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'Desire for more analgesic treatment': pain and patient-reported outcome after paediatric tonsillectomy and appendectomy

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Abstract

Background: Insufficiently treated pain after paediatric appendectomy and tonsillectomy is frequent. We aimed to identify variables associated with poor patient-reported outcomes.
Methods: This analysis derives from the European *PAIN OUT infant* registry providing information on perioperative pharmacological data and patient-reported outcomes 24 h after surgery. Variables associated with the endpoint 'desire for more pain treatment' were evaluated by elastic net regularisation (odds ratio [95% confidence interval]).
Results: Data from children undergoing appendectomy (n=472) and tonsillectomy (n=466) between 2015 and 2019 were analysed. Some 24.8% (appendectomy) and 20.2% (tonsillectomy) wished they had received more pain treatment in the 24 h after surgery. They reported higher composite pain scores (5.2 [4.8–5.5] *vs* 3.6 [3.5–3.8]), more pain-related interference, and more adverse events than children not desiring more pain treatment, and they received more opioids after surgery (morphine equivalents (81 [60–102] *vs* 50 [43–56] μg kg^{-1}). Regression analysis revealed that pain-related sleep disturbance (appendectomy odds ratio: 2.8 [1.7–4.6], tonsillectomy 3.7 [2.1–6.5]; P<0.001) and higher pain intensities (1.5-fold increase) increased the probability of desiring more pain treatment. There was an inverse association between the number of different classes of non-opioids administered preventively, and the desire for more analgesics postoperatively. Children not receiving any non-opioid analgesics before the end of a tonsillectomy had a 3.5-fold (2.1–6.5-fold) increase in the probability of desiring more pain treatment, compared with children receiving at least two classes of different non-opioid analgesics.
Conclusions: Preventive administration of at least two classes of non-opioid analgesics is a simple strategy and may improve patient-reported outcomes.

Keywords: appendectomy; desire for more pain treatment; non-opioid analgesics; opioids; paediatric postoperative pain; patient-reported outcomes; tonsillectomy

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Editor's key points

- Poorly controlled pain has been well documented after tonsillectomy and appendectomy in adults, with limited knowledge as to which factors may contribute to this in children.
- Using a European wide database of children aged 4 yr or older, assessing perioperative pain and its impact, around 22% of children expressed a desire for more pain treatment. This was associated with higher pain scores, and pain interference and more side-effects, but not opioid administration.
- Preventive administration of at least two classes of non-opioid analgesics was found in those less likely to want more treatment. This relatively straightforward modifiable factor could be used to improve perioperative pain outcomes.
- Interestingly, regional analgesia was rarely used. This warrants further study as it may provide an additional strategy to improve pain outcomes.

Severe postoperative pain is experienced frequently and is often not adequately treated. An analysis of patient-reported outcomes of more than 50 000 adults revealed that after minor surgeries such as appendectomy and tonsillectomy, pain intensity was high and analgesic treatment was insufficient in many patients.[1] Both types of surgery are also frequently performed in children; however, European data on the quality of postoperative pain management in daily clinical practice are scarce.

PAIN OUT infant is an international pain registry established in 2015 to evaluate quality of paediatric postoperative pain management.[2] At present, 23 hospitals in five countries participate, and data sets of 10 948 children are included. To improve clinical care, results of a standardised questionnaire on patient-reported outcomes on the first postoperative day and clinical data collected in routine hospital settings were analysed. The data reflect daily clinical practice in perioperative care, focussing not only on pain scores, but also on more global assessment of patient-reported outcome measures such as pain-related interference after surgery, and the patients' desire for more pain treatment.

We hypothesised that not only pain intensity, but also pain-related functional interference and perioperative analgesic treatment are associated with the desire for more pain treatment. The aim of this analysis of registry data was to identify variables associated with the desire for more pain treatment, a patient-reported outcome measured on the day after surgery which also reflects efficacy of analgesic treatment and patient satisfaction for the first 24 postoperative hours in clinical routine.

Methods

PAIN OUT infant registry

This analysis is based on the international registry *PAIN OUT infant*, in which children aged 4 yr or older are prospectively enrolled for quality control of postoperative pain management.[2] *PAIN OUT infant* is registered in clinicaltrials.gov (NCT02083835). Each participating centre obtained approval from its local ethics committee and (written) informed consent from the parents according to local requirements.[3] Exclusion criteria were parents', the patient's, or both refusal to participate, patients' cognitive impairment, communication problems, and discharge before data collection.

On the first postoperative day, about 24 h after surgery, older children and adolescents completed a standardised questionnaire of patient-reported outcomes. For younger children, this was completed by their parents or carers.[2,4] The faces pain scale revised was used to evaluate pain intensity at rest, pain on movement, and worst pain since surgery.[5] Pain-related functional interference (pain with coughing/taking a deep breath, waking up during the night as a result of pain), side-effects (nausea, vomiting, tiredness), and the desire for more pain treatment were addressed as dichotomous variables (yes/no answers). Patient characteristics, anaesthesia, analgesia, and surgery-related data, and pharmacological data relevant for the perioperative period, were retrieved from the patients' records. To prevent bias, trained surveyors not involved in patients' care collected the data using a standardised protocol. Automatically coded data were saved in an internet-based case report form.

