Effects of preoperative lornoxicam versus tramadol on postoperative pain and adverse effects in adult tonsillectomy patients

Tonsillektomilerde preoperatif uygulanan lornoksikamın analjezik etkinliğinin ve yan etkilerinin tramadol ile karşılaştırılması

Berrin IŞIK,[1] Mustafa ARSLAN,[1] Özgür ÖZSOYLAR,[1] Mehmet AKÇABAY[1]

Summary

Objectives: This study assessed the efficacy and adverse effects of preoperatively administered lornoxicam versus tramadol in adults, for post-tonsillectomy pain.

Methods: This prospective, double blind, randomized, clinical research was performed in the Ear, Nose and Throat Surgery Room in the Department of Anesthesia and Reanimation, Gazi University Faculty of Medicine. Forty American Society of Anesthesiologists (ASA) status I-II patients of both gender, aged 18-55 years, were included.

Results: Tonsillectomy patients were divided into two groups: Those in Group L received 8 mg lornoxicam and in Group T received 50 mg tramadol intravenously just before induction of general anesthesia. Induction and maintenance of anesthesia (propofol, atracurium, nitrous oxide and sevoflurane) were standardized. Heart rate and systolic and diastolic arterial pressure data were monitored during the anesthesia. Intra-operative bleeding was scored by the same operator using a 5-point scale at the end of the surgery. Postoperative pain on swallowing was scored by a blinded anesthesiologist using Verbal Rating Scale (VRS) on arrival in the Post Anesthesia Care Unit (T_0), at 30 min (T_1), 1h (T_2), 2h (T_3), 3h (T_4), 4h (T_5), 5h (T_6), and 6h (T_7) thereafter. During the first postoperative 6 hours, when VRS ≥2, 1mg.kg^{-1} im meperidine was used as a rescue analgesic. Adverse effects in the postoperative 6h period were noted. T_1 and T_2 pain scores in Group T were higher than in Group L (p=0.049, p=0.007, respectively). The number of patients requiring rescue analgesics during the first 6 hours in Group L was lower than in Group T. Nausea-vomiting, bleeding and postoperative hemorrhage values were similar between Group L and Group T.

Conclusion: Preoperative 8 mg lornoxicam was more effective than 50 mg tramadol with respect to early postoperative tonsillectomy pain in adult patients, and side effects were similar.

Key words: Analgesia/adult; lornoxicam; tonsillectomy; tramadol.

Özet

Amaç: *Erişkin hastalarda ameliyat öncesi uygulanan lornoksikam ile tramadolün tonsillektomi ağrısı üzerine etkinliği değerlendirildi.*

Gereç ve Yöntem: *Prospektif, çift kör, randomize ve klinik çalışma, Gazi Üniversitesi Tıp Fakültesi Kulak Burun Boğaz Cerrahisi Ameliyathanesinde ASA I-II, 18-55 yaş arası, kadın ve erkek 40 olguda gerçekleştirildi. Tonsillektomi hastaları iki gruba ayrıldı. Grup L'deki hastalara 8 mg lornoksikam ve Grup T'deki hastalara 50 mg tramadol genel anestezi indüksiyonundan hemen önce intravenöz yolla uygulandı. Anestezi indüksiyonu ve kontrollü ventilasyon altında sürdürülen anestezi idamesi (propofol, atraküryum, nitroz oksit ve sevoflurane) ve cerrahinin tipi standardize edildi.*

Bulgular: *Anestezi sırasında arter basıncı ve kalp atım hızı monitorize edildi. Ameliyattaki kanama miktarı aynı operatör tarafından 5 nokta skalası kullanılarak ameliyat sonunda değerlendirildi. Ameliyattan sonra yutkunma sırasındaki ağrı hastanın hangi gruba dahil olduğunu bilmeyen araştırmacı tarafından postanestzi bakım odasına gelişte (T_0), 30. dakikada (T_1), 1. saatte (T_2), 2. saatte (T_3), 3. saatte (T_4), 4. saatte (T_5), 5. saatte (T_6) ve 6. saatte (T_7) değerlendirildi. Ameliyat sonrası ilk 6 saatte VRS ≥2 olduğunda 1mg.kg^{-1} im meperidin ilave analjezik olarak yapıldı. Ameliyat sonrası ilk 6 saatteki yan etkiler (bulantı kusma ve ameliyat sonrası kanama) kaydedildi. T_1 ve T_2 ağrı skorları Grup T'de Grup L'den yüksek bulundu (sırasıyla p=0.049, p=0.007). İlk 6 saatte ilave analjezik gereksinimi olan olgu sayısı Grup L'de Grup T'den düşük bulundu. Bulantı kusma, ameliyattaki ve ameliyat sonrası kanama verilerinde gruplar arasında fark bulunmadı.*

