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# Analgesic use and favourable patient-reported outcome measures after paediatric surgery: an analysis of registry data

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## Abstract

**Background:** Pain after paediatric appendectomy and tonsillectomy is often undertreated. Benchmarking of hospitals could reveal which measures are associated with improved patient- or parent-reported pain-related outcomes.
**Methods:** A total of 898 anonymised cases from 11 European hospitals participating in PAIN OUT infant were analysed. The children completed a questionnaire on patient-reported outcomes (PROs) 24 h after surgery. According to a composite PRO measure, including pain intensity and pain-related interference, hospitals were allocated to Group I (favourable results), II (average results), and III (unfavourable results). Benchmarking of hospital groups was performed investigating process variables (dosing of non-opioid analgesics, opioids, and dexamethasone) associated with PROs, side-effects, and children's perception of care. Variables associated with PROs were analysed using multinomial regression analysis with the PRO score-related hospital group as a dependent variable (estimated odds ratios [OR], 95% confidence interval [CI]).
**Results:** During the first 24 h after surgery, 1.2 (1.1–1.3) full daily doses of non-opioid analgesics (non-steroidal anti-inflammatory drug [NSAID], paracetamol, metamizole) were administered in group I and 0.7 (0.6–0.8) in group III ($P<0.001$). Intraoperative dexamethasone was administered to 70.1 and 52.6% of the children in Group I and Group III, respectively ($P<0.001$). A lower number of full daily doses of non-opioid analgesics: 0.22 [0.15–0.31]), less dexamethasone (0.49 [0.33–0.71]), fewer non-opioid analgesics before the end of surgery (0.37 [0.22–0.62]) and higher opioid doses were associated with hospital allocation to group III *vs* group I (Nagelkerke's $R^2=0.433$).
**Conclusions:** The results indicated substantial deficits in the concept, application, and dosing of analgesics in paediatric patients after surgery. Timely administration of adequate analgesic doses can easily be introduced into daily clinical practice.
**Clinical trial registration:** clinicaltrials.gov NCT 02083835.

**Keywords:** appendectomy; non-opioid analgesics; paediatric analgesia; pain-related interference; patient-reported outcomes; tonsillectomy

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### Editor's key points

- Hospitals with favourable *versus* less favourable patient-reported outcomes (PROs) after paediatric surgery were compared.
- More nonopioid analgesics and fewer opioids were associated with better PROs assessed by a composite of pain intensity and pain-related functional interference.
- Most children received less than one full daily dose of a non-opioid analgesic.
- Timely and sufficient dosing of nonopioid analgesics can be easily implemented in daily clinical practice.

After appendectomy or tonsillectomy, pain management is often insufficient, and children may experience severe and frequent pain and pain-related functional interference.[1–3] Non-opioid analgesics are the mainstay of acute pain management. However, there are limited data from routine clinical settings on perioperative dosing of non-opioid analgesics.

The multinational pain registry 'PAIN OUT infant' was developed to improve perioperative pain management. Clinical data and patient-reported outcomes (PROs) reflecting the pain experience in the first 24 h were collected for two frequently performed paediatric surgeries, appendectomy and tonsillectomy.[4] For safety reasons, both procedures are generally performed in inpatients in the participating hospitals. PROs assessed included pain scores, functional interference, adverse events, and perception of care, which is in line with the recommendations of IMMPACT.[5,6] A tool for benchmarking PROs enables a comparison of hospitals and can reveal shortcomings of unfavourable patient outcomes (e.g. lacking or insufficiently implemented analgesic concepts).

These data from routine settings may better reflect clinical reality than those of controlled trials. We hypothesised that hospitals with favourable PROs, compared with those with less favourable PROs, use analgesics and dexamethasone differently in children undergoing appendectomy or tonsillectomy. Of specific interest were 24 h doses of non-opioid analgesics. Thus, this study aimed to evaluate the association of perioperative process variables with more favourable or less favourable PROs assessed in participating hospitals.

## Methods

### Study design and patient cohort

This is a planned secondary analysis of data retrieved from the pain registry PAIN OUT infant (ethics approval: Swissethics; BASEC 2020–00497).[7] PAIN OUT is a European project to improve perioperative pain management, originally funded by an EU grant (clinicaltrials.gov NCT02083835). The manuscript adheres to the STROBE/RECORD guidelines.