Patient cohort

A proposal for analysing pain-related outcome after paediatric appendectomies and tonsillectomies was submitted to the PAIN OUT publication board. After acceptance of the analysis plan, ethics approval was obtained for analysis of registry data (Kantonale Ethikkommission Bern; BASEC 2020-00497). Anonymised raw data were provided, encompassing all children and adolescents undergoing appendectomy (ICD-9 codes 47.0, 47.01, 47.11, 47.19, and 47.99) or tonsillectomy with or without adenoidectomy (ICD-9 codes: 28.2, 28.3 or combinations, e.g. 28.2+28.6 or 20.2+20.01/20.09) in participating European hospitals between February 2015 and November 2019. A plan for data cleaning aimed to exclude cases with missing questionnaires or incomplete data from analysis. The manuscript adheres to the applicable STROBE/RECORD guidelines.

Analgesic drugs

The *PAIN OUT infant* database provides detailed information on administered drugs, covering a time interval up to 24 h after surgery. For non-opioid analgesics, three drug classes were considered: NSAID, paracetamol (acetaminophen), and metamizole (dipyrone). These were given either preoperatively before incision by the rectal or oral route, or i.v. before emergence from anaesthesia. Patients were allocated to one of the following groups: no preventive non-opioid analgesic was given, one, two, or three different classes of non-opioid analgesics were administered.

For the postoperative period, the number of doses of non-opioid analgesics administered in the PACU and on the ward was evaluated. Opioid doses were converted to morphine equivalents (ME).

Data analysis

A pain composite score (PCS; mean of pain at rest, worst pain, and movement-evoked pain) was calculated from the patient-reported outcome measures.[6,7] Pain-related interference when coughing/taking a deep breath, or waking up from sleep during the night and adverse events (nausea, vomiting, tiredness) were summarised in an interference composite score. The primary endpoint was the dichotomous variable desire for

more pain treatment ('Would you have liked to receive more treatment for your pain?').

Statistical analysis.

A previous publication reported a 21% rate of patients indicating the desire for more pain treatment after tonsillectomies.[8] For reliable statistical analysis, we aimed at a sample size of at least 400 cases for each type of surgery, resulting in a representative cohort of at least 80 patients desiring more analgesic treatment in each group. Categorical data were presented as absolute and relative frequencies; normally distributed continuous data and composite scores as mean (standard deviation, SD), and pain scores as median and interquartile range (IQR). Differences in continuous outcomes were tested with a two-sided independent samples *t*-test, or with analysis of variance if the data were normally distributed; pain scores with the Mann–Whitney *U*-test, and categorical outcomes with the χ^2 test.

The regularised regression method elastic net was applied with a binary link function to determine variables (clinical data, patient-reported outcomes) increasing the probability of desiring more analgesic treatment.[9] Patient characteristics and hospitals were entered as possible confounders. In contrast to ordinary least squares regression, the elastic net algorithm performs well in highly correlated variables, either including all of them or excluding all of them from the best model. Generally, elastic net regularisation leads to parsimonious models, which are easier to interpret.[9] Variable selection is performed by shrinking parameters towards zero and attenuating overfitting, a well-known problem if regression models are applied with a large number of predictors. Ten-fold cross validation was applied to choose the best model with the lowest mean cross-validated error. As sensitivity analysis, elastic net was performed for the variables 'worst pain' and 'movement-evoked pain' instead of PCS for both types of surgery. Odds ratios (OR) with 95% confidence intervals (CI) were reported. *P*-values <0.05 were considered significant. Statistical analyses were performed with Statistica 13.0 (Dell Inc., Tulsa, OK, USA) and R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study cohort and patient characteristics

The download from the registry provided 932 anonymised cases from 12 different hospitals in Germany, The Netherlands, Switzerland, and the UK. After exclusion of