Sonuç: *Erişkin hastalarda, posttonsillektomi ağrısı üzerine ameliyat öncesi uygulanan 8 mg lornoksikam 50 mg tramadolden daha etkin, yan etkileri ise benzerdir.*

Anahtar sözcükler: Analjezi/erişkin; lornoksikam; tonsilektomi; tramadol.

[1]Department of Anesthesiology and Reanimation, Gazi University Faculty of Medicine, Ankara, Turkey

[1]Gazi Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, Ankara

Submitted - July 18, 2008 ***(Başvuru tarihi - 18 Temmuz 2008)*** **Accepted for publication - November 25, 2008** ***(Kabul tarihi - 25 Kasım 2008)***

Correspondence ***(İletişim):*** Mustafa Arslan, M.D. Gazi Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, Ankara, Turkey.
Tel: +90 - 318 - 212 05 26 **Fax** ***(Faks):*** +90 - 318 - 212 44 00 **e-mail** ***(e-posta):*** mustarslan@gmail.com

Introduction

Tonsillectomy is one of the most commonly performed operations in ear, nose and throat (ENT) surgery. Postoperative pain is a significant problem in this group of patients.[1-5]

Posttonsillectomy pain has traditionally been controlled with morphine, resulting in a high incidence of postoperative nausea and vomiting (PONV) compared with other forms of analgesia. The incidence of PONV following tonsillectomy may be as high as 50–80%.[6-8] Respiratory depression and sedation from morphine may also be hazardous after pharyngeal surgery[9,10] when a prompt return of airway reflexes is required. In view of these side effects, alternative analgesic strategies have been suggested.

Non-steroidal anti-inflammatory drugs (NSAIDs) have a well-documented effect on acute postoperative pain.[11,12] NSAIDs may be given preemptively or at the end of surgery.[1,4,13-17] Recent researches have shown preemptive analgesia to be effective in perioperative pain.[18-20] In adults, some studies report significantly better analgesia with NSAIDs administered before surgery.[13,17,21] The anti-inflammatory and analgesic effect of NSAIDs is appropriate for treatment of pain after tonsillectomy.[2,4,5,14,15]

Lornoxicam (also known as chlorotenoxicam) is a NSAID that decreases prostaglandin synthesis by inhibition of cyclooxygenase. It has analgesic, antipyretic, and anti-inflammatory effects. The short plasma half-life (approximately 4 hours) of lornoxicam may provide advantages over other NSAIDs. Those with long plasma half-lives have previously been linked to a high incidence of adverse effects.[12] Trampitsch[13] concluded that lornoxicam administered preemptively in patients undergoing gynecological operation appeared to improve the quality of postoperative analgesia and led to reduced consumption of opioid analgesics.

Tramadol is a centrally-acting analgesic with low affinity for the opioid receptor, which has a plasma half-life of approximately 6-7 hours.[3,22,23]

Very few studies have addressed preoperative administration of NSAIDs in ENT surgery, and fewer studies have considered the effects of preemptive analgesia with lornoxicam.[13,21,24]

The aim of the present prospective study was to compare the efficacy and adverse effects of 8 mg lornoxicam with 50 mg tramadol in preoperative administration for treatment of pain during the first 6 hours postoperatively in adult patients following tonsillectomy.

Materials and Methods

Following Ethical Committee approval and receipt of informed consent, 40 adults with American Society of Anesthesiologists (ASA) physical status I or II, aged 18-55 years of both gender and undergoing tonsillectomy were allocated by randomization list to receive 8 mg lornoxicam (Group L) (Xefo®) or 50 mg tramadol (Group T) (Contramal®) immediately before induction of anesthesia. Patients were excluded if they had a known hypersensitivity to the study medications, asthma, kidney or liver dysfunction, or hematological disorder. Prolongation of operation and occurrence of complications were accepted as exclusion criteria.