After approval of a research plan by the PAIN OUT consortium, anonymised data of 932 children/adolescents undergoing appendectomy or tonsillectomy, or a combination of tonsillectomy and adenoidectomy/myringotomy, enrolled between February 2015 and November 2019 were provided.[7] These are the two most frequently included types of surgery in the registry. During the data cleaning process, cases with incomplete questionnaires and missing information on analgesics were excluded.

For PAIN OUT, participating centres obtained approval from their local ethics committee and informed consent from patients and their parents, according to the local legal requirements.[4] Children were prospectively included if they were ≥4 yr old and had no cognitive impairment or communication problems. Trained personnel not involved in patients' care randomly collected data according to standardised procedures.[4]

Patient characteristics, anaesthesia, analgesia, and surgery-related data, and pharmacological data, were retrieved from the patients' records and saved on an internet-based, password-secured case report form. On the first postoperative day, ~24 h after surgery, patients (and in the case of younger children, their parents) filled out a questionnaire on PROs. Pain intensity at rest, movement-evoked pain, and worst pain after surgery were assessed using the Faces Pain Scale revised (FPS-R).[6,8] Pain-related functional interference, adverse events, and desire for more pain treatment were dichotomous.

### Data analysis

The doses of analgesics administered before surgical incision, at the end of surgery, or both ('preventive loading doses'), in the PACU, and on the ward ('postoperative analgesics') were calculated as mg $kg^{-1}$ body weight. For the first 24 h after surgery, the administered body weight-related dose of each NSAID, paracetamol, and metamizole (dipyrone) was divided by the recommended full daily dose of the specific drug, resulting in a measure of, for example, 0 (no non-opioid analgesic was given), 1.0 (one full 24 h dose was given), or 1.5 (one and a half doses were administered; details Supplementary Material). Using a conservative approach based on manufacturers' instructions, paracetamol 60 mg $kg^{-1}$ (i.v., p.o., or p.r.), metamizole 60 mg $kg^{-1}$, diclofenac 3 mg $kg^{-1}$, ibuprofen 30 mg $kg^{-1}$, and ketorolac 1.5 mg $kg^{-1}$ were used as one daily dose. As recommended doses of some drugs are considerably higher, we performed a second analysis ('liberal approach'), which referred to daily doses of paracetamol p.r. 90 mg $kg^{-1}$, paracetamol p.o. 80 mg $kg^{-1}$, and metamizole 75 mg $kg^{-1}$.

For opioids, i.v. morphine equivalents (ME; μg $kg^{-1}$) were calculated according to standard conversion factors.

There has been an emphasis on taking a broader approach to the multidimensional phenomenon of pain, including two or more domains that are important to patients.[5,6] Thus, we calculated a PRO score encompassing pain intensity and pain-related interference to describe children's pain experience more adequately. Mean pain scores at rest, worst pain, and movement-evoked pain (getting out of bed, swallowing) during the first 24 h after surgery, each assessed on the FPS-R, were summarised as mean. Additionally, one point each was added if the child had pain-related interference when coughing/taking a deep breath or woke up at night because of pain. This PRO score resulted in a number between 0 and 12 (PRO score=0: no pain and no pain-related interference; PRO score=12: maximum with all FPS-R scores at 10 plus 2 points for the presence of both pain-related interference items).

### Allocation to hospital groups based on PROs

To compare the processes between hospitals with more or less favourable PROs, hospitals were allocated to one of three groups, each comprising about one-third of the cohort: Group I (lowest, most favourable PRO scores), Group II with average PRO scores, and Group III (highest PRO scores).

### Aim of the study

This study aimed at differences in clinical practice in the perioperative use of analgesics for appendectomy and tonsillectomy in three hospital groups. The patient characteristics, surgery-related data, and process data (primary endpoint: number of weight-based doses of non-opioid analgesics administered during the first 24 h) were compared. Adverse events and children's desire for additional pain treatment were evaluated.

### Statistics

Categorical data were presented as absolute and relative frequencies, continuous data, composite scores as means (95% confidence intervals [CI]), and ordinal data (pain scores) as medians with inter-quartile ranges. Differences in continuous outcomes were tested with a two-sided independent samples *t*-test or analysis of variance (ANOVA) if the data were normally distributed; otherwise, the Mann–Whitney *U*-test or Kruskal–Wallis test was applied. Differences in the frequency of categorical outcomes among hospital groups were analysed using the $\chi^2$ test. Statistical significance was set at $P<0.05$, adjusted for multiple testing.

