The Journal of Laryngology & Otology

cambridge.org/jlo

Peritonsillar infiltration of lidocaine with adrenaline is associated with increased risk of secondary post-tonsillectomy haemorrhage

H K Tolska[1], A J Takala[1] and J Jero[2]

[1]Division of Anesthesiology, Department of Anesthesiology, Intensive Care and Pain Medicine, University of Helsinki and Helsinki University Hospital, and [2]Department of Otorhinolaryngology – Head and Neck Surgery, Turku University Hospital, Finland

Main Article

Dr H K Tolska takes responsibility for the integrity of the content of the paper

Cite this article: Tolska HK, Takala AJ, Jero J. Peritonsillar infiltration of lidocaine with adrenaline is associated with increased risk of secondary post-tonsillectomy haemorrhage. *J Laryngol Otol* 2018;**132**:911–922. https://doi.org/10.1017/S0022215118001731

Accepted: 5 April 2018
First published online: 9 October 2018

Key words:
Tonsillectomy; Non-Steroidal Anti-Inflammatory Agents; Dexamethasone; Lidocaine; Adrenaline

Author for correspondence:
Dr Hanna Kaisa Tolska,
Division of Anesthesiology,
Department of Anesthesiology,
Intensive Care and Pain Medicine,
University of Helsinki and Helsinki University Hospital, Kasarmikatu 11–13,
PO Box 263, 00029 HUS, Finland
E-mail: kaisa.tolska@hus.fi

Abstract

Objectives. In order to evaluate the safety of tonsillectomy among children, we retrospectively studied the incidence of post-operative complications, adverse events and their association with peri-operative medication.

Methods. Data were collected from the medical records of 691 patients aged 1–16 years, including details of post-operative complications (any unplanned contact with the hospital), analgesics, dexamethasone, 5-HT_3 antagonists, local anaesthetic and haemostatic agents.

Results. Recovery was complicated in 13.6 per cent of patients, of whom 8.4 per cent were re-admitted to the ward. The most common complication was post-tonsillectomy haemorrhage, experienced by 7.1 per cent of patients. Re-operation under general anaesthesia (for grade III post-tonsillectomy haemorrhage) was required by 4.2 per cent of patients. Peritonsillar infiltration of lidocaine with adrenaline increased the risk of post-tonsillectomy haemorrhage (odds ratio = 4.1; 95 per cent confidence interval = 2.1 to 8.3).

Conclusion. Every seventh paediatric patient experienced a complicated recovery after tonsillectomy, caused by post-tonsillectomy haemorrhage in most cases. Local peritonsillar infiltration of lidocaine with adrenaline was associated with an increased risk of post-tonsillectomy haemorrhage.

Introduction

Elective tonsillectomy is among the most common paediatric out-patient operations and should be as safe as possible. However, recovery after tonsillectomy may be complicated by such morbidities as bleeding, intense pain, post-operative nausea and vomiting, dehydration, respiratory complications, and fever.[1,2] A systematic review of paediatric out-patient tonsillectomy reported an overall complication rate of 8.8 per cent within the first 24 hours of operation and an unplanned re-admission rate of 3–16 per cent.[3] Prospective research from our institution revealed that 17 per cent of patients' caregivers called healthcare professionals for instructions and 13 per cent visited a physician in person following tonsillectomy.[4]

The risk of post-tonsillectomy haemorrhage varies in different reports because of inconsistent criteria. Registry-based studies tend to underestimate the frequency of post-tonsillectomy haemorrhage, as they include only the most severe cases.[5]

Post-tonsillectomy haemorrhage is often divided into two categories based on timing. Primary post-tonsillectomy haemorrhage occurs within 24 hours of the operation. Secondary post-tonsillectomy haemorrhage occurs after 24 hours following the operation, with a maximal occurrence on post-operative days 6–7.[6]

Post-tonsillectomy pain has been reported as the most common reason to contact healthcare professionals, yielding a re-admission rate of 5–10 per cent.[7,8] Non-steroidal anti-inflammatory drugs (NSAIDs) have an opioid-sparing effect and are suitable for post-operative analgesia at home.[9] The association between NSAID administration and increased risk of post-tonsillectomy haemorrhage has been studied over the years, with conflicting results.[10,11] Local anaesthetics have been used as part of a multimodal anaesthesia and their beneficial effect has been confirmed in some studies.[12,13]

The reported incidence of post-operative nausea and vomiting after tonsillectomy is 35–75 per cent without anti-emetic prophylaxis; it results in poor oral intake, dehydration, an inability to take oral analgesics and prolonged hospital stay.[14] Dexamethasone and 5-HT_3 antagonists are effective in preventing post-operative nausea and vomiting.[14–16] Dexamethasone also reduces post-operative pain; however, its use in tonsillectomies has been questioned for safety reasons.[17–19]

Post-operative fever is common, usually low-grade and benign, and does not correlate with bacteraemia; it is considered being part of the acute phase reaction to surgical trauma.[20]

To characterise the safety of paediatric tonsillectomy, we retrospectively analysed the incidence of post-operative complications and their possible association with the use of

Table 1. Patients' characteristics

Characteristic	All patients*	Aged 1–7 years†	Aged 8–16 years‡	*p*
Age (median (range); years)	6.8 (1.0–16)	5.0 (1.0–7)	10.9 (8–16)	NA
Operation duration (median (range); minutes)	20 (3–88)	20 (5–88)	20 (3–73)	ns
Females/males (*n* (%))	338 (54) / 353 (51)	170 (43) / 223 (57)	168 (56) / 130 (44)	0.001
ASA I/II/III (*n*)	592 / 93 / 7	334 / 54 / 5	258 / 38 / 2	ns

*$n = 691$; †$n = 393$; ‡$n = 298$. NA = not applicable; ns = non-significant; ASA = American Society of Anesthesiology risk classification

NSAIDs, dexamethasone, acetaminophen and 5-HT_3 antagonists, local infiltration of lidocaine with adrenaline, and haemostatic agents.

Materials and methods

The study was performed at the Department of Otorhinolaryngology, Helsinki University Hospital, Finland, with approval of the institutional ethics committee.

We retrospectively collected data for patients aged 1–16 years who underwent out-patient tonsillectomy, with or without adenoidectomy, during a 12-month period (from 1 May 2007 to 30 April 2008). National Statistics Finland provided the 28-day mortality data for patients with a benign post-operative diagnosis. Each patient's medical records provided details regarding demographics, indication (post-operative diagnosis), operation time, peri-operative medication and type of post-operative complications. A complication was defined as any unplanned contact with the hospital's health-care professionals that resulted in medical treatment within a one-month post-operative period.

Bleeding episodes were classified according to the criteria proposed by Windfur and Seehafer: grade I = bleeding stopped spontaneously or after clot removal; grade II = direct pressure or minor electrocautery under local anaesthesia required; and grade III = re-operation under general anaesthesia required.[21] If a patient experienced multiple episodes of post-tonsillectomy haemorrhage, only the first bleeding episode was considered for that patient, to ensure that only post-tonsillectomy haemorrhage associated with the primary operation was included in the analysis.

The haemostatic procedure for paediatric patients aged under seven years is usually performed under general anaesthesia, and for older patients it is carried out either under local or general anaesthesia depending on their co-operation.

Dehydration was diagnosed as reported in the medical record based on the clinical examination. Infection was determined based on empirical antibiotic treatment given in light of the clinical presentation. Pneumonia was diagnosed with a clinical examination and chest X-ray.

Patients are not routinely screened for haemostasis abnormalities; however, a questionnaire is used to assess their history of unexceptional bleeding or tendency for bruises. Patients with positive results receive a more thorough questionnaire and specific laboratory tests are ordered.

During the study period, 272 patients underwent tonsillectomy and 422 patients underwent adenotonsillectomy. Three tonsillectomies were performed as part of a combined surgical procedure (neck cyst operations); these patients were excluded from the analysis. Thus, the study patient population consisted of 691 patients (269 primarily operated on for tonsillectomy, and 422 for tonsillectomy combined with adenoidectomy). A total of 626 patients (91 per cent) were discharged on the day of the operation.

Two age groups were analysed separately: 1–7 years (median of 5.0 years) and 8–16 years (median of 10.9 years). The two groups were comparable in terms of demographics, except for the female-to-male ratio (Table 1). In the younger age group, males were over-represented, whereas in the older group they were under-represented (Table 1).