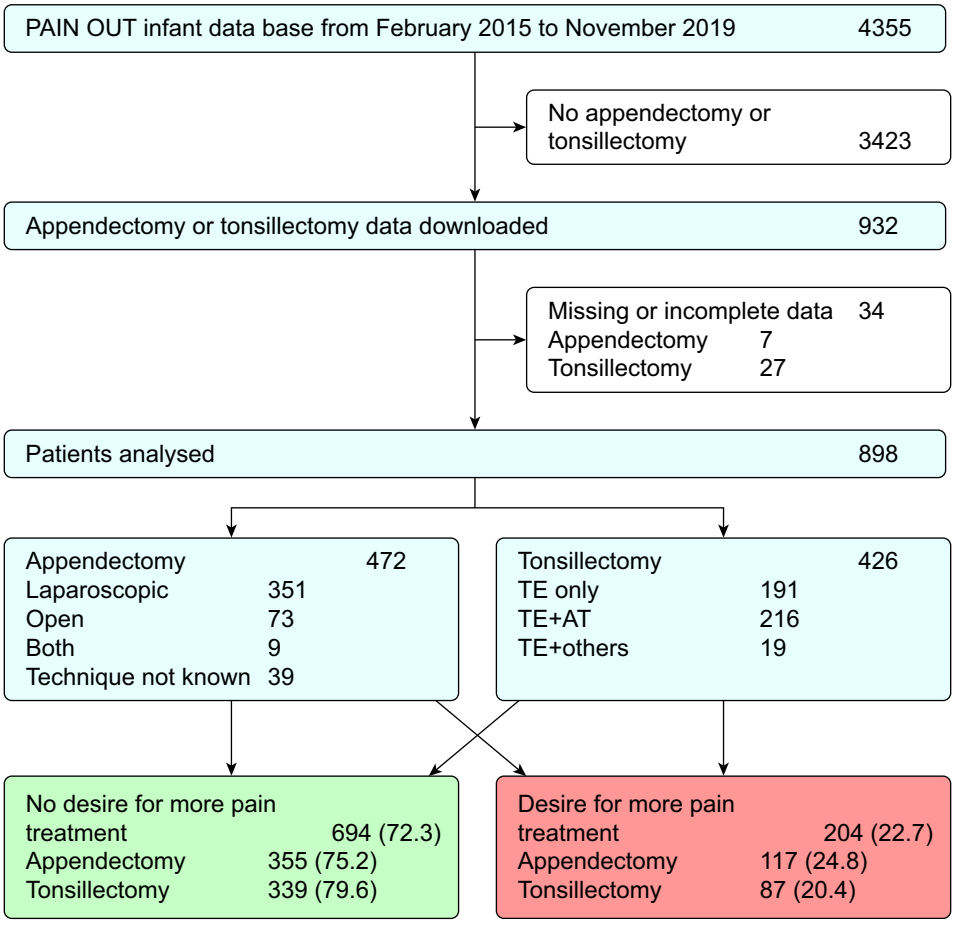

Fig 1. Flow chart with number (%) of patients undergoing appendectomy and tonsillectomy who were enrolled and analysed and those who would have liked to receive more pain treatment. AT, adenoidectomy; TE, tonsillectomy.

incomplete data, 898 were analysed (Fig. 1). Patient characteristics and anaesthesia-related data are presented in Supplementary Table S1. Most children received general anaesthesia supplemented by an opioid. An additional peripheral nerve block, neuraxial analgesia, or wound infiltration were rarely performed.

Pain and pain-related interference on the first postoperative day

The *PAIN OUT infant* questionnaire was filled in by 42.2% of the children on their own (age 12.6 [2.5] yr) and by 46.2% with assistance (someone reading it aloud or explaining words, 8.0 [2.9] years). Parents filled in the questionnaire for younger participants (11.6%; 5.5 [2.2] years).

PCS were higher after appendectomy compared with tonsillectomy (4.3 [4.1–4.5] *vs* 3.7 [3.5–3.9]; $P<0.001$), whereas pain-related interference scores were comparable (2.3 [2.2–2.4] *vs* 2.1 [2.0–2.3]). The surgical technique used for appendectomy—either laparoscopic surgery, open surgery, or a combination of the two—had no influence on pain scores (PCS: 4.4 [4.2–4.6], 4.0 [4.0–4.4], 4.0 [2.7–5.3]; $P=0.25$).

Desire for more pain treatment

Of the children, 22.7% answered that they would have liked to receive more pain treatment during the first 24 h after surgery, with no difference between appendectomies and tonsillectomies (Table 1). Pain and interference scores were higher and side-effects were more frequent in patients who desired more treatment compared with those who did not (Table 1).

Intraoperative opioid doses administered for anaesthesia did not differ between the groups, nor did the proportion of patients receiving an opioid before emergence from anaesthesia (Table 2). After surgery (PACU and ward), more children were given opioids and doses were higher in the group desiring more pain treatment (Table 2 and Fig. 2a).

Preventive non-opioid analgesics

More children undergoing tonsillectomy received preventive non-opioid analgesics before the end of surgery compared with the appendectomy group (92.0% *vs* 79.2%; $P<0.001$). A single dose was given to the majority, whereas the others received combinations of two or three different classes of non-opioid analgesics (Supplementary Table S2).

There was an inverse association between the number of different classes of non-opioid analgesics administered and the desire for more analgesic treatment in the tonsillectomy group ($P=0.031$; Table 2). There was the same tendency in the appendectomy group. Scores for worst pain, movement-evoked pain, and the PCS were lowest for the patients receiving three non-opioid analgesics (Supplementary Fig. S1). This decrease was especially pronounced for movement-evoked pain in the appendectomy group ($P=0.018$) and worst pain in the tonsillectomy groups ($P=0.012$). Overall, receiving three different classes compared with no non-opioid analgesic decreased worst pain, movement-evoked pain, and the PCS by 18.8%, 24.4%, and 21.0%, respectively.

