

The presence of pain, a predisposing factor for postoperative agitation, explains the effectiveness of analgesic drugs such as fentanyl and ketorolac given either as prophylaxis or for treatment of agitation.[18]

Although pain may be one of the causes of agitation following general anesthesia; it is not the only cause. Cravero et al concluded that emergence agitaiton was seen in 56% of pediatric patients after sevoflurane anesthesia without surgery.[25] Rapid awakening from anesthesia in a hostile environment may not necessarily be the reason of emergence agitation in sevoflurane anesthesia. Picard et al compared the quality of anesthetic emergence after sevoflurane and propofol anesthesia in children undergoing tonsillectomy. They concluded that sevoflurane anesthesia resulted in higher incidence of emergence agitation, although both anesthesia techniques showed similar emergence and recovery times.[26]

Shibata et al speculated that the cause of sevoflurane agitation was related to the residual sevoflurane at awakening. Cohen et al, also speculated that variable rate of neurological recovery from sevoflurane result in a dissociative state which may increase the sensitivity and the reactivity of children to their environment.[18,19]

Early anecdotal and descriptive reports suggested that emergence agitation was encountered more frequently in young people who underwent tonsillectomy and head and neck surgery.[18] Furthermore Voepel-Lewis et al have found oto-laryngologic procedures to be an independent risk factor for development of emergence agitation in children.[27] Hence this study was based on the population at risk for emergence agitation.

In our study, preoperative anxiety scores did not differ between groups, this may be caused by ineffective blood level of gabapentin since we gave the drug just half an hour ago before the operation due to our ambulatory ward conditions. One limitation of our study is that we did not use most validated PAED scale for emergence delirium.[23]

As a conclusion; gabapentin premedication decreases postoperative 24 hour analgesic consumption and attenuates emergence agitation after sevoflurane anesthesia. Further investigations are required to determine a dose–response relationship and the effect of timing.

Conflict-of-interest issues regarding the authorship or article: None declared.

Peer-rewiew: Externally peer-reviewed.

References

1. Turan A, Memiş D, Karamanlioğlu B, Yağiz R, Pamukçu Z, Yavuz E. The analgesic effects of gabapentin in monitored anesthesia care for ear-nose-throat surgery. Anesth Analg 2004;99(2):375-8.
2. Fassoulaki A, Stamatakis E, Petropoulos G, Siafaka I, Hassiakos D, Sarantopoulos C. Gabapentin attenuates late but not acute pain after abdominal hysterectomy. Eur J Anaesthesiol 2006;23(2):136-41.
3. Ménigaux C, Adam F, Guignard B, Sessler DI, Chauvin M. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesth Analg 2005;100(5):1394-9.
4. Uezono S, Goto T, Terui K, Ichinose F, Ishguro Y, Nakata Y, et al. Emergence agitation after sevoflurane versus propofol in pediatric patients. Anesth Analg 2000;91(3):563-6.
5. Kuratani N, Oi Y. Greater incidence of emergence agitation in children after sevoflurane anesthesia as compared with halothane: a meta-analysis of randomized controlled trials. Anesthesiology 2008;109(2):225-32.
6. Moos DD. Sevoflurane and emergence behavioral changes in pediatrics. J Perianesth Nurs 2005;20(1):13-8.
7. Cravero JP, Beach M, Dodge CP, Whalen K. Emergence characteristics of sevoflurane compared to halothane in pediatric patients undergoing bilateral pressure equalization tube insertion. J Clin Anesth 2000;12(5):397-401.
8. Mayer J, Boldt J, Röhm KD, Scheuermann K, Suttner SW. Desflurane anesthesia after sevoflurane inhaled induction reduces severity of emergence agitation in children undergoing minor ear-nose-throat surgery compared with sevoflurane induction and maintenance. Anesth Analg