All 43 surgeons used the same technique of cold dissection with bipolar cautery haemostasis. The most frequent indications for the operations were: hypertrophy of tonsils, with or without adenoid hypertrophy (69 per cent), and chronic tonsillitis (14 per cent).

All operations were performed under standard general anaesthesia; the airway was secured with an intubation tube, and anaesthesia was maintained with sevoflurane 1.5–3 per cent and nitrous oxide 50 per cent in a mixture of oxygen. Intravenous dexamethasone and 5-HT_3 antagonists were used to prevent post-operative nausea and vomiting.

Non-steroidal anti-inflammatory drugs, acetaminophen and tramadol were used to prevent and treat post-operative pain peri-operatively. An intravenous haemostatic agent (systemic tranexamic acid) was used in cases of increased bleeding tendency. Twenty-eight surgeons used peritonsillar infiltration of lidocaine 10 mg ml^{-1} containing adrenaline 10 μg ml^{-1} for 130 patients before tonsil removal to facilitate the operation and prevent post-operative pain. Twenty-one surgeons used the topical haemostatic agent bismuth subgallate paste for 52 patients, and 14 surgeons used a combination of lidocaine with adrenaline and topical bismuth subgallate for 47 patients. Patients were monitored in the post-anaesthesia care unit for adverse effects. Intravenous oxycodone served as a rescue analgesic.

We analysed the data to determine the incidence of adverse events and post-operative complications and examine their association with peri-operative medication. The results are presented as medians with ranges. We performed the statistical analysis using the Mann–Whitney U test for continuous data and the Pearson chi-square test for categorical data. We calculated the odds ratio with 95 per cent confidence interval (CI) for factors predisposing to post-operative complications. Multicollinearity and confounding factors were analysed using a regression analysis. Statistical significance was set at $p < 0.05$. IBM SPSS Statistics version 22 was used to perform the statistical analysis. Confidence interval analysis software, CIA version 2.1.2 (Trevor Bryant, London, UK), was used to calculate the CI limit of the difference.

Results

Of the 691 patients included in the study, recovery was complicated (i.e. there was unplanned contact with the hospital)

https://doi.org/10.1017/S0022215118001731 Published online by Cambridge University Press

Table 2. Post-operative complications after tonsillectomy with or without adenoidectomy

Complication	All patients*	Aged 1–7 years†	Aged 8–16 years‡	p**
All complications	94 (13.6)	60 (15.2)	34 (11.4)	ns
Post-tonsillectomy haemorrhage	49 (7.1)	28 (7.1)	21 (7.0)	ns
– Primary	4 (0.6)	3 (0.8)	1 (0.3)	ns
– Secondary	45 (6.5)	25 (6.3)	20 (6.7)	ns
– Grade I	8 (0.2)	7 (1.0)	1 (0.3)	ns
– Grade II	12 (1.7)	3 (0.8)	9 (3.0)	0.025
– Grade III	29 (4.2)	18 (4.6)	11 (3.7)	ns
Pain	21 (3.0)	15 (3.8)	6 (2.0)	ns
Fever	16 (2.3)	12 (3.1)	4 (1.3)	ns
Infections other than pneumonia	12 (1.7)	8 (2.0)	4 (1.3)	ns
Pneumonia	3 (0.4)	2 (0.5)	1 (0.3)	ns
Post-operative nausea & vomiting	6 (0.9)	3 (0.8)	3 (1.0)	ns
Re-admission	58 (8.4)	34 (8.7)	24 (8.1)	ns

Data represent numbers and percentages of patients. *$n = 691$; †$n = 393$; ‡$n = 298$. **P-value calculated for the difference between patients aged 1–7 years and 8–16 years. ns = non-significant

in 94 patients (13.6 per cent) (Table 2). Sixty-nine patients (10.0 per cent) visited a physician and 58 patients (8.4 per cent) were re-admitted to the ward.

The most common post-operative complication was post-tonsillectomy haemorrhage. This was experienced by 49 patients (7.1 per cent), all of whom were admitted to the ward for follow up (Table 2). Twenty-nine patients experienced grade III post-tonsillectomy haemorrhage (4.2 per cent risk of re-operation). Seven patients experienced several episodes of post-tonsillectomy haemorrhage (five patients had two episodes and two patients had three episodes). Five patients required red blood cell transfusion because of secondary post-tonsillectomy haemorrhage, of which three had received either lidocaine with adrenaline, or lidocaine combined with adrenaline and bismuth subgallate (all were male). All post-tonsillectomy haemorrhage episodes occurred within 18 days of the primary operation; the highest number (of first bleeding episodes) occurred on post-operative day 7 (Figure 1). Two patients suffered two types of complications, both after secondary post-tonsillectomy haemorrhage; one suffered pneumonia (above), and the other experienced fever and cough with a normal chest X-ray and without the need for antibiotics. There were no 28-day or 1-year mortalities.

Post-operative complication rates were comparable between the younger (1–7-year-old) and the older (8–16-year-old) patients. However, older patients experienced more grade II bleeding events than younger patients (3.0 per cent *vs* 0.8 per cent, $p = 0.025$). This is explained by the more common use of haemostatic procedures performed under local anaesthesia in the older age group.

Non-steroidal anti-inflammatory drugs, acetaminophen, oxycodone, dexamethasone and 5-HT_3 antagonists were used commonly (Table 3); they were not associated with an increased risk of any post-operative complications.

Patients who received intravenous tranexamic acid had a comparable risk of post-tonsillectomy haemorrhage as those patients who did not ($p = 0.6$). Patients who received local anaesthetic or topical haemostatic agents, or both, experienced post-tonsillectomy haemorrhage more often than those who did not (13.6 per cent *vs* 3.8 per cent, $p < 0.001$; 9.8 per cent difference (95 per cent CI of difference = 6 to 1 per cent), odds ratio = 4.0 (95 per cent CI = 2.2 to 7.4)).

The use of lidocaine with adrenaline was associated with an increased risk of secondary post-tonsillectomy haemorrhage in both age groups, and a risk of grade III post-tonsillectomy haemorrhage among patients aged 8–16 years (Table 4). Bismuth subgallate alone did not alter the risk of post-tonsillectomy haemorrhage. The combination of lidocaine with adrenaline and bismuth subgallate increased the risk of secondary post-tonsillectomy haemorrhage in both age groups, and increased the risk of grade III post-tonsillectomy haemorrhage among patients aged one to seven years (Table 4). The frequency of secondary post-tonsillectomy haemorrhage started to increase on post-operative days 6–7 (Figures 2 and 3). The use of NSAIDs, acetaminophen, dexamethasone or tramadol did not have any multicollinearity regarding the association with an increased risk of post-tonsillectomy haemorrhage due to lidocaine with adrenaline, or the combination of lidocaine with adrenaline and bismuth subgallate.

In order to evaluate the influence of surgeons on the risk of post-tonsillectomy haemorrhage, they were divided into two categories based on their individual overall risk of post-tonsillectomy haemorrhage. Group 1 surgeons had less than 14 per cent risk of post-tonsillectomy haemorrhage (39 surgeons). Group 2 surgeons had more than 14 per cent risk of post-tonsillectomy haemorrhage (4 surgeons). When no local anaesthetic or topical haemostatic were used, the risk of post-tonsillectomy haemorrhage was similar in both groups (group 1 = 3.6 per cent; group 2 = 4.4 per cent). Local anaesthetic or topical haemostatic was used in 28 per cent of cases in group 1, and in 58 per cent of cases in group 2.