Surgery type and anesthetic induction and management were standardized. After application of routine noninvasive monitors, an intravenous (iv) cannula was inserted. Immediately before the induction of anesthesia, the patients in Group T received iv tramadol 50 mg and the patients in Group L received iv lornoxicam (8 mg) according to the randomization list. The drugs were prepared and administered by an anesthesiologist who was not involved in the management of anesthesia or follow-up period to maintain the double-blind nature of the study.

Anesthesia was induced with 2 $mg.kg^{-1}$ propofol (Diprivan®), and tracheal intubation was facilitated with 0.5 $mg.kg^{-1}$ atracurium (Tracrium®). Anesthesia was maintained with 0.8±1.2% sevoflurane (Sevorane®) (end tidal concentration) in nitrous oxide (50%) and oxygen (50%), with intermittent positive pressure ventilation (IPPV) of the lungs. Controlled ventilation of the lung was continued throughout the anesthetic at a rate of 8-12 $breaths.min^{-1}$, tidal volume of 7-10 $mL.kg^{-1}$ and end-tidal

CO_2 concentration ($EtCO_2$) of 30-35%. During surgery, Ringer's lactate was infused at a rate of 5-8 $ml.kg^{-1}.h^{-1}$. Neuromuscular function was not measured. Residual neuromuscular block was reversed with 0.04 $mg.kg^{-1}$ neostigmine and 0.02 $mg.kg^{-1}$ atropine at the end of the surgery, and the patients' lungs were ventilated with 100% oxygen. The pharynx was visualized and suctioned, and the tracheal tube was removed.

All the procedures were performed by the same four surgeons, all with clinical experience of more than five years, using the same surgical technique. Surgeons were blinded to the patient groups. Perioperative bleeding was estimated by surgeons using the Five-Point Scale (Table 1).

An anesthesiologist who was blinded to the patient's group determined recovery times to awakening (opening eyes in response to a verbal command) and orientation to person, date and place at 1 min intervals after discontinuation of the anesthetics. After recovery, the patients were transferred to the post-anesthesia care unit (PACU). All the patients stayed at least 1 h in the PACU independent of whether or not they had gained discharge criteria earlier. Pain was assessed by Verbal Rating Scale (VRS) (Table 2) at arrival time to PACU (T_0), at T_0+30 min (T_1) in the PACU, and at T_0+60 min (T_2), T_0+2h (T_3), T_0+3h (T_4), T_0+4h (T_5), T_0+5h (T_6), and T_0+6h (T_7) in the ward during the first postoperative 6-h period.

Pain intensity was assessed by the anesthesiologist during swallowing. If the VRS was >2, 1 $mg.kg^{-1}$ meperidine was given intramuscularly (im). Patients requiring additional analgesics in the postoperative 6 hours were noted.

Nausea/vomiting and other adverse effects were also assessed in the postoperative 6-h period. Nausea and vomiting was assessed by Nausea Vomiting Scale (NVS) (Table 3). In case of vomiting (NVS ≥2), 10 mg metoclopropamide (Metpamide®) was administered by iv route.

If postoperative hemorrhagia was more than usual, it was assessed by the surgeon according to Table 4. The patients were observed by an anesthesiologist in the ward. The close observation was discontinued in the postoperative 6th hour.

Table 1. Preoperative bleeding

Clinical attidute	Score
No bleeding	0
Bleeding as usual	1
Bleeding more than usual	2
Profuse	3
Excessive	4
Excessive and continuously	5

Table 2. Verbal Rating Scale

Pain intensity	Score
No pain	0
Mild pain	1
Moderate pain	2
Severe pain	3
Excruciating pain	4

Table 3. Nausea and vomiting score

Nausea vomiting degree	Score
No any complaint	0
Mild degree nausea	1
Moderate degree nausea and vomit	2
Frequently vomit	3
Severely (continuously) vomit	4

Table 4. Postoperative haemorragia scale

Clinical attidute	Importance of haemorragia
No medical attention was required	Insignificant
Medical attention was required and iv fluid or suction of the clot was initiated	Minor
Electro-coater, re-operation, or blood transfusion was required	Major

Table 5. Patient demographics, duration of anesthesia and surgery

	Group L (n: 20)	Group T (n: 20)	p
Age (year)	29.3±8.2	28.9±9.8	0.889
Weight (kg)	66.4±10.8	66.2±13.7	0.959
Height (cm)	168.2±7.6	168.5±10.2	0.889
ASA (I/II)	18/2	19/1	0.545
Gender (F/M)	12/8	8/12	0.206
Duration of anesthesia (min)	72.3±17.1	83.9±33.4	0.177
Duration of surgery (min)	58.8±16.7	68.1±27.6	0.207

Values are presented as mean ± SD and number;
ASA: American Society of Anesthesiologists (physical status).