Postoperative analgesics used in the PACU and on the wards

After surgery, two to three doses of non-opioid analgesics were given on average (Table 2). In the PACU, 38% (appendectomy 21.9%, tonsillectomy 43.4%) and on the ward, 27% of the children (appendectomy 26.5%, tonsillectomy 27.6%) received an opioid, in most cases i.v. morphine or piritramide. Oral oxycodone was given only to a few adolescents (3.1%); five patients after appendectomy self-administered an opioid via patient-controlled analgesia.

Table 1 Patient-reported outcomes of children after appendectomy and tonsillectomy.

Variables		Appendectomy			Tonsillectomy		
		Desire for more pain treatment		p	Desire for more pain treatment		p
		No n = 355	Yes n = 117		No n = 339	Yes n = 87	
Males	n (%)	160 (73.4)	58 (26.6)	0.396	183 (83.9)	35 (16.1)	0.022
Females	n (%)	195 (76.8)	59 (23.2)		156 (75.0)	52 (25.0)	
Duration of surgery	(min)	56.6 (54.3–58.9)	60.5 (55.3–65.6)	0.708	32.7 (30.3–35.1)	35.7 (31.1–40.2)	0.261
Pain composite score	FPS	3.9 (3.7–4.1)	5.5 (5.2–5.9)	<0.001	3.4 (3.2–3.6)	4.9 (4.4–5.3)	<0.001
Pain at rest	FPS	2 (0/2)	2 (2/4)	>0.001	2 (0/2)	2 (0/4)	<0.001
Pain on movement	FPS	2 (2/6)	6 (4/8)	<0.00	4 (2/6)	6 (4/8)	<0.001
Worst pain	FPS	6 (4/8)	8 (6/10)	<0.001	4 (4/8)	6 (6/8)	<0.001
Interference composite score		2.1 (1.8–2.2)	2.9 (2.7–3.1)	<0.001	2.0 (1.8–2.1)	2.8 (2.5–3.1)	<0.001
Cough/deep breath	no	69 (19.4)	11 (9.4)	0.012	153 (45.1)	19 (21.8)	<0.001
	yes	286 (80.6)	106 (90.6)		186 (54.9)	68 (78.2)	
Sleep interference	no	256 (72.1)	41 (35.0)	<0.001	235 (69.3)	27 (31.0)	<0.001
	yes	99 (27.9)	76 (65.0)		104 (30.7)	60 (69.0)	
Nausea	no	270 (76.1)	71 (60.7)	0.001	239 (70.5)	56 (64.4)	0.269
	yes	85 (23.9)	46 (39.3)		100 (29.5)	31 (35.6)	
Vomiting	no	314 (88.5)	92 (78.6)	0.008	273 (80.5)	62 (71.3)	0.059
	yes	41 (11.5)	25 (21.4)		66 (19.5)	25 (28.7)	
Tiredness	no	133 (37.5)	29 (24.8)	0.012	128 (37.8)	29 (33.3)	0.445
	yes	222 (62.5)	88 (75.2)		211 (62.2)	58 (66.7)	

Data are presented as *n* (%) patients, composite scores as mean (95% confidence interval), measures of the faces pain scale (FPS) revised[5] as median (inter-quartile range). Pain composite score: mean of the three pain scores; interference composite score: one point each if the children answered yes to the respective question, maximum value: 5 points. *P*-values refer to comparisons by χ^2 test, *t*-test, or Mann–Whitney *U*-test.

Table 2 Intra- and postoperative analgesics for the appendectomy and tonsillectomy groups: Patients (n (%)) receiving different classes of nonopioid analgesics administered before emergence from anaesthesia, number of nonopioid analgesics administered after surgery, and opioids given intraoperatively, in the recovery room and on the ward.