In group 2 surgeons, the risk of post-tonsillectomy haemorrhage was higher among patients who received lidocaine with adrenaline compared to those who did not receive any local anaesthetic or haemostatic agent (24.6 per cent (14 out of 57) *vs* 4.4 per cent (3 out of 68), $p = 0.001$; 20.2 per cent difference (95 per cent CI of difference = 8 to 33 per cent), odds ratio = 7.1 (95 per cent CI = 1.9 to 26.1)); whereas, in group 1, the risk was similar (7.1 per cent (4 out of 73) *vs* 3.6 per cent (14 out of 387), $p < 0.45$; 3.5 per cent of difference (95 per cent CI of difference = −2 to 9.8 per cent)). In group 2, patients who received the combination of lidocaine with adrenaline and bismuth subgallate had a higher risk of

https://doi.org/10.1017/S0022215118001731 Published online by Cambridge University Press

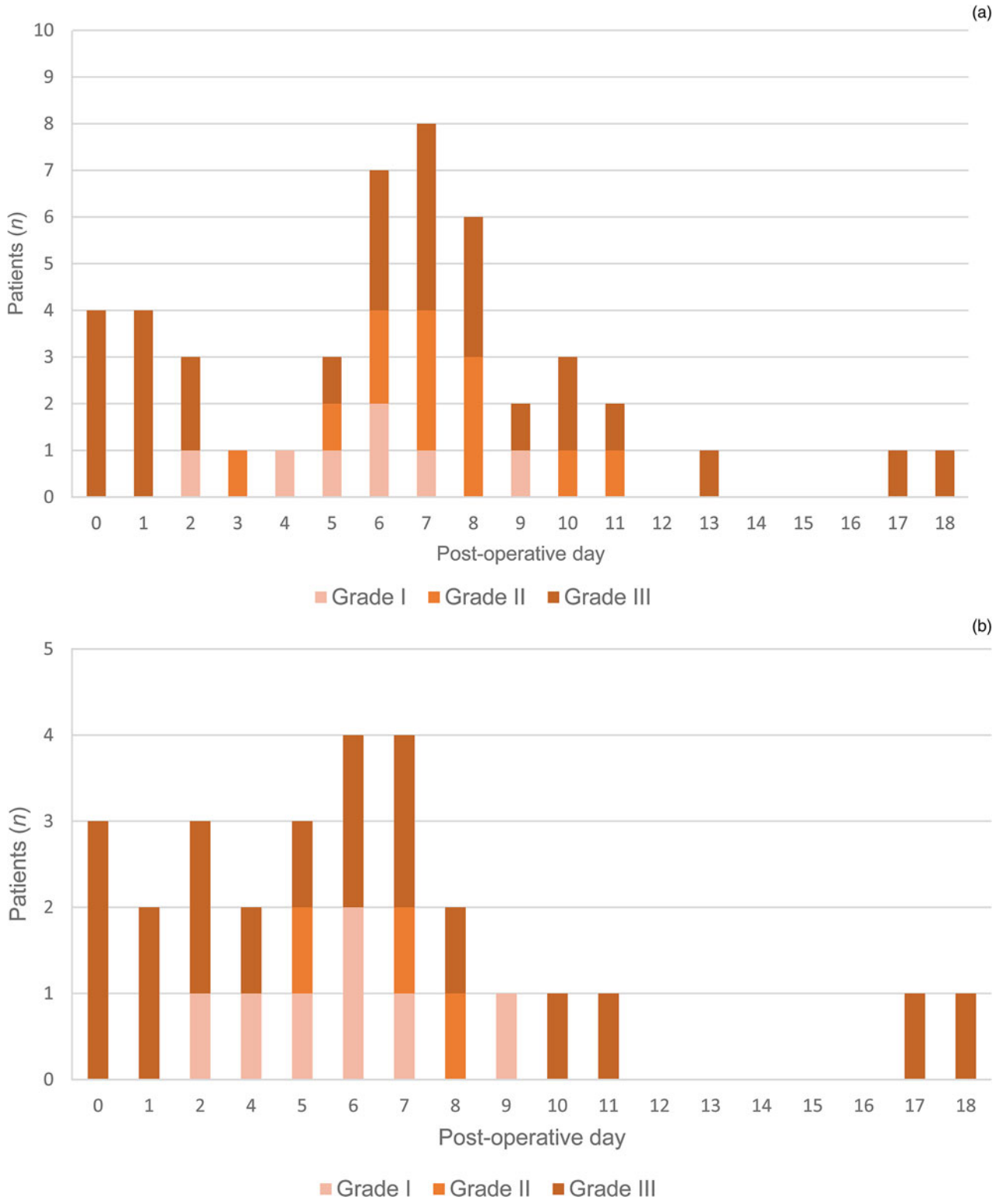

Fig. 1. Grade of post-operative haemorrhage episodes in relation to post-operative days for: (a) all patients, (b) patients aged 1–7 years and (c) patients aged 8–16 years. Grade I = bleeding stopped spontaneously or after clot removal; grade II = bleeding required direct pressure or minor electrocautery under local anaesthesia; and grade III = bleeding required re-operation under general anaesthesia. If a patient experienced several post-tonsillectomy haemorrhage episodes, only first one was included.

post-tonsillectomy haemorrhage compared to those who did not receive any local anaesthetic or haemostatic agent (24.1 per cent (7 out of 29) *vs* 4.4 per cent (3 out of 68), $p < 0.001$; 19.7 per cent of difference (95 per cent CI of difference = 5.5 to 37.9 per cent), odds ratio = 12.7 (95 per cent CI = 2.9 to 55.9) (all bleeding episodes occurred with one out of two surgeons); whereas in group 1 the risk was similar (11.1 per cent (2 out of 18) *vs* 3.6 per cent (14 out of 387), $p = 0.35$, 7.5 per cent difference (95 per cent CI of difference = −0.9 to 29.2) (2 out of 12 surgeons).

Tonsillectomy performed with or without adenoidectomy was not associated with post-operative complication rates other than post-operative nausea and vomiting. Patients who underwent tonsillectomy experienced more post-operative nausea and vomiting than those who underwent tonsillectomy with adenoidectomy (5 out of 269 (1.8 per cent) *vs* 1 out of 422

https://doi.org/10.1017/S0022215118001731 Published online by Cambridge University Press

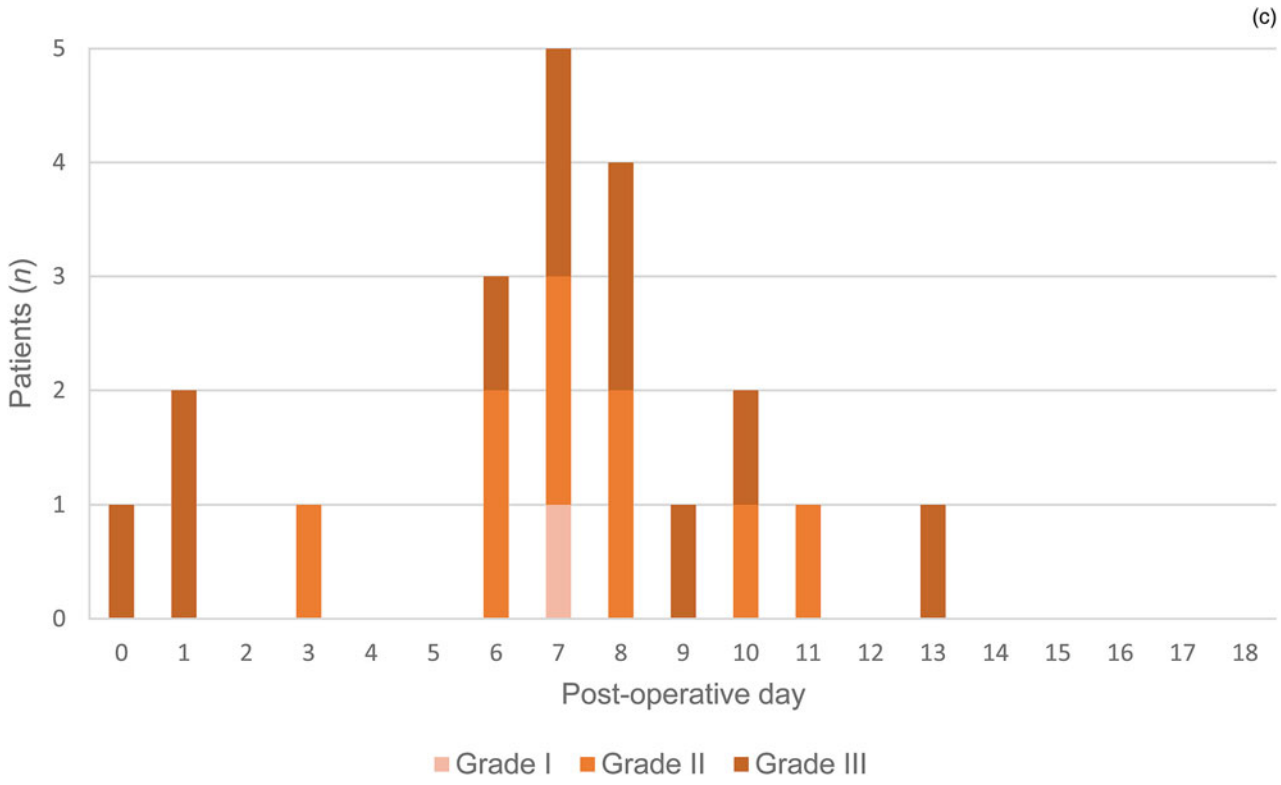

Fig. 1. (*continued*)

(0.2 per cent), $p = 0.025$; odds ratio = 0.13 (95 per cent CI = 0.2 to 1.1)); however, the number of patients was small and the difference did not appear in separate age groups.