Table 6. Recovery parameters

	Group L (n: 20)	Group T (n: 20)	p
Opening eyes in response to a verbal command (min)	4.1±2.6	4.8±2.8	0.379
Orientation to person (min)	8.3±2.7	8.2±4.6	0.934
Orientation to place (min)	8.6±2.7	8.6±4.8	1.000
Orientation to time (min)	8.8±2.2	8.9±4.6	0.896

Values are presented as mean ± SD.

The patients were discharged from the hospital after 24 h if they were alert and cooperative and had only mild pain without nausea and vomiting. Patients were asked by the surgeon to present for follow-up on the postoperative 5th day, and to inform the anesthesiologist by telephone of any problems occurring during this period.

Statistical analysis

Before initiating the study, a power analysis suggested that a sample size of 20 patients in each group should be adequate to detect a 25% reduction in the total additional analgesic consumption with a power of 0.8 and α of 0.05.

Data were computer-processed for analyses. Demographic data, duration of anesthesia and surgery and recovery time of the groups were compared using Students'*t* test. Repeated measurements (heart rate [HR], systolic/diastolic artery blood pressure [SABP/DABP]) were analyzed using repeated-measures analysis of variance (ANOVA). Total additional analgesic consumption and pain scores (VRS) were studied with Mann-Whitney U test. Nominal data (ASA, gender, the need for "rescue" analgesics and incidence of side effects) were compared between groups using the chi-square or Fisher's exact test. Data are presented as mean, median values [±SD (25%-75%)], and numbers (n). A p value of <0.05 was considered significant.

Results

The study involved 40 patients, with 20 patients in each treatment group. No patient was excluded from the study for any reason, and the drugs were well-tolerated. There were no significant differences between the two groups with regard to demographic data, ASA physical status, the duration of surgery and anesthesia (Table 5) or recovery parameters in the early postoperative period (Table 6). Both groups had insignificant changes in SABP, DABP, saturation of oxygen (SpO_2) and HR in the perioperative period.

In the PACU, VRS scores at T_1 and T_2 were lower

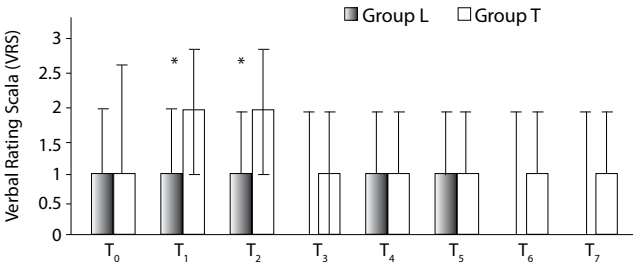

Fig. 1. Intensity of postoperative pain noted by Verbal Rating Scale (VRS). Data are presented as median (25%-75%). *p<0.05 for Group L vs Group T (Pain was assessed by VRS at arrival time to PACU (T_0), at T_0+30 min (T_1) in the PACU, and at T_0+60 min (T_2), T_0+2h (T_3), T_0+3h (T_4), T_0+4h (T_5), T_0+5h (T_6), and T_0+6h (T_7) in the ward during the first postoperative 6-h period).

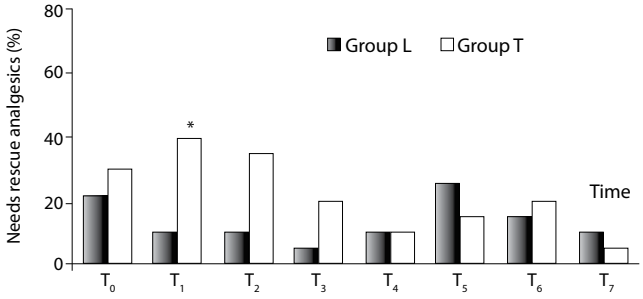

Fig. 2. Needs for meperidine as additional analgesics. Data are presented as n (%). *p<0.05 for Group L vs Group T (PACU (T_0), at T_0+30 min (T_1) in the PACU, and at T_0+60 min (T_2), T_0+2h (T_3), T_0+3h (T_4), T_0+4h (T_5), T_0+5h (T_6), and T_0+6h (T_7) in the ward during the first postoperative 6-h period).

in Group L than in Group T (p=0.049, p=0.007, respectively). However, the difference was not statistically significant at T_3, T_4, T_5, T_6 and T_7 time points in the ward (Fig. 1).