A multinomial regression model was fitted to the dependent categorical variable, *hospital group*. Group I (favourable PROs) was used as reference. Independent variables were patient characteristics, type and duration of surgery, the administration of intraoperative dexamethasone for prophylaxis of emesis, as co-analgesic, or both, intraoperative non-opioid analgesics, the postoperative 24 h dose of non-opioid analgesics, and ME administered in the ward. Estimated odds ratios (OR) with 95% CI were calculated to evaluate the difference between Groups I and III, and between Groups I and II. Nagelkerke's $R^2$ was reported to assess the goodness-of-fit of the model. Sensitivity analyses aimed at subgroups appendectomy and tonsillectomy or used the conservative approach to calculate 24 h doses of non-opioid analgesic. Statistical analyses were performed using SPSS Statistics 27.0 (IBM, SPSS Inc., Chicago, IL, USA).

## Results

### Patient cohort

Of the 4355 patients enrolled in PAIN OUT infant, 898 who underwent either appendectomy or tonsillectomy in Germany, the Netherlands, Switzerland, and the UK were analysed (Fig 1). According to their PRO score, three hospitals were allocated to Group I, three to Group II, and five to Group III (Supplementary Table S1). PRO scores were higher after appendectomy (5.5 [5.3–5.7]) than after tonsillectomy (4.7 [4.4–4.9]; $P<0.001$). Group I had the lowest scores for both types of surgery. The patient characteristics, type of surgery, and anaesthesia-related data are shown in Table 1. Fewer patients were affected by pain-related interference in Group I than in Group III. Supplementary Figure S1 provides detailed information on patients' pain scores reported at each participating hospital. When considering the entire cohort, 61.0% of the children reported pain scores ≥6 for worst pain.

### Results of benchmarking

Nausea rates in hospitals ranged from 18.1% to 44.4% and vomiting from 6.9% to 47.6%, with the lowest rates in Group I

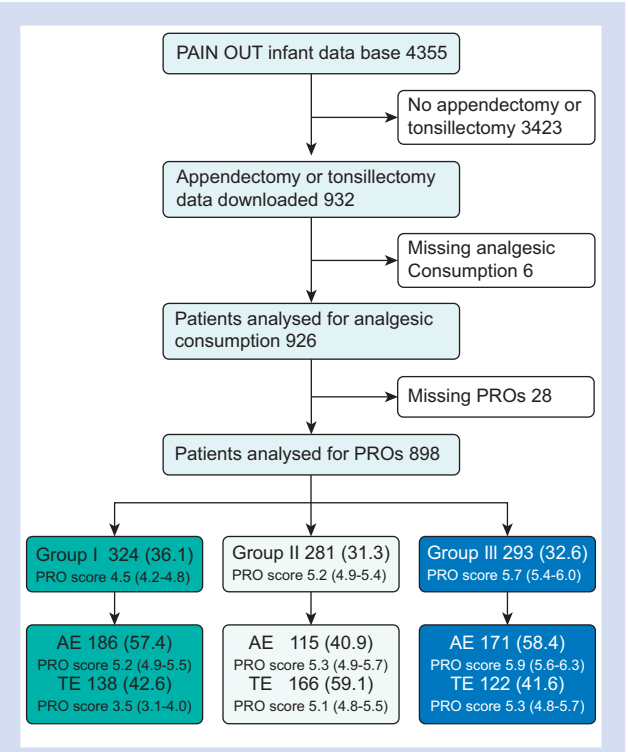


Fig 1. Flow chart. PRO scores are means with 95% confidence interval. AE, appendectomy; PRO, patient-reported outcome; TE, tonsillectomy.

(Supplementary Fig. S2 with separate analysis for appendectomy and tonsillectomy). When considering the entire cohort, 579 children (64.5%) reported tiredness, with large variations between hospitals. The proportion of patients who would have liked to receive more analgesic treatment was the lowest in Group I (17.9% *vs* 31.4% in Group III; $P<0.001$; Supplementary Fig. S2).

### Preventive non-opioid analgesics

Preventive non-opioid analgesics were administered to 89.8% of the children in Group I and 74.7% in Group III (Table 2). There was a wide range of loading doses, as shown in Fig 2. Mean i.v. loading doses of paracetamol were 18.4 (7.8) mg $kg^{-1}$ in Group I compared with 15.6 (4.6) mg $kg^{-1}$ in Group III (not significant after correction for multiple testing). The doses administered to individual patients varied greatly, with 43.2% of children (76/176) receiving doses <15 μg $kg^{-1}$.