Discussion

In the present study, unplanned contact with the hospital (13.6 per cent), visits (10.0 per cent) and re-admissions (8.4 per cent) were less frequent than in the previous study conducted in our clinic, although more common than in some other studies.[3,4,22,23] In a prospective cohort study that included 614 out-patient tonsillectomy patients (73 per cent under the age of 16 years), unplanned post-operative hospital contact was observed among 23 per cent of patients (for pain in 12 per cent, bleeding in 4 per cent, and post-operative nausea and vomiting in 2.4 per cent), and 5 per cent were re-admitted to the hospital.[22] In a registry-based study of 39 906 children aged under 18 years, unplanned return visits to the hospital were observed among 6.3 per cent of patients (for bleeding in 2.3 per cent, dehydration in 2.3 per cent and pain in 1.2 per cent), and 0.6 per cent were re-admitted.[23]

The most frequent post-operative complication was post-tonsillectomy haemorrhage; the overall institutional risk of post-tonsillectomy haemorrhage was 7.1 per cent and the risk of grade III bleeding was 4.2 per cent. These results are in line with other institutions. A literature review by Blakley reported a mean post-tonsillectomy haemorrhage rate (typically grade III post-tonsillectomy haemorrhage) of 4.5 per cent among various institutions, suggesting that rates around 5 per cent are typical and rates above 14 per cent require monitoring.[24] In our study, we included grade I post-tonsillectomy haemorrhage (minor bleeding events); this may appear as a higher overall risk of post-tonsillectomy haemorrhage in our institution compared to other institutions. Three of five patients who required red blood cell transfusion because of secondary post-tonsillectomy haemorrhage had received local anaesthetic or topical haemostatic agents. These transfusions could theoretically be related to an unprofitable effect of these agents; however, the number of patients was too small to draw any conclusions. All patients were male, which is a known predisposing risk factor for post-tonsillectomy haemorrhage.[25]

Lidocaine with adrenaline was unexpectedly associated with an increased risk of secondary post-tonsillectomy haemorrhage in all patient groups, and a risk of grade III post-tonsillectomy haemorrhage among patients aged 8–16 years. The combination of lidocaine with adrenaline and bismuth subgallate increased the risk of secondary post-tonsillectomy haemorrhage among all patients even more than lidocaine with adrenaline alone. Lidocaine with adrenaline has vasoconstrictor and platelet aggregation properties. Bismuth subgallate enhances factor XII function and accelerates the intrinsic clotting cascade that promotes coagulation. Both adrenaline and bismuth subgallate have been shown to reduce peri-operative blood loss, operation time, and incidence of primary post-tonsillectomy haemorrhage, with no influence on secondary post-tonsillectomy haemorrhage.[26–28] Historically, lidocaine with adrenaline has been suspected of increasing the risk of post-tonsillectomy haemorrhage because it masks inadequate haemostasis arising from vasoconstriction, but to our knowledge this has not been reported.[29]

The frequency of secondary post-tonsillectomy haemorrhage associated with the use of lidocaine with adrenaline started to rise on days 6–7 post-operatively. Its appearance so many days post-operatively is surprising. It would have been more logical for secondary post-tonsillectomy haemorrhage to occur much earlier (e.g. on post-operative days 0–2), as the vasoconstrictive effect of adrenaline wears off. This phenomenon may be explained by an impaired wound healing process due to both adrenaline and lidocaine. Systemically or locally administered

https://doi.org/10.1017/S0022215118001731 Published online by Cambridge University Press

Table 3. Drugs administered on operation day and differences between age groups

Drugs administered	All patients*		Patients aged 1–7 years†		Patients aged 8–16 years‡		p**
	Patients (n (%))	Dose (median (range); mg kg^{-1})	Patients (n (%))	Dose (median (range); mg kg^{-1})	Patients (n (%))	Dose (median (range); mg kg^{-1})	
Intravenous							
– Oxycodone	650 (94.1)	0.09 (0.03–0.25)	374 (95.2)	0.9 (0.0–0.3)	276 (92.6)	0.09 (0.0–0.3)	ns
– Ketoprofen	618 (89.4)	2.5 (0.9–6.0)	350 (89.1)	2.7 (1.0–6.0)	268 (89.9)	2.4 (0.9–5.0)	ns
– Diclofenac	34 (4.9)	2.0 (0.9–5.0)	14 (3.6)	2.1 (0.9–5.0)	20 (6.7)	1.8 (1.3–3.7)	ns
– Acetaminophen	373 (54.0)	20.0 (1.6–76.9)	204 (51.9)	22 (2.9–76.9)	169 (56.7)	18.2 (1.6–66.7)	ns
– Tramadol	27 (3.9)	1.9 (1–3)	19 (4.8)	2.0 (1–3)	8 (2.7)	1.4 (1–2)	ns
– Dexamethasone	541 (78.3)	0.3 (0–1)	314 (79.9)	0.4 (0–1)	227 (76.1)	0.2 (0.03–0.7)	0.001
– Ondansetron	100 (14.5)	0.06 (0.02–0.1)	64 (16.3)	0.06 (0.1–0.15)	36 (12.1)	0.05 (0.02–0.1)	0.013
– Granisetron	15 (2.2)	0.02 (0.01–0.1)	5 (1.3)	0.03 (0.02–0.05)	10 (3.4)	0.02 (0.01–0.1)	ns
Haemostatic agents							
– All	256 (37.0)		140 (35.6)		116 (38.9)		ns
– Intravenous (tranexamic acid)	23 (3.3)		10 (2.5)		13 (4.4)		ns
– Intravenous & local	3 (0.4)		2 (0.5)		1 (0.3)		NA
– Local	236 (34.1)		132 (33.6)		104 (34.9)		ns
– Lidocaine with adrenaline	130 (18.8)		67 (17.0)		63 (21.1)		ns
– Bismuth subgallate	59 (8.5)		38 (9.7)		21 (7.0)		ns
– Lidocaine with adrenaline & bismuth subgallate	47 (6.8)		27 (6.9)		20 (6.7)		ns

*n = 691; †n = 393; ‡n = 298. **P-value is calculated for the difference between patients aged 1–7 years and 8–16 years. ns = non-significant; NA = not available

Table 4. Association of local lidocaine with adrenaline alone and in combination with topical bismuth subgallate to post-tonsillectomy haemorrhage