			Appendectomy			Tonsillectomy		
			Desire for more pain treatment			Desire for more pain treatment		
			No	Yes	p	No	Yes	p
Patients receiving no, 1, 2 or 3 classes of different nonopioid analgesics before emergence from anaesthesia								
0 nonopioid analgesic		n (%)	70 (19.7)	28 (23.9)	0.409	25 (7.4)	9 (10.3)	0.031
1 class of nonopioid analgesic			224 (63.1)	76 (65.0)		173 (51.0)	56 (64.4)	
2 classes of nonopioid analgesics			57 (16.1)	12 (10.3)		84 (24.8)	16 (18.4)	
3 classes of nonopioid analgesics			4 (1.1)	1 (0.9)		57 (16.8)	6 (6.9)	
Nonopioid analgesics PACU + ward					p			p
Number of doses			2.5 (2.3-2.8)	3.1 (2.5-3.6)	0.087	2.6 (2.3-2.8)	2.6 (2.1-3.1)	0.730
Opioids					p			p
Intraoperative opioids for anaesthesia i.v.[a]								
fentanyl	μg kg^{-1}	n: 231/73	3.6 (3.3-4.0)	3.3 (2.6-3.8)	0.658	2.9 (2.6-3.2)	2.7 (2.2-3.3)	0.600
sufentanil	μg kg^{-1}	n: 117/44	0.45 (0.42-0.48)	0.44 (0.39-0.49)	0.881	0.26 (0.22-0.29)	0.25 (0.18-0.32)	0.867
remifentanil	μg kg^{-1}/min	n: 81/19	0.31 (0.24-0.38)	0.24 (0.14-9.34)	0.392	0.32 (0.27-0.36)	0.39 (0.25-0.53)	0.196
Preventive opioids up to end of surgery								
Patients		n (%)	131 (36.9)	36 (30.8)	0.137	105 (31.0)	31 (35.6)	0.187
	ME μg kg^{-1}		26.7 (22.1-31.3)	22.2 (15.7-28.7)		22.2 (18.1-26.3)	28.6 (18.3-38.9)	
Only patients with opioid	ME μg kg^{-1}		72.3 (64.9-79.7)	72.3 (64.6-79.9)		71.6 (65.0-78.2)	80.3 (62.1-98.4)	
Opioid in the PACU	Patients	n (%)	100 (28.2)	47 (40.2)		149 (44.0)	46 (52.9)	
	ME μg kg^{-1}		17.7 (13.8-21.5)	28.3 (19.4-37.2)	0.013	35.3 (29.3-41.2)	51.9 (35.4-68.4)	0.023
Only patients with opioid	ME μg kg^{-1}		62.7 (53.9-71.5)	70.6 (54.6-86.4)		80.2 (70.6-89.8)	98.2 (73.7-122.7)	
Opioid on the ward	Patients	n (%)	80 (22.5)	40 (34.2)		90 (26.5)	29 (33.3)	
	ME μg kg^{-1}		17.9 (12.9-23.0)	29.3 (13.0-45.7)	0.081	29.1 (21.3-37.1)	59.4 (27.5-91.3)	0.007
Only patients with opioid	ME μg kg^{-1}		79.7 (63.2-96.3)	85.8 (42.0-129.7)		109.9 (87.3-132.6)	178.4 (95.9-260.7)	
Opioid PACU + ward	Patients	n (%)	156 (43.9)	70 (59.8)		182 (53.7)	56 (64.4)	
	ME μg kg^{-1}		35.6 (29.4-41.8)	57.7 (39.0-76.3)	0.004	64.5 (53.2-75.6)	111.4 (69.7-153.1)	0.002
Only patients with opioid	ME μg kg^{-1}		81.1 (70.7-91.5)	96.4 (68.5-124.4)		120.1 (102.8-137.7)	173.0 (113.7-232.3)	

Opioid doses given for postoperative analgesia are expressed as intravenous morphine equivalents (ME) μg kg^{-1} body weight. Data are *n* (%) or mean (95% CI); *p* values refer to the comparison by χ^2 test or t-test; PACU: postanaesthesia care unit.