The proportion of the patients requiring additional analgesic was significantly lower in Group L at T_1 and T_2 (χ^2 =4.800, p=0.028, χ^2 =3.752, p=0.048, respectively) (Fig. 2). Twelve patients in Group L and 8 in Group T were not administered any meperidine.

Table 7. Per-operative bleeding

	Group L (n: 20)	Group T (n: 20)
No bleeding	–	–
Bleeding as usual	15 (75)	14 (70)
Bleeding more than usual	3 (15)	4 (20)
Profuse	2 (10)	2 (10)
Excessive	–	–
Excessive and continuously	–	–

Values are presented as (n (%)).

Additional meperidine consumption in patients who required meperidine was 48.8±9.5 mg in Group L and 65.5±14.5 mg in Group T, and the difference was statistically significant (p=0.006).

Perioperative bleeding by scoring the Five-Point Scale was similar in the two study groups (Table 7). Two patients from each group (n=4) were reported to have insignificant hemorrhage (more than usual but no medical attention was required) in the ward in the postoperative first six hours.

In the postoperative first six hours, 50% of the patients in Group T had nausea and vomiting (NVS ≥2), compared with 45% of the patients in Group L (NVS ≥2). Nevertheless, the differences were not significant at each time point (p=0.752) (Table 8). No patient reported a complication during the first five postoperative days.

Discussion

Recent trials have shown that pain after tonsillectomy is still a significant problem.[1-5]

Surgical trauma generates powerful nociceptive impulses that are generated by the procedure itself and by the action of proteolytic and inflammatory agents that are released following tissue injury. This release of inflammatory mediators may result in pain for several hours.

NSAIDs have analgesic effects that have been attributed to their peripheral anti-inflammatory actions in inhibiting the synthesis of prostaglandins through the inactivation of cyclooxygenase. This peripheral receptor action of the NSAIDs can thus indirectly inhibit central neural sensitization and consequently reduce the amplification of pain.[13,20,21]

Recent researches have shown preemptive analgesia by NSAIDs to be effective.[13,17,18,20,21]

In the preemptive analgesia, selection of the drug and dose are very important. It is concluded that 8

Table 8. Postoperative nausea and vomiting (NVS ≥2)

	T_0	T_1	T_2	T_3	T_4	T_5	T_6	T_7
Group L	1 (5)	2 (10)	2 (10)	0	1 (5)	1 (5)	1 (5)	1 (5)
Group T	3 (15)	2 (10)	3 (15)	0	0	2 (10)	0	0

Values are presented as (n (%)).

mg lornoxicam given preoperatively or postoperatively is effective in postoperative pain management.[13,25,26]

We did not find any clinical research comparing tramadol versus lornoxicam, which was administered preoperatively. But Ilias and Jansen[26] reported that iv lornoxicam at a dose of 8 mg is superior to placebo and at least as effective an iv tramadol 50 mg in relieving moderate to intolerable post hysterectomy pain. Staunstrup et al.[27] decided that im 16 mg lornoxicam offers a useful alternative to 100 mg tramadol for the treatment of moderate to severe pain. We determined that the pain scores (VRS) and the numbers of the patients requiring additional analgesic were significantly reduced in Group L as compared to Group T at T_1 and T_2. The number of patients who needed additional analgesics was fewer in Group L than in Group T at T_1 and T_2. Total meperidine consumption as an additional analgesic was less in Group L than in Group T in the postoperative first 6 hours. We believe the short half-life of lornoxicam, which we used in one dose in our study, also affected the decrease in the analgesic efficacy in Group L as determined at the other measurement times.

The dosage of iv tramadol used for preemptive analgesia was lower than the dosage recommended in the recent studies.[3,22] Therefore, we can only conclude that lornoxicam is significantly superior to tramadol at this dosage. The same study should be performed with a higher dosage of tramadol to confirm or refute our results. Nevertheless, the differences obtained during the first hour suggest that iv lornoxicam is better in the early postoperative period compared to tramadol.

One of the aims of analgesic premedication is to reduce the dose of the analgesics that will be used in the postoperative period. In our study, we observed that the number of patients needing analgesia was less in the lornoxicam group as was the amount of meperidine consumed.