	All patients*				Patients aged 1–7 years†				Patients aged 8–16 years‡			
Haemostatic agents	Yes (*n* (%))	No (*n* (%))	*p***	OR (95% CI)	Yes (*n* (%))	No (*n* (%))	*p***	OR (95% CI)	Yes (*n* (%))	No (*n* (%))	*p***	OR (95% CI)
Lidocaine with adrenaline	130 (19)	455 (66)			67 (17)	261 (66)			63 (21)	194 (65)		
Post-tonsillectomy haemorrhage	18 (13.8)	17 (3.7)	<0.001	4.1 (2.1–8.3)	8 (12)	10 (4)	0.009	3.4 (1.3–9.0)	10 (16)	7 (4)	0.001	5.0 (1.8–13.9)
– Grade I	4 (3.1)	2 (0.4)	0.008	7.2 (1.3–40)	3 (5)	2 (1)	0.03	6.1 (1.0–37.1)	1 (2)	0 (0)	0.8	
– Grade II	4 (3.1)	4 (0.9)	0.06		2 (3)	0 (0)	0.005		2 (3)	4 (2)	0.6	
– Grade III	10 (7.7)	11 (2.4)	0.004	3.4 (1.4–8.1)	3 (5)	8 (3)	0.6		7 (11.1)	3 (1.5)	0.001	8.0 (2.0–31.8)
– Primary	1 (0.7)	2 (0.4)	0.6		0 (0)	2 (0.8)	NA		1 (1.6)	0 (0)	0.8	
– Secondary	17 (13.1)	15 (3.3)	<0.001	4.4 (2.1–9.1)	8 (12)	8 (3)	0.003	4.3 (1.5–11.9)	9 (14.3)	7 (3.6)	0.002	4.5 (1.6–12.5)
Lidocaine with adrenaline & bismuth subgallate	47 (6.8)	455 (66)			27 (6.9)	261 (66)			20 (6.7)	194 (66)		
Post-tonsillectomy haemorrhage	9 (19)	17 (10.3)	<0.001	6.1 (2.5–14.6)	6 (22)	10 (4)	<0.001	7.2 (2.4–21.7)	3 (15)	8 (4)	0.04	4.1 (1–17)
– Grade I	2 (4)	2 (0.4)	0.005	10 (1.4–73.2)	2 (7.4)	2 (0.8)	0.005	10 (1.4–76.7)	0 (0)	0 (0)	NA	
– Grade II	3 (6)	4 (0.9)	0.002	7.7 (1.7–35.5)	1 (3.8)	0 (0)	0.002		2 (10)	5 (2)	0.07	
– Grade III	4 (9)	11 (2)	0.02	3.8 (1.1–12.3)	3 (11.1)	8 (3)	0.04	4 (1.0–15.9)	1 (5.0)	3 (1.5)	0.3	
– Primary	0 (0)	2 (0.4)	0.7	NA	0 (0)	2 (0.8)	0.7		0 (0)	0 (0)		
– Secondary	9 (19)	15 (3)	<0.001	6.9 (2.9–16.9)	6 (22.2)	8 (3)	<0.001	9.0 (2.9–28.5)	3 (15)	8 (4)	0.04	4.1 (1–17)

*$n = 691$; †$n = 393$; ‡$n = 298$. **P-value is calculated for the difference between patients who received lidocaine with adrenaline alone or in combination with bismuth subgallate, and those patients who did not receive any local anaesthetic or topical haemostatic agents.
OR = odds ratio; CI = confidence interval; NA = not available

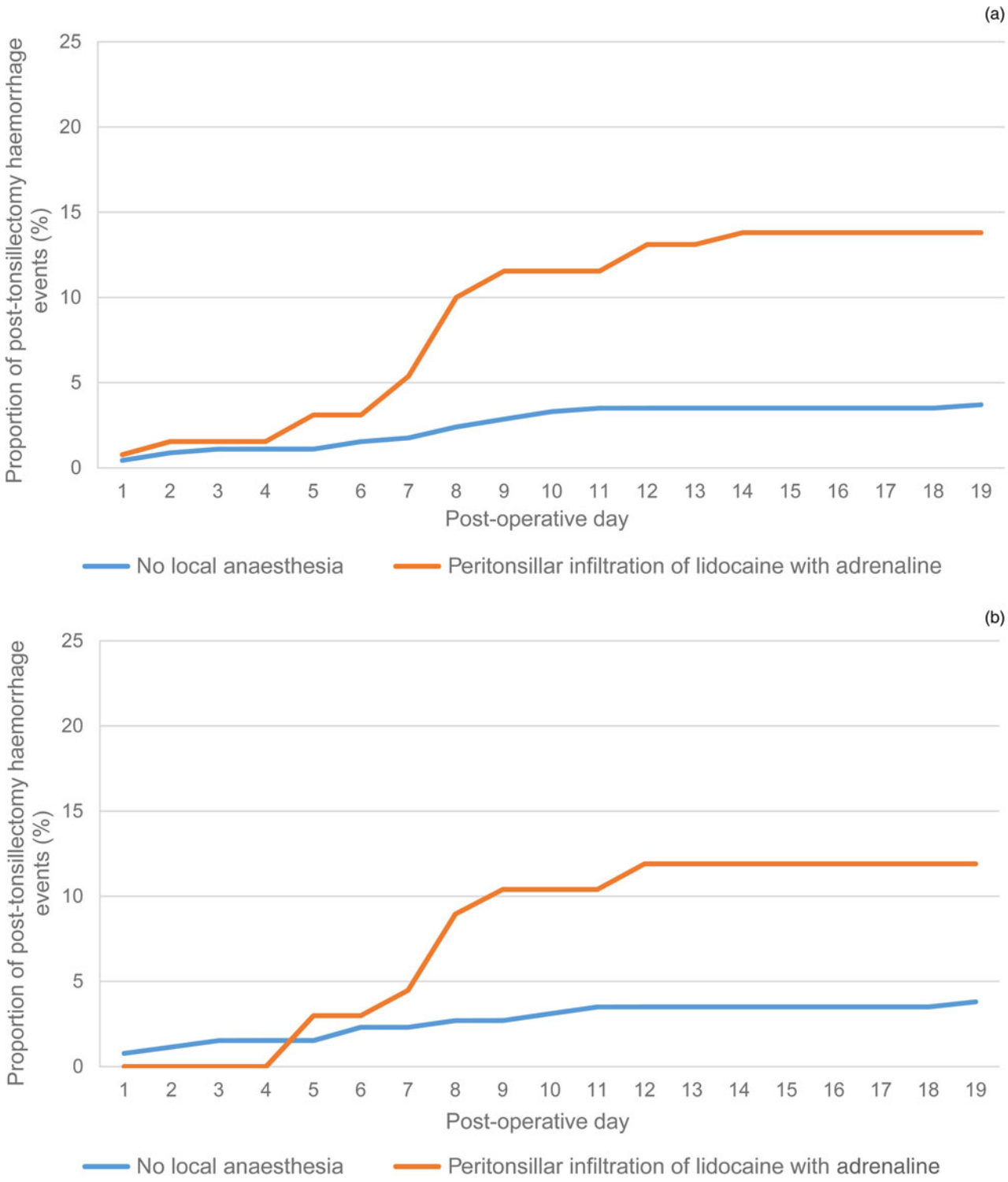

Fig. 2. Cumulative proportion of post-tonsillectomy haemorrhage events in relation to peritonsillar infiltration of lidocaine with adrenaline for: (a) all patients ($p < 0.001$), (b) patients aged 1–7 years ($p = 0.009$) and (c) patients aged 8–16 years ($p = 0.001$).

adrenaline has been shown to decrease cell migration and potentiate persistent inflammation, especially in infected wounds.[30–32] Local anaesthetics have been reported to inhibit wound healing by their antiproliferative effect on many cell types including mesenchymal stem cells essential in wound healing (based on *in vitro* and animal models, in which local anaesthetics were administered in a dose-dependent manner).[33–36] Separation of the fibrin clot from the tonsillar bed on post-operative days 6–7 exposes regenerative capillaries in the vascular stroma, and if the healing process is impaired, post-tonsillectomy haemorrhage occurs more easily in this vulnerable time slot.[37]

The use of lidocaine with adrenaline was associated with an increased risk of post-tonsillectomy haemorrhage among patients operated on by surgeons in group 2 (with a more than 14 per cent risk of post-tonsillectomy haemorrhage). When none of these agents were used, the risk of post-tonsillectomy haemorrhage was similar in both surgeon groups (group 1 (with a less than 14 per cent risk of post-tonsillectomy haemorrhage) = 3.6 per cent; group 2 = 4.4 per cent). The reason why there were more bleeding episodes in group 2 is unclear – it may be because of the more common use of local anaesthetic and topical agents (two

https://doi.org/10.1017/S0022215118001731 Published online by Cambridge University Press