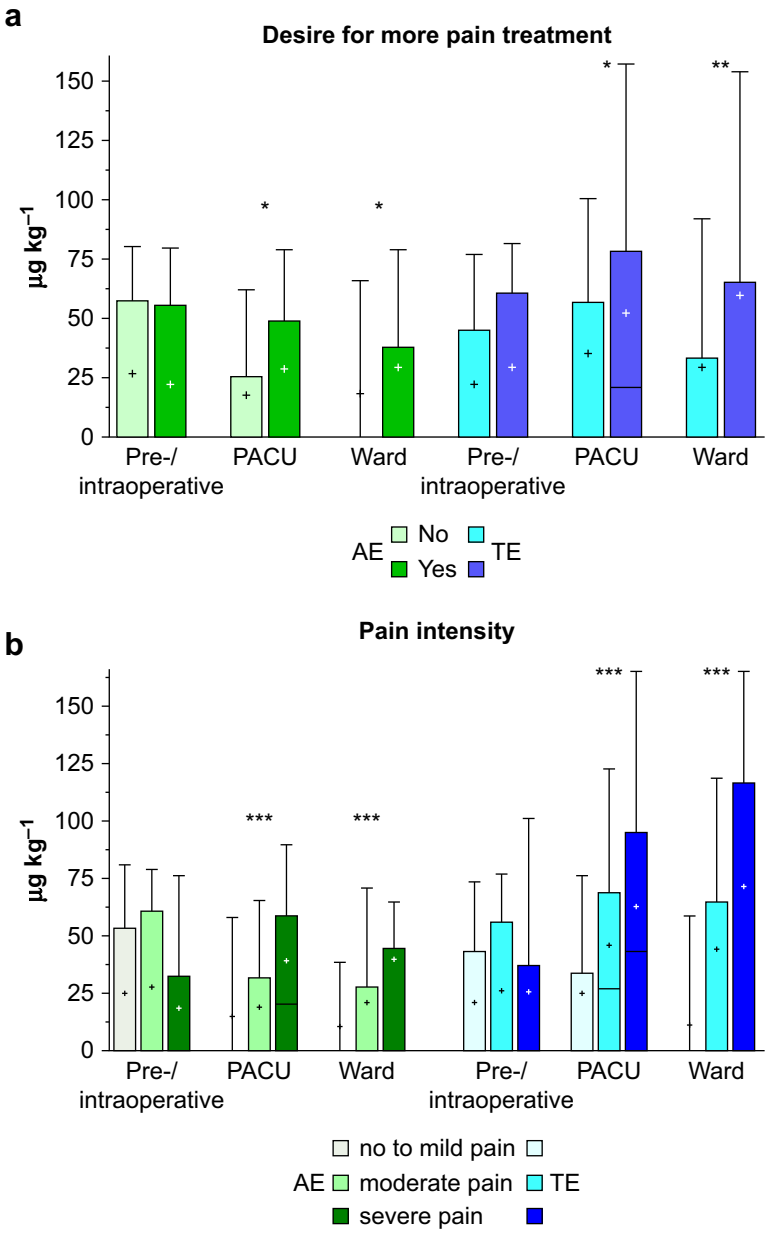

Fig 2. Morphine equivalents in µg kg^{-1} body weight administered pre- and intraoperatively, in the PACU and on the ward, for the appendectomy (AE) and tonsillectomy groups (TE) in (a) children without or with desire for more pain treatment (for number of patients in each group see Table 1), (b) children with no to mild pain (PCS 0–3; appendectomy n=121; tonsillectomy n=172), moderate pain (PCS>3 and ≤6; appendectomy n=284; tonsillectomy n=203) and severe pain (PCS>6; appendectomy n=67; tonsillectomy n=51). Box and whisker plot with median, 1st/3rd quartile, 10%–90% percentiles, + mean; t-test or analysis of variance. *P=0.05; **P<0.01; ***P<0.0001. PCS, pain composite score.

Allocation of the patients to the groups 'no to mild pain', 'moderate pain' and 'severe pain' demonstrated that those with higher PCS had received larger doses of MEs for postoperative analgesia (Fig. 2b). Opioid doses were also higher in children reporting side-effects such as nausea, vomiting, tiredness, or pain-related functional impairment compared with those without these complaints (Fig. 3).

Variables associated with the desire for more pain treatment

Patient characteristics, surgery, and anaesthesia-related variables, hospital, the number of different classes of non-opioid analgesics administered before emergence from anaesthesia, ME µg kg^{-1} body weight administered postoperatively (PACU and on the ward), and variables of the patient questionnaire

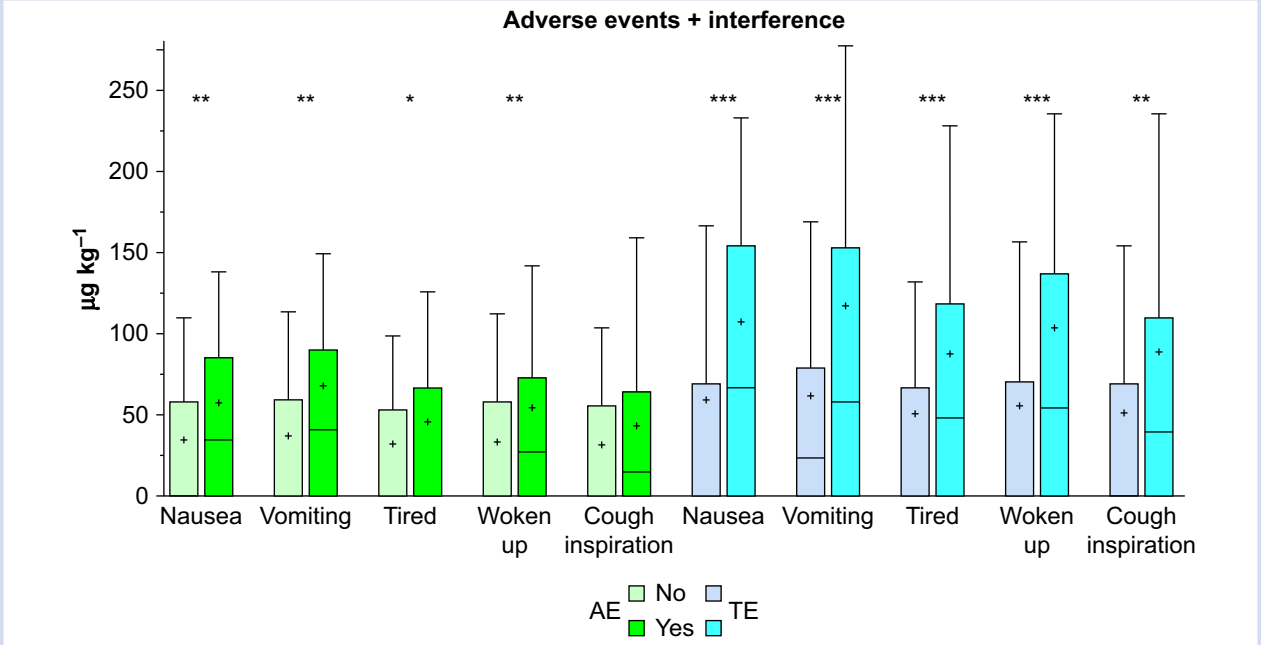

Fig 3. Postoperative morphine equivalents in µg kg^{-1} body weight in children after appendectomy (AE: green) and tonsillectomy (TE: blue) not reporting or reporting adverse events or pain-related interference (answer no/yes). Number of patients in each subgroup see Table 1. Box and whisker plot with median, 1st/3rd quartile, 10%–90% percentiles, + mean; *t*-test. *P=0.01; **P<0.005; ***P<0.0001.

were introduced into the elastic net model, with the desire for more pain treatment as a dependent variable. For both types of surgery, waking up during the night because of pain was associated with a 2.8- and 3.7-fold increase in the probability of desiring more pain treatment after appendectomy and tonsillectomy, respectively (Table 3). An increase in pain intensity in the PCS by one point increased the probability 1.4- and 1.3-fold.