Rectal paracetamol was administered on a regular basis in only two hospitals, one each from Groups II (28.4 [5.8] mg) and III (30.6 [7.2] mg). Compared with these two hospitals, rectal doses were lower in hospitals where paracetamol was given sporadically (13–18 mg $kg^{-1}$). Overall, 13.0% (12/92) of the children received doses <20 μg $kg^{-1}$. Preventive i.v. metamizole was administered in 10 hospitals. Doses showed a wide range and did not vary between hospital groups (17.3 [5.4] mg $kg^{-1}$). Doses of <15 mg $kg^{-1}$ were administered to 34.4% (146/424) of children.

Rectal ibuprofen and diclofenac were not routinely used in Group I. Before surgical incision, oral or rectal paracetamol, or

Table 1 Demographical, process–related and outcome–related data of patients allocated to hospital group I, II or III.

| | | Hospital Groups | | | |
|---|---|---|---|---|---|
| | | I ($n$=324) | II ($n$=281) | III ($n$=293) | $p$ |
| **Demographical data** | | | | | |
| Females | 436 (48.5) | 137 (42.3) | 158 (56.2) | 141 (48.1) | 0.145[d] |
| Males | 462 (51.5) | 187 (57.7) | 123 (43.8) | 152 (51.9) | |
| Age | years | 9.0 (8.6–9.4) | 10.6 (10.1–11.0) | 9.4 (9.0–9.8) | 0.177[d] |
| Weight | kg | 37 (35–39) | 44 (41–47) | 37 (35–39) | 0.749[d] |
| **Process–related data** | | | | | |
| Appendectomy | 472 (52.6) | 186 (57.4) | 115 (40.9) | 171 (58.4) | 0.811[d] |
| Tonsillectomy | 426 (47.4) | 138 (42.6) | 166 (59.1) | 122 (41.6) | |
| Duration of surgery | min | 54.3 (51.6–57.0) | 30.7 (28.4–33.1) | 51.2 (48.2–54.2) | 0.127[d] |
| Regional or local analgesia | | 23 (7.1) | 4 (1.4) | 37 (12.6) | 0.021[d] |
| Outcome–related data | | | | | |
| PRO–score | measure 0–12 | 4.5 (4.2–4.7) | 5.2 (4.9–5.4) | 5.7 (5.4–5.9) | <0.001 |
| Pain–related interference | | | | | |
| None | | 94 (29.0) | 52 (18.5) | 48 (16.4) | <0.001 |
| Woke up at night due to pain | | 22 (6.8) | 19 (6.8) | 17 (5.8) | 0.311 |
| Cough / deep breath | | 136 (42.0) | 110 (39.2) | 119 (40.6) | 0.499 |
| Both | | 72 (22.2) | 100 (35.6) | 109 (37.2) | <0.001 |
| Desire for more pain treatment | | 58 (17.9) | 54 (19.2) | 92 (31.4) | <0.001 |

Data are n (%) or mean (CI of mean). P–values refer to a comparison between hospital groups I, II and III, if not indicated with d (comparison group I versus group III) using either ANOVA or the two–sided independent samples t–test or the $\chi^2$ test.

Table 2 Analgesic consumption of patients allocated to hospital Group I, II or III.