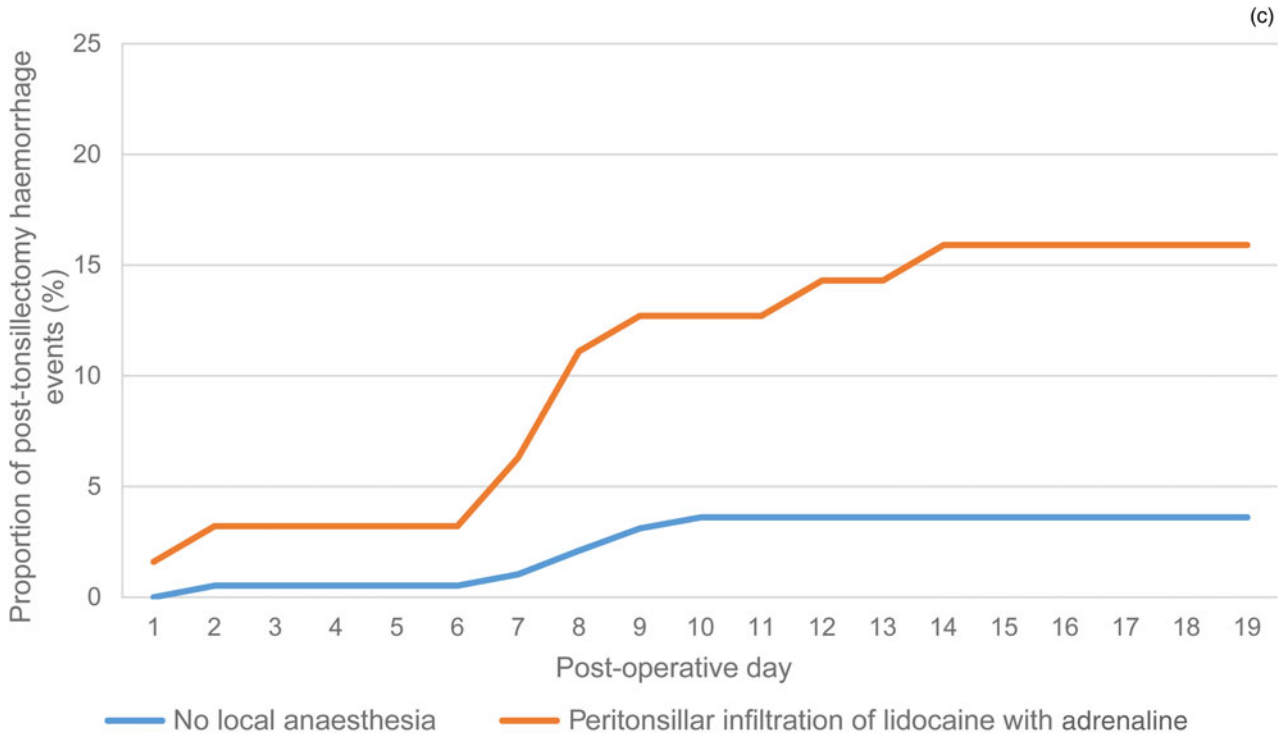

Fig. 2. (*continued*)

times more common than in group 1) or the surgeons' skills.

It is unclear why the risk of post-tonsillectomy haemorrhage was even higher with the combination of lidocaine with adrenaline and bismuth subgallate than with lidocaine with adrenaline alone. Although the combination was mainly used out of habit, it may have also been used for haemostasis in patients who received lidocaine with adrenaline and nevertheless had a bleeding tendency, and thus the underlying need for surgical haemostasis was missed. The groups were small, and a significant difference was observed only among patients operated by one surgeon in group 2; thus, the finding is without clinical significance.

Twenty-one patients (3 per cent) contacted the hospital because of post-operative pain. Non-steroidal anti-inflammatory drugs were used commonly (in 94 per cent of patients), and, fortunately, they did not increase the risk of post-tonsillectomy haemorrhage. A meta-analysis (published in 2003) that included both children and adults reported an increased risk of re-operation in those who received NSAIDs; the incidence was 0.8 per cent for control individuals and 4.2 per cent for NSAID-treated patients.[10] However, a Cochrane review (published in 2005) on NSAIDs and peri-operative bleeding in paediatric tonsillectomy did not demonstrate an increased risk of post-tonsillectomy haemorrhage.[11] An updated Cochrane review (published in 2013) concluded that insufficient data exist to refute an increased risk of post-tonsillectomy haemorrhage; the use of NSAIDs was associated with a non-significant increased risk of post-tonsillectomy haemorrhage requiring surgical intervention.[38] A recent retrospective study on paediatric tonsillotomy demonstrated an increased overall risk (primary and secondary) of post-tonsillectomy haemorrhage requiring re-operation when ibuprofen was used, compared with analgesics other than NSAIDs (1.6 per cent *vs* 0.5 per cent).[39]

The US Food and Drug Administration has banned the use of codeine for post-tonsillectomy pain in patients aged under 18 years. This is because of the sudden deaths of children operated on for obstructive sleep apnoea who had received codeine for post-tonsillectomy pain.[40] The respiratory depressant effect of codeine results from its rapid metabolism to morphine due to cytochrome CYP2D6 polymorphism, and sleep apnoea patients are especially sensitive to this effect.[41] Consequently, other analgesics need to be used. Based on our study findings, the existing evidence and the fact that post-tonsillectomy pain is intense for several days post-operatively, we consider the use of NSAIDs more beneficial than harmful. Improving patient education on the nature and intensity of post-tonsillectomy pain will help patients and reduce unplanned contact with the hospital.

The incidence of post-operative nausea and vomiting was very low in our study (0.9 per cent). This is because of the common use of the anti-emetics dexamethasone (78.3 per cent) and 5-HT_3 antagonists (16.6 per cent). Although the dexamethasone dose was quite high (median of 0.3 mg kg^{-1} (range, 0–1 mg kg^{-1})), it was not associated with an increased risk of complications. In a prospective study by Czarnetzki *et al.*, single-dose dexamethasone was reported to increase the risk of post-tonsillectomy haemorrhage in a dose-dependent manner.[19]

Debate on the subject of anti-emetics for tonsillectomy has been ongoing; post-tonsillectomy haemorrhage has been argued to be a secondary outcome and statistical tests have been considered inappropriate.[42] A Cochrane review on steroids and paediatric post-tonsillectomy bleeding (published in 2011) did not report increased bleeding rates with dexamethasone use, instead describing reduced post-operative morbidity.[43] Moreover, another systematic review did not demonstrate an increased risk of post-tonsillectomy haemorrhage with dexamethasone (with or without NSAIDs); however, a clinically relevant doubling in risk could not be excluded on the grounds of unavoidable imprecisions in statistical tests.[44]

The recent guideline from the American Academy of Otolaryngology – Head and Neck Surgery Foundation for

https://doi.org/10.1017/S0022215118001731 Published online by Cambridge University Press