In children undergoing tonsillectomy, the variable with high impact was the administration of preventive non-opioid analgesics. Compared with children receiving at least two different classes of non-opioid analgesics, administration of none or only one of these resulted in 3.5- or two-fold increases in the probability of desiring more pain treatment. For appendectomy, this variable was not included in the model, as children received fewer preventive non-opioid analgesics. Female sex (OR 2.58, 95% CI 1.45–4.58) was also included in the best model for tonsillectomies. Within the elastic net algorithm, variables remain in the model if the prediction error averaged over the 10 cross-validation samples is reduced. Therefore, although not significant, vomiting, providing PONV prophylaxis, dexamethasone, clonidine, MEs administered postoperatively, and duration of surgery were also included. Overall, these models explained 16% and 20% of the variance of the dependent variable 'desire' for appendectomy and tonsillectomy, respectively. The same variables remain in the models for appendectomy and tonsillectomy if worst pain or movement-evoked pain was used instead of PCS in the sensitivity analyses. Furthermore, the regression coefficients shown in Supplementary Table S2 were similar to the results of the models for PCS.

Discussion

This analysis of registry data provides insights into paediatric perioperative pain management and patient-reported outcomes after appendectomy and tonsillectomy. Overall, pain management seems to be highly heterogeneous, with large differences between hospitals, and obviously no standardised use of non-opioid analgesics in some of them. Pain management was insufficient in nearly one-quarter of the children who would have liked more treatment. This desire for more pain treatment was used as a global patient-reported outcome measure of patient satisfaction,[10] encompassing various further variables such as pain-related interference, pain intensity, individual pain tolerance, preference for specific treatment modalities, expected or experienced side-effects, and perceived or actual adequacy of treatment. For tonsillectomies, an interesting result not previously reported for children was the use of different classes of non-opioid analgesics given as a preventive dose, which seemed to improve patient-reported outcome.[11] Not receiving a preventive non-opioid analgesic was associated with an increased desire for more pain medication, higher opioid doses, more adverse events, and more pain-related interference.

During the past decade, pain after even small paediatric surgeries has been repeatedly described as severe,

Table 3 Regularised regression by elastic net with the desire for more pain treatment as dependent variable. Odds ratios (OR) with 95% confidence interval (CI) of the predictors in the best model. ME, morphine equivalents; PONV, postoperative nausea and vomiting.

Variables	OR	95% CI	P-value
Appendectomy R^2 (McFadden) = 0.161			
Woke up because of pain	2.817	1.730–4.589	<0.001
Pain composite score	1.476	1.286–1.695	<0.001
Tonsillectomy R^2 (McFadden) = 0.203			
Woke up because of pain	3.656	2.060–6.489	<0.001
Reference 2 or 3 non-opioid analgesics			
No non-opioid analgesic	3.519	1.219–10.158	0.020
One non-opioid analgesic	2.015	1.066–3.812	0.031
Sex (female *vs* reference=male)	2.580	1.454–4.578	0.001
Pain composite score	1.245	1.081–1.433	0.002
Cough	1.904	1.003–3.617	0.049
Vomiting	1.298	0.686–2.458	0.423
PONV prophylaxis	1.258	0.842–1.880	0.262
Dexamethasone	1.372	0.648–2.905	0.409
Clonidine	0.964	0.897–1.006	0.314
ME PACU+ward (μg kg^{-1})	2.529	0.341–18.737	0.364
Duration of surgery (min)	1.002	0.990–1.015	0.713

inadequately assessed, and often undertreated.[12,13] Children undergoing tonsillectomy experienced severe pain and severe functional limitations for about a week after surgery.[14] Substantial postoperative pain has also been described after laparoscopic appendectomy.[13] The present study confirmed high variability in patient-reported outcomes, but also in the use of analgesics.[8,15] Regional/local analgesic techniques were rarely used for appendectomies. This is a field with the potential for improvement in the future.

Desire for more pain treatment

Although pain is expected to be associated with a desire for more pain treatment, the fact that sleep disturbance showed a higher impact in both surgical groups underlined that pain-related impairment is relevant for patients' outcomes. In contrast to chronic pain states, pain-related sleep interference has not been well studied in the acute pain setting.[16] The importance of a global judgment of improvement and satisfaction with treatment and physical recovery has been emphasised before. This is also reflected by the core outcome domains defined by Pediatric Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (Ped-IMMPACT), in which pain, physical and emotional functioning, adverse events, and global judgment and satisfaction with treatment are mentioned.[16]

The association between increasing the number of different classes of non-opioid analgesics given before emergence from anaesthesia and the desire for additional pain treatment is interesting, and a measure which could easily be transferred to clinical practice. A mean 21.0% and 24.4% decrease of movement-evoked and composite pain scores associated with additional non-opioid analgesics might not meet a minimal clinically important difference in all children.[17] However, a mean change implies that some children experience even greater pain resolution whereas others experience less. Other patient-reported outcome measures, now recommended for use in the paediatric acute pain setting, also improved, suggesting that these findings are clinically relevant.