| | | Hospital Groups | | | |
|---|---|---|---|---|---|
| | | I ($n$=324) | II ($n$=281) | III ($n$=293) | $p$ |
| **Non–opioid analgesics** | | | | | |
| Preventive non–opioid analgesics [a] | | | | | |
| Yes | 766 (85.3) | 291 (89.9) | 256 (91.1) | 219 (74.7) | <0.001 |
| No | 132 (14.7) | 33 (10.2) | 25 (8.9) | 74 (25.3) | |
| Non–opioid analgesics PACU+ward | | 315 (97.2) | 252 (89.7) | 265 (90.4) | <0.001 |
| Number of full daily doses | | | | | |
| conservative approach | | 1.2 (1.1–1.3) | 0.6 (0.5–0.6) | 0.7 (0.6–0.8) | <0.001 |
| liberal approach | | 1.1 (1.0–1.2) | 0.5 (0.5–0.6) | 0.6 (0.5–0.6) | <0.001 |
| Appendectomy (conservative) | | 1.4 (1.3–1.5) | 0.4 (0.4–0.5) | 0.6 (0.5–0.7) | <0.001 |
| Tonsillectomy (conservative) | | 1.1 (1.0–1.3) | 0.6 (0.6–0.7) | 0.8 (0.7–0.9) | <0.001 |
| Patients with <1 full dose, liberal | | 181 (55.9) | 251 (89.3) | 254 (86.7) | <0.001 |
| conservative | | 141 (43.5) | 246 (87.5) | 226 (77.1) | <0.001 |
| **Opioids** | | | | | |
| Opioids pain prevention | 303 (33.7) | 82 (25.3) | 114 (40.5) | 107 (36.5) | 0.493 |
| ME μg kg$^{-1}$ [b] | | 74.4 (64.9–83.9) | 75.1 (67.6–82.6) | 69.3 (63.0–75.7) | 0.035[e] |
| Opioids PACU | 345 (38.4) | 121 (37.3) | 114 (40.6) | 110 (37.5) | |
| ME μg kg$^{-1}$ [b] | | 70.1 (59.0–81.1) | 71.9 (62.1–81.7) | 86.5 (74.8–98.2) | 0.075 |
| Opioids ward | 239 (26.6) | 75 (23.1) | 94 (33.5) | 70 (23.9) | |
| ME μg kg$^{-1}$ [b] | | 79.2 (54.8–103.5) | 83.9 (71.0–97.0) | 157.9 (114.7–201.0) | <0.001 |
| Opioids PACU + ward | 465 (51.8) | 167 (51.5) | 156 (55.5) | 142 (48.5) | |
| ME μg kg$^{-1}$ [b] | | 86.3 (71.9–100.6) | 102.9 (90.9–115.0) | 144.3 (114.3–174.2) | <0.001 |
| **Prophylactic antiemetic and co–analgesic** | | | | | |
| Intraoperative dexamethasone [c] | | | | | |
| Yes | 592 (65.9) | 227 (70.1) | 211 (75.1) | 154 (52.6) | <0.001 |
| No | 306 (34.1) | 97 (29.9) | 70 (24.9) | 139 (47.4) | |
| Number of intraoperative antiemetic drugs [d] | | | | | |
| $n$=783 | none | 36 (12.4) | 32 (12.8) | 55 (22.6) | <0.001 |
| | 1 antiemetic | 106 (36.6) | 138 (55.2) | 93 (38.3) | |
| | 2–3 antiemetics | 148 (51.0) | 80 (32.0) | 95 (39.1) | |

Data are n (%), or mean (95% CI of mean). ME: morphine equivalents i.v.; a: preventive non–opioid analgesics were either an NSAID, paracetamol, metamizole or a combination of these; b: mean ME were calculated for patients having received an opoioid; c: given either as analgesic or anti–emetic or for both indications; d: PONV: postoperative nausea and vomiting; drugs include 5–$HT_3$ receptor antagonists, dimenhydrinate, droperidol and dexamethasone. Missing data on PONV prophylaxis for 115 patients. P–values refer to a comparison between hospital groups I, II and III using either the $\chi^2$ test or ANOVA; e: comparison group I versus group III using the two–sided independent samples t–test.

ibuprofen were favoured, whereas i.v. metamizole (45.2% of the children) and paracetamol (30.3%) were preferred for intraoperative use. For appendectomy, metamizole was the non-opioid analgesic of choice during surgery (53.8% of the children; paracetamol: 16.1%). In contrast, for tonsillectomy, paracetamol and metamizole were administered in 42.3% and 38.7% of patients, respectively. NSAID were used less frequently during surgery (11.0%).

## Postoperative non-opioid analgesics

The number of full daily doses of non-opioid analgesics administered in the PACU and ward differed significantly between the hospital groups. Using the conservative approach, mean full doses of non-opioid analgesics in Group I amounted to 1.2 (1.1–1.3). This was significantly higher than in Group III ($P<0.001$; Table 2). If the calculation was performed with the liberal approach, the full daily dose was also nearly twice as high in Group I compared with Group III ($P<0.001$; Table 2). Overall, 68.3% of the children received less than one full daily dose during the first 24 h (liberal approach: 76.4%).