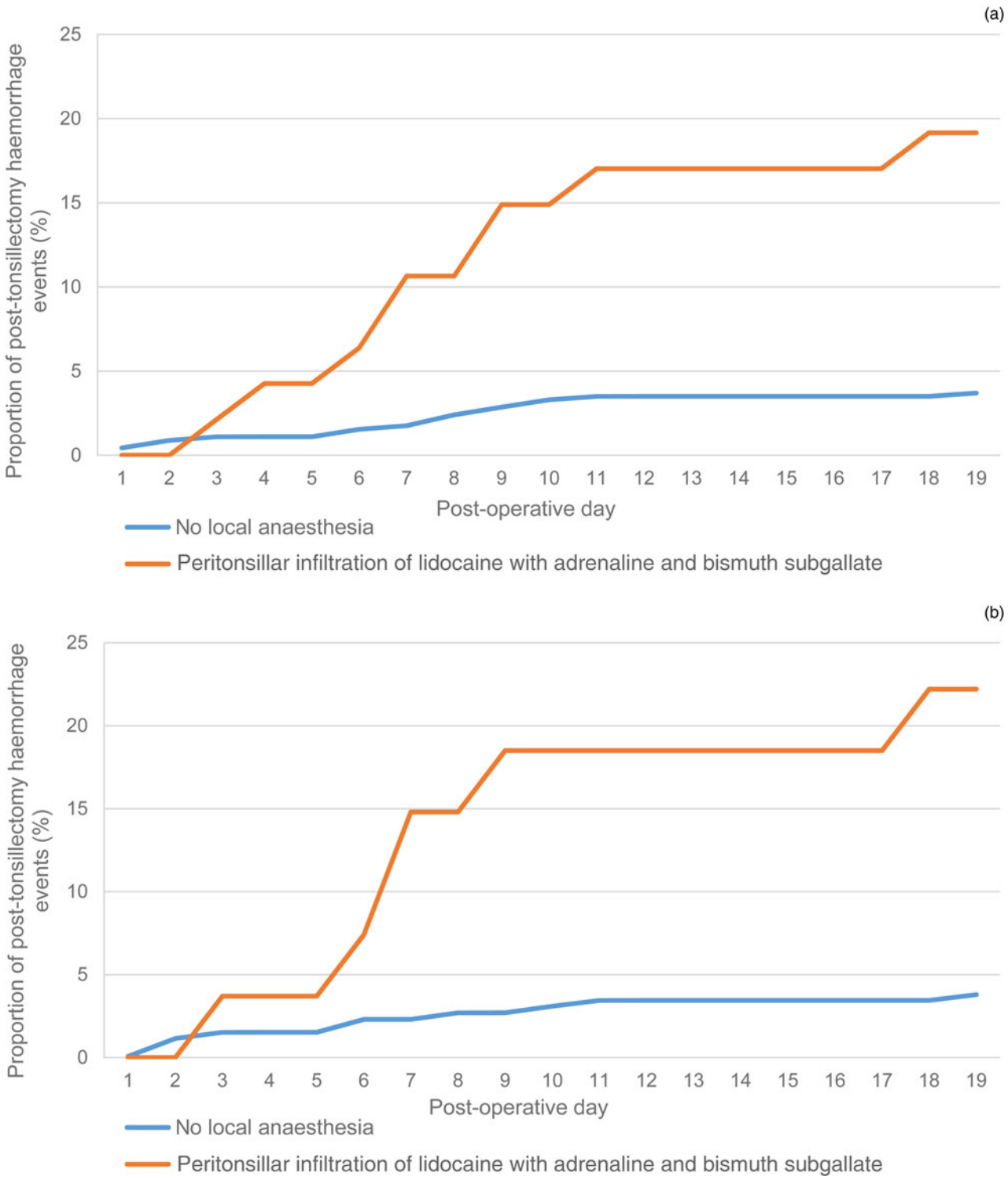

Fig. 3. Cumulative proportion of post-tonsillectomy haemorrhage events in relation to peritonsillar infiltration of lidocaine with adrenaline and bismuth subgallate for: (a) all patients ($p < 0.001$), (b) patients aged 1–7 years ($p < 0.001$) and (c) patients aged 8–16 years ($p = 0.02$).

tonsillectomy in children strongly recommends the use of single-dose dexamethasone in children undergoing tonsillectomy. This recommendation is based on benefit over harm, including decreased throat pain, decreased post-operative nausea and vomiting, and earlier resumption of oral intake, which are crucial in terms of hydration, especially when NSAIDs are used.[45]

Given the complicated nature of post-tonsillectomy haemorrhage pathophysiology, several other simultaneous factors influence the risk of post-tonsillectomy haemorrhage. These include the heterogeneity of patients, indications for tonsillectomy (hypertrophy or chronic inflammation), surgical technique, extent of tonsil removal and possible undiagnosed bleeding disorders.

It could be argued that the usefulness of the results is limited given the time when data were collected. In fact, the use of local lidocaine with adrenaline in tonsillectomies has decreased over the years in our clinic. However, it is used commonly when tonsillotomies are performed. The observed effect of lidocaine with adrenaline on the increased risk of bleeding

https://doi.org/10.1017/S0022215118001731 Published online by Cambridge University Press

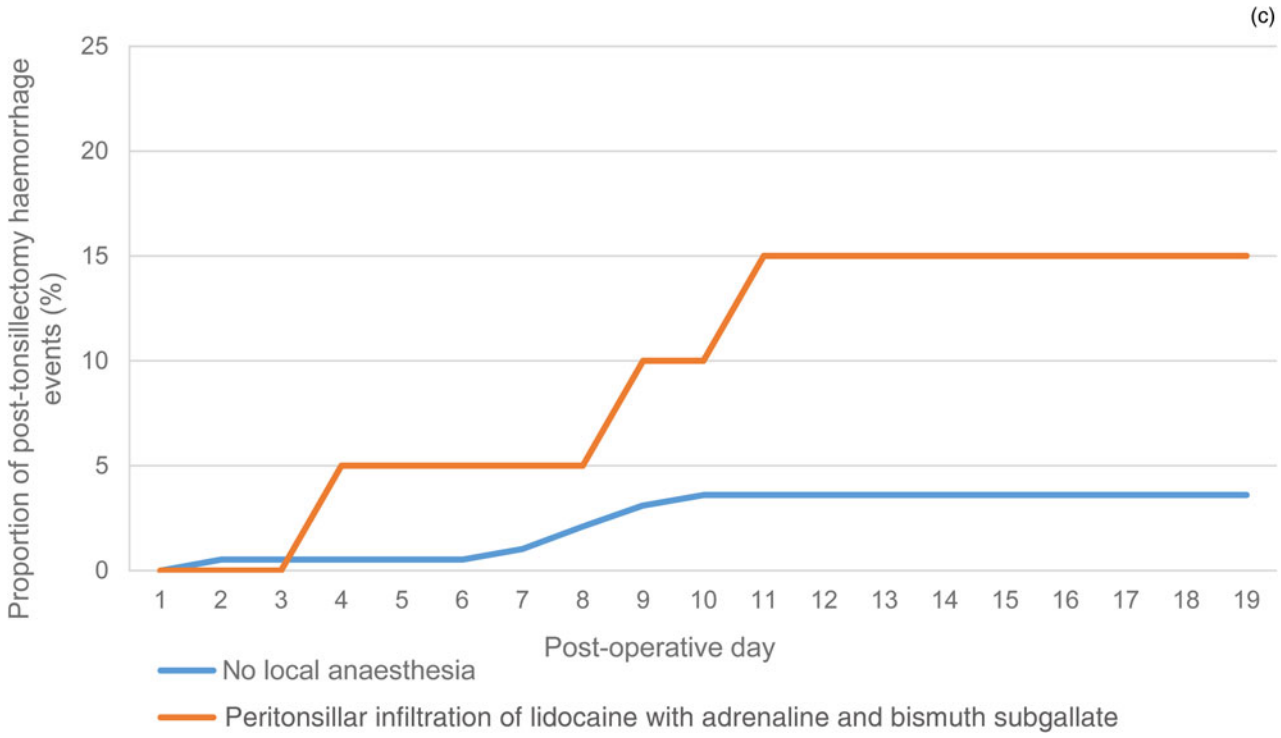

Fig. 3. (*continued*)

in tonsillectomies may be similar in tonsillotomies, which is worth exploring in future prospective studies.

- Recovery after tonsillectomy was mostly uneventful; 14 per cent of patients reported post-operative complications and 5 per cent were re-admitted
- The most common post-operative complication was haemorrhage (7.1 per cent)
- Paracetamol, non-steroidal anti-inflammatory drugs, tramadol, oxycodone, dexamethasone and 5-HT_3 antagonists were not associated with post-operative complications
- Lidocaine with adrenaline was a risk factor for secondary post-tonsillectomy haemorrhage, which may result from impaired wound healing due to their use
- Paediatric out-patient tonsillectomy is considered safe
- Local infiltration of lidocaine with adrenaline is questionable because of increased post-tonsillectomy haemorrhage risk

In conclusion, every seventh paediatric tonsillectomy patient experienced a complicated recovery. The most frequent post-operative complication was post-tonsillectomy haemorrhage. The use of local anaesthetic with adrenaline may create better surgical conditions, but may carry an increased risk of post-tonsillectomy haemorrhage.