The most important reason why the use of NSAIDs with the aim of providing postoperative analgesia should be avoided is the concern that they may cause bleeding. NSAIDs are known to increase the possibility of bleeding by inhibiting cyclooxygenase and thus inhibiting thrombocyte aggregation.[11,12] The incidence of perioperative bleeding, as well as many factors (kind of surgery, hemostatic problems) affecting this risk have been investigated. Studies estimate that 0.28-20% of normal patients have bleeding associated with tonsillectomy.[25,28-32]

While Castellano and Lopez-Escamez[28] have reported that ASA group is a good parameter to determine the incidence of bleeding after tonsillectomy, Krishna et al.,[29] after their meta-analysis including 1368 patients, indicated that the use of NSAID does not affect the incidence of postoperative bleeding in tonsillectomy. Moiniche's[30] quantitative systematic review analyzed 25 studies and concluded that although there is some evidence of an increased risk of reoperation because of bleeding with NSAIDs, the evidence is equivocal and the risk-benefit ratio is not straightforward. The review suggests that the agenda should be one of further research rather than clinical recommendations.

Lornoxicam has been used successfully in adults undergoing hysterectomy without any major perioperative bleeding.[13]

In this study, we decided to use a fairly small dose of lornoxicam, and 8 mg lornoxicam did not increase peroperative bleeding; however, two patients from each group experienced insignificant (more than normal but no medical attention was required) bleeding in the early postoperative period. Previous-

ly reported incidence rates of postoperative hemorrhage for patients undergoing tonsillectomy are similar.[25,28-32] However, further studies are required to show the safety of lornoxicam in this respect, and lornoxicam should be avoided for tonsillectomy in patients where increased blood loss poses a special risk as hemorrhagic diathesis.[12]

Previous studies indicate that vomiting occurs commonly after tonsillectomy and that vomiting is induced not only by opioids, but also by swallowed blood and oropharyngeal irritation.[33] In the present study, the incidence of early vomiting was only 5% in the lornoxicam group and 15% in the tramadol group. Although tramadol is reported to have high incidence of nausea and vomiting,[23] a significantly lower incidence of postoperative nausea occurred in the tramadol group. This may be due to the lower tramadol dose used (50 mg).

Lornoxicam and tramadol were well-tolerated, and adverse events were similar between the two groups. Preoperatively administered 8 mg lornoxicam appears more effective than 50 mg tramadol for use in adults as an early postoperative analgesic following tonsillectomy; side effects were similar between the two groups.