Type of non-opioid analgesics used and their dosing varied between hospital groups, with highest i.v. doses of paracetamol and metamizole in Group I (Fig 3). Rectal paracetamol and diclofenac were frequently relied upon in Group III. Ketorolac was used only in one hospital in Group I ($n=64$; 1.2 [1.0–1.3] μg kg$^{-1}$). Oral paracetamol was administered sporadically on the wards in all hospitals (dose range: 13–40 mg kg$^{-1}$). Paracetamol doses <15 mg kg$^{-1}$ per 24 h were used in 28.0%, whereas doses >60 mg kg$^{-1}$ were used in 12.1% of the children.

## Opioids

The proportion of patients receiving postoperative opioids did not differ between the hospital groups. Doses were lowest in Group I (Table 2).

## Intraoperative dexamethasone and antiemetic prophylaxis

For prevention of nausea and vomiting, as co-analgesic, or both, a single dose of dexamethasone was more frequently administered intraoperatively in Group I than in Group III (Table 2). The frequency was comparable between children undergoing appendectomy (63.8%) and tonsillectomy (68.3%; $P=0.152$). The doses varied between 0.03 and 0.4 mg kg$^{-1}$. Prophylaxis for nausea and vomiting was more frequently performed in Group I than in Group III.

## Results of the regression analysis

The multinomial regression analysis revealed four variables associated with PRO-dependent hospital group III *vs* I: lower number of full 24 h doses of non-opioid analgesics (liberal approach; OR [95% CI]: 0.22 [0.15–0.31]), higher opioid doses in the ward (1.005 [1.002–1.007]), less dexamethasone (0.49 [0.33–0.71]), and fewer preventive non-opioid analgesics (0.37 [0.22–0.62]) before the end of surgery (Table 3). The comparison between Group II and Group I confirmed the lower 24 h dose of non-opioid analgesics associated with allocation to Group II (higher PRO score). Overall, the model provided a good fit for the data ($R^2=0.433$). Using the conservative approach showed comparable results ($R^2=0.425$; Supplementary Table S2). The separate analysis of appendectomies and tonsillectomies slightly increased the goodness-of-fit of the regression model (Supplementary Tables S3 and S4).

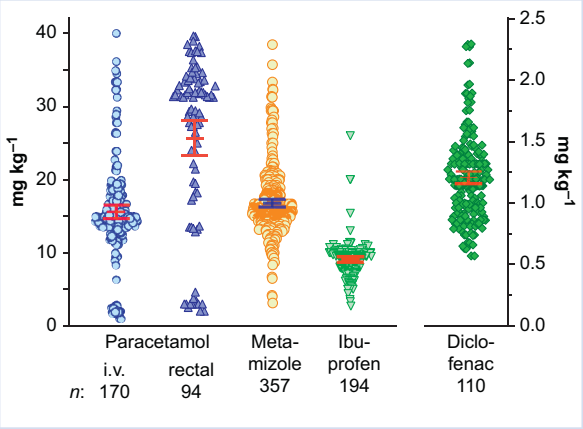


Fig 2. Loading doses of different non-opioid analgesics (mg kg$^{-1}$ body weight) administered preoperatively or intraoperatively. Scatterplot with mean and 95% confidence interval. The number of patients receiving each specific drug are displayed below the x-axis. Metamizole was administered i.v., ibuprofen, and diclofenac p.r. For paracetamol and ibuprofen p.r., some children seemed to have received a small infant dose suppository instead of an age-/weight-adapted child's dose. For i.v. paracetamol and metamizole, the very low doses might be because of calculation or documentation errors by a factor of 10.