Administration of three different non-opioid classes was performed in one single department in about one-third of the patients, and in other hospitals only sporadically. As the total number of patients receiving three non-opioid analgesics was low, we cannot confirm that this regimen produces a more favourable outcome. It could be that a third drug class does not further improve outcome, especially if this is paracetamol, which is considered the drug with the lowest analgesic efficacy.[18–21] A study in adults showed a dose-dependent association between the preventive use of non-opioid analgesics and postoperative pain scores, a finding which could be confirmed in our tonsillectomy group.[11]

Some previous trials underlined that the addition of paracetamol to an NSAID did not always improve analgesia compared with an NSAID alone.[18–21] For metamizole, data on efficacy are scarce, specifically on the combinations with other non-opioid classes, as it is not marketed in all countries.[22] However, it is frequently used in others and well appreciated by clinicians.[23,24] Overall, these registry data indicate that the preventive use of non-opioid analgesics was insufficient in many children, particularly for appendectomy, and could be improved in the future.

Opioids

Morphine alone is not considered the most suitable analgesic for pain relief after paediatric surgery.[25] No relationship between postoperative dosages and analgesic efficacy has been detected, whereas the incidence of side-effects increases dose-dependently, a phenomenon already observed in previous trials.[25,26] The positive association between higher opioid doses and the desire for more pain treatment does not imply that opioids are not efficacious; rather, administration of high doses may simply be a reaction to severe pain. As opioids are mainly given as needed in the PACU and on the ward, effects of such on-demand interventions are difficult to capture in PAIN OUT, where pain intensity is only assessed once.

Controversies exist with regard to opioids for analgesia after tonsillectomy. Children undergoing tonsillectomy frequently suffer from sleep disordered breathing, which can

present as obstructive sleep apnoea. Opioids can increase apnoeic events leading to oxygen desaturation, possibly resulting in fatal respiratory depression.[27] Overall, opioid consumption in the present study was lower than described by other working groups, specifically those favouring PCA.[28,29] This might in part be attributable to more extensive use of non-opioid analgesics. Regional techniques such as wound infiltration or peripheral nerve blocks were rarely used in the participating hospitals, although these are recommended as part of a multimodal analgesia regimen.[12,30,31]

Limitations and strengths of the study

Several possible confounders are not considered in *PAIN OUT infant*. Among these are children's medical histories, and psychological variables such as parental and child anxiety, pain-coping efficacy, pain catastrophising, and preoperative expectations of pain.[32–35] No differentiation was possible between chronic tonsillitis or appendicitis and severe acute inflammation, such as peritonsillar abscess or perforated appendicitis with peritonitis, both of which can be expected to cause increased pain, and no details of surgical technique were collected.[36,37] Furthermore, patient-reported outcomes were assessed only once, 1 day after surgery.

The main strength of this study is a standardised assessment of process and outcome parameters within the PAIN OUT network, representing everyday clinical practice and no artificial study settings.[38] In contrast to previous trials using pain scores, which only reflect a unidimensional assessment of pain, the present data refer to the patients' own views of pain-related functional interference, and the side-effects of treatment.[16 38] These are considered to better mirror patients' outcomes; however, they have rarely been used in children up to now.[34] Future studies should consider more global measures of pain-related outcome and patients' perceptions of care.[16] Furthermore, a more detailed analysis of dosing of non-opioid analgesics might provide further information on the current practice in perioperative paediatric analgesia and possible areas to improve.

Conclusions

The amount of analgesia given after paediatric surgery seems to be insufficient in many hospitals. Patient-reported outcome—measured as desire for more pain treatment—was not only associated with pain-related interference and pain intensities, but also, at least for tonsillectomies, with the number of different classes of non-opioid analgesics administered before emergence from anaesthesia. The latter is a variable which can easily be implemented in clinical practice. Opioid-related side-effects and pain-related interference might also be improved by preventive administration of at least two classes of non-opioid analgesics. Further studies are needed to demonstrate the superiority of this regimen.

Authors' contributions

Study conception and design: UMS, TL, FS, WM.
Acquisition of data, analysis and interpretation of data: UMS, KB, TL, MS, FS, MK, WM.
Drafting the manuscript and revising it critically: KB, UMS, TL, MS, MK, FS, WM.

Approval of the final version: all authors

All authors agree to be accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declarations of interest

UMS received honoraria and reimbursement for travel costs from Syntetica and Grünenthal. WM received honoraria from Bionorica, BioQPharm, Böhringer, Grünenthal, Kyowa, Mundipharma, Northern-Swan, Sanofi, TAD, and Tilray. The other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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