References

1. Salonen A, Kokki H, Nuutinen J. Recovery after tonsillectomy in adults: a three-week follow-up study. Laryngoscope 2002;112:94-8.
2. Salonen A, Kokki H, Nuutinen J. The effect of ketoprofen on recovery after tonsillectomy in children: a 3-week follow-up study. Int J Pediatr Otorhinolaryngol 2002;62:143-50.
3. Ozköse Z, Akçabay M, Kemaloğlu YK, Sezenler S. Relief of posttonsillectomy pain with low-dose tramadol given at induction of anesthesia in children. Int J Pediatr Otorhinolaryngol 2000;53:207-14.
4. Hiller A, Silvanto M, Savolainen S, Tarkkila P. Propacetamol and diclofenac alone and in combination for analgesia after elective tonsillectomy. Acta Anaesthesiol Scand 2004;48:1185-9.
5. Thorneman G, Akervall J. Pain treatment after tonsillectomy: advantages of analgesics regularly given compared with analgesics on demand. Acta Otolaryngol 2000;120:986-9.
6. Furst SR, Rodarte A. Prophylactic antiemetic treatment with ondansetron in children undergoing tonsillectomy. Anesthesiology 1994;81:799-803.
7. Hamid SK, Selby IR, Sikich N, Lerman J. Vomiting after adenotonsillectomy in children: a comparison of ondansetron, dimenhydrinate, and placebo. Anesth Analg 1998;86:496-500.
8. Morton NS, Camu F, Dorman T, Knudsen KE, Kvalsvik O, Nellgard P, et al. Ondansetron reduces nausea and vomiting after paediatric adenotonsillectomy. Paediatr Anaesth 1997;7:37-45.
9. Watters CH, Patterson CC, Mathews HM, Campbell W. Diclofenac sodium for post-tonsillectomy pain in children. Anaesthesia 1988;43:641-3.
10. Bone ME, Fell D. A comparison of rectal diclofenac with intramuscular papaveretum or placebo for pain relief following tonsillectomy. Anaesthesia 1988;43:277-80.
11. Kokki H. Nonsteroidal anti-inflammatory drugs for postoperative pain: a focus on children. Paediatr Drugs 2003;5:103-23.
12. Skjodt NM, Davies NM. Clinical pharmacokinetics of lornoxicam. A short half-life oxicam. Clin Pharmacokinet 1998;34:421-8.
13. Trampitsch E, Pipam W, Moertl M, Sadjak A, Dorn C, Sittl R, Likar R. Preemptive randomized, double-blind study with lornoxicam in gynecological surgery. Schmerz 2003;17:4-10.
14. Turan A, Emet S, Karamanlioğlu B, Memiş D, Turan N, Pamukcu Z. Analgesic effects of rofecoxib in ear-nose-throat surgery. Anesth Analg 2002;95:1308-11.
15. White MC, Nolan JA. An evaluation of pain and postoperative nausea and vomiting following the introduction of guidelines for tonsillectomy. Paediatr Anaesth 2005;15:683-8.
16. Forrest JB, Camu F, Greer IA, Kehlet H, Abdalla M, Bonnet F, et al. Ketorolac, diclofenac, and ketoprofen are equally safe for pain relief after major surgery. Br J Anaesth 2002;88:227-33.
17. Priya V, Divatia JV, Sareen R, Upadhye S. Efficacy of intravenous ketoprofen for pre-emptive analgesia. J Postgrad Med 2002;48:109-12.
18. Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia I: physiological pathways and pharmacological modalities. Can J Anaesth 2001;48:1000-10.
19. Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia II: recent advances and current trends. Can J Anaesth 2001;48:1091-101.
20. Kissin I. Preemptive analgesia. Anesthesiology 2000;93:1138-43.
21. Oztekin S, Hepağuşlar H, Kar AA, Ozzeybek D, Artikaslan O, Elar Z. Preemptive diclofenac reduces morphine use after remifentanil-based anaesthesia for tonsillectomy. Paediatr Anaesth 2002;12:694-9.
22. Courtney MJ, Cabraal D. Tramadol vs. diclofenac for post-tonsillectomy analgesia. Arch Otolaryngol Head Neck Surg 2001;127:385-8.
23. Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. Drugs 2000;60:139-76.
24. O'Hanlon DM, Thambipillai T, Colbert ST, Keane PW, Given HF. Timing of pre-emptive tenoxicam is important for postoperative analgesia. Can J Anaesth 2001;48:162-6.
25. Rosenow DE, Krieken F. Intravenous administration of lornoxicam, a new NSAID, and pethidine for postoperative pain. A placebo-controlled pilot study. Clin Drug Invest 1996;11:11-9.
26. Ilias W, Jansen M. Pain control after hysterectomy: an observer-blind, randomised trial of lornoxicam versus tramadol. Br J Clin Pract 1996;50:197-202.
27. Staunstrup H, Ovesen J, Larsen UT, Elbaek K, Larsen U, Krøner K. Efficacy and tolerability of lornoxicam versus tramadol in postoperative pain. J Clin Pharmacol 1999;39:834-41.
28. Castellano P, López-Escámez JA. American Society of Anesthesiology classification may predict severe post-tonsillectomy haemorrhage in children. J Otolaryngol 2003;32:302-7.

29. Krishna S, Hughes LF, Lin SY. Postoperative hemorrhage with nonsteroidal anti-inflammatory drug use after tonsillectomy: a meta-analysis. Arch Otolaryngol Head Neck Surg 2003;129:1086-9.
30. Møiniche S, Rømsing J, Dahl JB, Tramèr MR. Nonsteroidal antiinflammatory drugs and the risk of operative site bleeding after tonsillectomy: a quantitative systematic review. Anesth Analg 2003;96:68-77.
31. Bhattacharyya N. Evaluation of post-tonsillectomy bleeding in the adult population. Ear Nose Throat J 2001;80:544-9.
32. Collison PJ, Weiner R. Harmonic scalpel versus conventional tonsillectomy: a double-blind clinical trial. Ear Nose Throat J 2004;83:707-10.
33. Hall DJ, Littlefield PD, Birkmire-Peters DP, Holtel MR. Radiofrequency ablation versus electrocautery in tonsillectomy. Otolaryngol Head Neck Surg 2004;130:300-5.