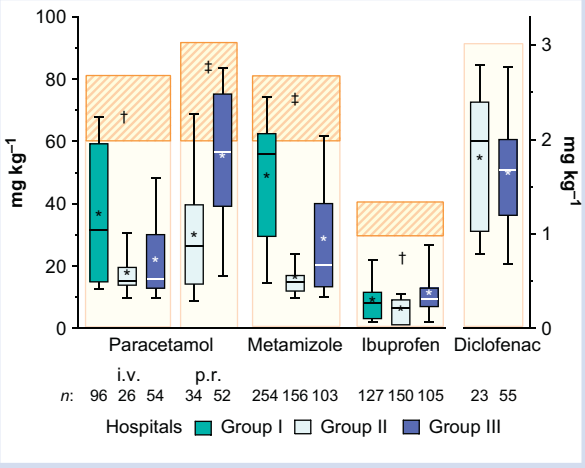


Fig 3. Cumulative postoperative doses (PACU and ward) of paracetamol, metamizole, ibuprofen, and diclofenac administered in the hospital groups. The shading behind the boxes and whiskers indicates the maximum daily doses in mg kg$^{-1}$ body weight, which are provided by the manufacturers (light yellow background) or recommended in various publications (light yellow hatched background). *n* below the x-axis: number of patients analysed in each subgroup. Box and whisker plots with median, inter-quartile range and 10th–90th percentiles. *Mean. †$P<0.01$. ‡$P<0.001$.

Table 3 Results of the multinomial regression analysis with hospital group according to PRO–score as dependent variable. For the postoperative full 24 h doses, the liberal approach was used. Nagelkerke's $R^2$: 0.433.

| | Group III versus reference group I | | | Group II versus reference group I | | |
|---|---|---|---|---|---|---|
| Variables | OR | 95% CI | P | OR | 95% CI | P |
| Appendectomy *vs* tonsillectomy (reference) | 0.720 | 0.46–1.13 | 0.154 | 0.857 | 0.52–1.46 | 0.608 |
| Duration of surgery, min | 1.000 | 0.99–1.01 | 0.873 | 0.951 | 0.94–0.96 | <0.001 |
| Sex, females *vs* males (reference) | 1.282 | 0.90–1.84 | 0.175 | 1.480 | 1.00–2.19 | 0.050 |
| Age, yr | 1.134 | 1.03–1.25 | 0.011 | 1.209 | 1.09–1.34 | <0.001 |
| Weight, kg | 0.979 | 0.95–1.00 | 0.021 | 0.991 | 0.97–1.01 | 0.342 |
| Number of postoperative full 24 h doses of non-opioid analgesics (liberal approach) | 0.220 | 0.15–0.31 | <0.001 | 0.120 | 0.08–0.19 | <0.001 |
| Opioids on the ward, ME μg $kg^{-1}$ | 1.005 | 1.002–1.007 | 0.002 | 1.002 | 1.00–1.01 | 0.319 |
| Dexamethasone, yes/no (reference) | 0.488 | 0.33–0.71 | <0.001 | 1.116 | 0.72–1.73 | 0.623 |
| Preventive non-opioid analgesics, yes/no (ref) | 0.371 | 0.22–0.62 | <0.001 | 1.169 | 0.61–2.24 | 0.636 |

OR: Odds ratio; ME: morphine equivalents in μg $kg^{-1}$ body weight.

## Discussion

These 'real-life data' from PAIN OUT infant describe perioperative analgesic care in children undergoing tonsillectomy and appendectomy. Comparative analysis revealed that in hospitals with better PROs, children received more non-opioid analgesics, more dexamethasone, and fewer opioids, independent of type of surgery.

### Non-opioid analgesics

The use of non-opioid analgesics is consistently recommended.[9–15] Thus, the present results, with 68.3% of all children (liberal approach 76.4%) receiving less than one full daily dose of a non-opioid analgesic, are disillusioning, and suggest that care may have been substandard. Twenty-four hour doses of non-opioid analgesics had a significant influence on differentiation between Groups I and II or III. We conclude that regular administration of non-opioid analgesics has not been widely implemented in clinical practice, particularly in the wards. Furthermore, the combination of two non-opioid analgesics from different classes might be beneficial, as they resulted in less pain and less opioid consumption when compared with one non-opioid analgesic, particularly when compared with paracetamol alone.[7,9–13,16–18]

Worldwide, paracetamol is frequently used in children. Publications have demonstrated analgesic effects for both paracetamol and NSAID, frequently compared with placebo,[14,19] whereas others report lower analgesic potency of paracetamol compared with NSAID.[16,18–21]

For NSAID, reductions in postoperative opioid consumption, nausea and vomiting, and pain have been reported.[14,16,18–25] Ibuprofen and diclofenac were found to be safe and effective and are recommended for paediatric pain management.[9–11,14,21] There have been some restrictions on the use of NSAID, owing to possible bleeding complications, which could be particularly hazardous after tonsillectomy. Meta-analyses and Cochrane reviews did not confirm a significant increase in bleeding problems associated with NSAID treatment in children. A non-inferiority trial could not exclude a higher rate of bleeding requiring a return to the operating room for ibuprofen than for paracetamol.[14,26–28]