2006;102(2):400-4.
9. Turan A, White PF, Karamanlioglu B, Memis D, Tasdogan M, Pamukçu Z, et al. Gabapentin: an alternative to the cyclooxygenase-2 inhibitors for perioperative pain management. Anesth Analg 2006;102(1):175-81.
10. Rusy LM, Hainsworth KR, Nelson TJ, Czarnecki ML, Tassone JC, Thometz JG, et al. Gabapentin use in pediatric spinal fusion patients: a randomized, double-blind, controlled trial. Anesth Analg 2010;110(5):1393-8.
11. Aldrete JA. Modifications to the postanesthesia score for use in ambulatory surgery. J Perianesth Nurs 1998;13(3):148-55.
12. Cole JW, Murray DJ, McAllister JD, Hirshberg GE. Emergence behaviour in children: defining the incidence of excitement and agitation following anaesthesia. Paediatr Anaesth 2002;12(5):442-7.
13. Norden J, Hannallah RS, Getson P, O'Donnell R, Kelliher G, Walker N. Concurrent validation of an objective pain scale for infants and children. Anesthesiology 1997;75:934.
14. Mikkelsen S, Hilsted KL, Andersen PJ, Hjortsø NC, Enggaard TP, Jørgensen DG, et al. The effect of gabapentin on post-operative pain following tonsillectomy in adults. Acta Anaesthesiol Scand 2006;50(7):809-15.
15. Hurley RW, Cohen SP, Williams KA, Rowlingson AJ, Wu CL. The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. Reg Anesth Pain Med 2006;31(3):237-47.
16. Fassoulaki A, Patris K, Sarantopoulos C, Hogan Q. The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. Anesth Analg 2002;95(4):985-91.
17. Isik B, Arslan M, Tunga AD, Kurtipek O. Dexmedetomidine decreases emergence agitation in pediatric patients after sevoflurane anesthesia without surgery. Paediatr Anaesth 2006;16(7):748-53.
18. Aouad MT, Nasr VG. Emergence agitation in children: an update. Curr Opin Anaesthesiol 2005;18(6):614-9.
19. Cohen IT, Finkel JC, Hannallah RS, Hummer KA, Patel KM. Rapid emergence does not explain agitation following sevoflurane anaesthesia in infants and children: a comparison with propofol. Paediatr Anaesth 2003;13(1):63-7.
20. Ibacache ME, Muñoz HR, Brandes V, Morales AL. Single-dose dexmedetomidine reduces agitation after sevoflurane anesthesia in children. Anesth Analg 2004;98(1):60-3.
21. Ghosh SM, Agarwala RB, Pandey M, Vajifdar H. Efficacy of low-dose caudal clonidine in reduction of sevoflurane-induced agitation in children undergoing urogenital and lower limb surgery: a prospective randomised double-blind study. Eur J Anaesthesiol 2011;28(5):329-33.
22. Dong YX, Meng LX, Wang Y, Zhang JJ, Zhao GY, Ma CH. The effect of remifentanil on the incidence of agitation on emergence from sevoflurane anaesthesia in children undergoing adenotonsillectomy. Anaesth Intensive Care 2010;38(4):718-22.
23. Patel A, Davidson M, Tran MC, Quraishi H, Schoenberg C, Sant M, et al. Dexmedetomidine infusion for analgesia and prevention of emergence agitation in children with obstructive sleep apnea syndrome undergoing tonsillectomy and adenoidectomy. Anesth Analg 2010;111(4):1004-10.
24. Kulka PJ, Bressem M, Wiebalck A, Tryba M. Prevention of "post-sevoflurane delirium" with midazolam. [Article in German] Anaesthesist 2001;50(6):401-5. [Abstract]
25. Cravero JP, Beach M, Thyr B, Whalen K. The effect of small dose fentanyl on the emergence characteristics of pediatric patients after sevoflurane anesthesia without surgery. Anesth Analg 2003;97(2):364-7.
26. Picard V, Dumont L, Pellegrini M. Quality of recovery in children: sevoflurane versus propofol. Acta Anaesthesiol Scand 2000;44(3):307-10.
27. Voepel-Lewis T, Malviya S, Tait AR. A prospective cohort study of emergence agitation in the pediatric postanesthesia care unit. Anesth Analg 2003;96(6):1625-30.