Competing interests. None declared

References

1 Windfuhr JP. Hemorrhage following pediatric tonsillectomy before puberty. *Int J Pediatr Otorhinolaryngol* 2001;**58**:197–204
2 Randall D, Hoffer M. Complications of tonsillectomy and adenoidectomy. *Otolaryngol Head Neck Surg* 1998;**118**:61–8
3 MacCallum PL, MacRae DL, Sukerman S, MacRae E. Ambulatory adenotonsillectomy in children less than 5 years of age. *J Otolaryngol* 2001;**30**:75–8
4 Kanerva M, Tarkkila P, Pitkäranta A. Day-case tonsillectomy in children: parental attitudes and consultation rates. *Int J Pediatr Otorhinolaryngol* 2003;**67**:777–84
5 Wei JL, Beatty CW, Gustafson RO. Evaluation of posttonsillectomy hemorrhage and risk factors. *Otolaryngol Head Neck Surg* 2000;**123**:229–35
6 Liu JH, Anderson KE, Willging JP, Myer 3rd CM, Shott SR, Bratcher GO *et al.* Posttonsillectomy haemorrhage: what is it and what should be recorded? *Arch Otolaryngol Head Neck Surg* 2001;**127**:1271–5
7 Valtonen H, Qvarnberg Y, Blomgren K. Patient contact with healthcare professionals after elective tonsillectomy. *Acta Otolaryngol* 2004;**124**:1086–9
8 Drake-Lee A, Stokes M. A prospective study of the length of stay of 150 children following tonsillectomy and/or adenoidectomy. *Clin Otolaryngol Allied Sci* 1998;**23**:491–5
9 Beaulieu P. Non-opioid strategies for acute pain management. *Can J Anaesth* 2007;**6**:481–5
10 Marret E, Flahault A, Samama C-M, Bonnet F. Effects of postoperative, nonsteroidal, anti-inflammatory drugs on bleeding risk after tonsillectomy. *Anesthesiology* 2003;**98**:1497–502
11 Cardwell M, Siviter G, Smith A. Non-steroidal anti-inflammatory drugs and perioperative bleeding in pediatric tonsillectomy. *Cochrane Database Syst Rev* 2005;(18):CD003591
12 Hollis LJ, Burton MJ, Millar JM. Perioperative local anesthesia for reducing pain following tonsillectomy. *Cochrane Database Syst Rev* 2000;(2):CD001874
13 Grainger J, Saravanappa N. Local anaesthetic for post-tonsillectomy pain: a systematic review and meta-analysis. *Clin Otolaryngol* 2008;**33**:411–19
14 Patel RI, Hannallah RS. Anesthetic complications following pediatric ambulatory surgery: a 3-yr study. *Anesthesiology* 1988;**6**:1009–12
15 Rose JB, Brenn BR, Corddry DH, Thomas PC. Preoperative oral ondansetron for pediatric tonsillectomy. *Anesth Analg* 1996;**82**:558–62
16 Gan TJ, Meyer TA, Apfel CC, Chung F, Davis PJ, Habib AS *et al.* Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 2007;**105**:1615–28
17 Holte K, Kehlet H. Perioperative single-dose glucocorticoid administration: pathophysiologic effects and clinical implications. *J Am Coll Surg* 2002;**195**:694–712
18 Afman CE, Welge JA, Steward DL. Steroids for post-tonsillectomy pain reduction: meta-analysis of randomized controlled trials. *Otolaryngol Head Neck Surg* 2006;**134**:181–6
19 Czarnetzki C, Elia N, Lysakowski C, Dumont L, Landis BN, Giger R *et al.* Dexamethasone and risk of nausea and vomiting and postoperative bleeding after tonsillectomy in children: a randomized trial. *JAMA* 2008;**300**:2621–30

https://doi.org/10.1017/S0022215118001731 Published online by Cambridge University Press

20 Anand VT, Phillipps JJ, Allen D, Joynson DH, Fielder HM. A study of postoperative fever following paediatric tonsillectomy. *Clin Otolaryngol Allied Sci* 1999;**24**:360–4
21 Windfuhr J, Seehafer M. Classification of haemorrhage following tonsillectomy. *J Laryngol Otol* 2001;**115**:457–61
22 Ovesen T, Kamarauskas G, Dahl M, Mainz J. Pain and bleeding are the main determinants of unscheduled contacts after outpatient tonsillectomy. *Dan Med J* 2012;**59**:A4382
23 Duval M, Wilkes J, Korgenski K, Srivastava R, Meier J. Causes, costs, and risk factors for unplanned return visits after adenotonsillectomy in children. *Int J Pediatr Otorhinolaryngol* 2015;**79**:1640–6
24 Blakley BW. Post-tonsillectomy bleeding: how much is too much? *Otolaryngol Head Neck Surg* 2009;**140**:288–90
25 Coordes A, Soudry J, Hofmann VM, Lenarz M. Gender-specific risk factors in post-tonsillectomy hemorrhage. *Eur Arch Otorhinolaryngol* 2016;**273**:4535–41
26 Thorisdottir H, Ratnoff OD, Maniglia AJ. Activation of Hageman factor (factor XII) by bismuth subgallate, a hemostatic agent. *J Lab Clin Med* 1998;**112**:481–6
27 Callanan V, Curran AJ, Smyth DA, Gormley PK. The influence of bismuth subgallate and adrenaline paste upon operating time and operative blood loss in tonsillectomy. *J Laryngol Otol* 1995;**109**:206–8
28 Hatton RC. Bismuth subgallate-epinephrine paste in adenotonsillectomies. *Ann Pharmacother* 2000;**34**:522–5
29 Papangelou L. Hemostasis in tonsillectomy. A comparison of electrocoagulation and ligation. *Arch Otolaryngol* 1972;**96**:358–60
30 Sivamani RK, Pullar CE, Manabat-Hidalgo CG, Rocke DM, Carlsen RC, Greenhalgh DG *et al.* Stress-mediated increases in systemic and local epinephrine impair skin wound healing: potential new indication for beta blockers. *PLoS Med* 2009;**6**:e12
31 Peitzman ER, Zaidman NA, Maniak PJ, O'Grady SM. Agonist binding to β-adrenergic receptors on human airway epithelial cells inhibits migration and wound repair. *Am J Physiol Cell Physiol* 2015;**309**:C847–55
32 Dasu MR, Ramirez SR, La TD, Gorouhi F, Nguyen C, Lin BR *et al.* Crosstalk between adrenergic and toll-like receptors in human mesenchymal stem cells and keratinocytes: a recipe for impaired wound healing. *Stem Cells Transl Med* 2014;**3**:745–59
33 Lucchinetti E, Awad AE, Rahman M, Feng J, Lou PH, Zhang L *et al.* Antiproliferative effects of local anesthetics on mesenchymal stem cells: potential implications for tumor spreading and wound healing. *Anesthesiology* 2012;**116**:841–56
34 Rodrigues FV, Hochman B, Wood VT, Simões MJ, Juliano Y, Ferreira LM. Effects of lidocaine with epinephrine or with buffer on wound healing in rat skin. *Wound Repair Regen* 2011;**19**:223–8
35 Doğan N, Uçok C, Korkmaz C, Uçok O, Karasu HA. The effects of articaine hydrochloride on wound healing: an experimental study. *J Oral Maxillofac Surg* 2003;**61**:1467–70
36 Waite A, Gilliver SC, Masterson GR, Hardman MJ, Ashcroft GS. Clinically relevant doses of lidocaine and bupivacaine do not impair cutaneous wound healing in mice. *Br J Anaesth* 2010;**104**:768–73
37 Isaacson G. Tonsillectomy healing. *Ann Otol Rhinol Laryngol* 2012;**121**:645–9
38 Lewis SR, Nicholson A, Cardwell ME, Siviter G, Smith AF. Nonsteroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy. *Cochrane Database Syst Rev* 2013;(18):CD003591
39 D'Souza JN, Schmidt RJ, Xie L, Adelman JP, Nardone HC. Postoperative nonsteroidal anti-inflammatory drugs and risk of bleeding in pediatric intracapsular tonsillectomy. *Int J Pediatr Otorhinolaryngol* 2015;**79**:1472–6
40 FDA Drug Safety Communication. Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy. In: https://www.fda.gov/downloads/Drugs/DrugSafety/UCM339116.pdf [20 February 2013]
41 Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. *N Engl J Med* 2009;**361**:827–8
42 Gunter JB, Willging JP, Myer 3rd CM. Dexamethasone and postoperative bleeding after tonsillectomy in children. *JAMA* 2009;**301**:1765–6
43 Steward DL, Grisel J, Meinzen-Derr J. Steroids for improving recovery following tonsillectomy in children. *Cochrane Database Syst Rev* 2011;(10):CD003997
44 Bellis JR, Pirmohamed M, Nunn AJ, Loke YK, De S, Golder S *et al.* Dexamethasone and haemorrhage risk in paediatric tonsillectomy: a systematic review and meta-analysis. *Br J Anaesth* 2014;**113**:2023–42
45 Baugh RF, Archer SM, Mitchell RB, Rosenfeld RM, Amin R, Burns JJ *et al.* Clinical practice guideline: tonsillectomy in children. *Otolaryngol Head Neck Surg* 2011;**144**:S1–30

https://doi.org/10.1017/S0022215118001731 Published online by Cambridge University Press