### Dosing of non-opioid analgesics

The present results confirm that maximum daily doses were not fully utilised.[29] There are several potential reasons for these findings. In the ward, concepts to guide adequate dosing and timing may be lacking, particularly if patients undergo surgery outside of regular working hours. Some information provided by manufacturers, pharmacokinetic studies, review articles, and recommendations published thus far are conflicting.[2,11,21,30,31] For paracetamol, product information recommends 15 mg $kg^{-1}$ as a single dose, independent of the route of administration. However, this dose is not sufficient to achieve analgesic serum concentrations >10 μg $ml^{-1}$ after rectal administration.[32–36] Enteral paracetamol 10–15 mg $kg^{-1}$ is considered not more effective than placebo.[9] Furthermore, the slow onset of rectal paracetamol—with plasma concentrations peaking 1.5–3.0 h after administration—makes timely administration necessary.[33,35]

Based on pharmacokinetic–pharmacodynamic studies, increased paracetamol loading doses have been published (e.g. 30–40 mg $kg^{-1}$ for the oral route or 40–60 μg $kg^{-1}$ for the rectal route), with a maximum daily dose of 80–100 mg $kg^{-1}$ for 2–3 days, and subsequent dose reduction to 60–75 mg $kg^{-1}$.[2,9,11,12,30,32–36] For i.v. administration, which achieves more predictable plasma concentrations, an initial 15–20 mg $kg^{-1}$ dose and a daily maximum dose of 60–80 mg $kg^{-1}$ are recommended for the first 2–3 days.[2,9,11,14,21,36]

As the potential hepatotoxicity of paracetamol is well known, medical staff may be reluctant to use higher doses and choose to follow the manufacturer's instructions. However, this dosing could be considered antipyretic rather than analgesic.[14] It should be noted that in Group I, if paracetamol was administered, the i.v. route was favoured.

For NSAID, recommendations and expert opinions are more consistent. For metamizole, single doses range between 15 and 20 mg $kg^{-1}$.[11,37–39]

Clear concepts for the provision of safe and effective dosing, particularly for rectal paracetamol and drug combinations, are helpful. Because of the rapid onset of analgesia and more reliable plasma concentrations compared with the enteral route, i.v. paracetamol could be preferred depending on its availability and the presence of an i.v. line. Joint

interdisciplinary standards should be agreed upon by surgeons, paediatricians, anaesthesiologists, and nurses.

### Opioids

Opioids are considered rescue medications in multimodal treatment approaches. They are administered as needed if analgesia with non-opioids and regional techniques are not sufficient. The higher opioid doses in Group III were likely because of the higher pain scores in these children. Whether the amount of non-opioid analgesics is causally related to opioid doses, pain scores, or both cannot be derived from the data.

Hyperplasia of the tonsils can cause obstruction of the upper airway, and opioids can exaggerate respiratory problems, particularly in children suffering from sleep apnea.[9,10,21,40] Adequate monitoring of these patients is crucial.[10,40] In the present analysis, 26% of all patients received opioids on the ward, a much lower percentage than the 58.3% in a United States study.[41]

### Dexamethasone

For tonsillectomy, intraoperative dexamethasone is strongly recommended for prophylaxis of nausea and vomiting and as a co-analgesic to reduce pain and prolong latency times to analgesic administration.[9–11,21,42] Furthermore, it decreases the time to oral intake of fluids and solids, side-effects are rare, and it is inexpensive.[14,42] A single dose of 0.15–1.0 mg $kg^{-1}$ is proposed, with some guidelines restricting the maximum dose to 0.25–0.3 mg $kg^{-1}$ as a result of one report of increased bleeding episodes with higher doses.[9,14,21,42] However, evidence for optimal analgesic and safe dosing of dexamethasone is scarce. From the present results we can conclude that with 34.1% of the children receiving no dexamethasone at all and a further 40% being underdosed (<0.15 mg $kg^{-1}$), a department-specific standard operating procedure/guideline on routine use and sufficient dosing of dexamethasone could improve perioperative care of children.

### Limitations and strengths

Within the PAIN OUT infant registry, only the first 24 h after surgery are assessed. Comorbidities, urgency of surgery, and psychological and parental factors are not considered and might contribute to children's outcomes. Regional analgesia and co-analgesics, such as ketamine or clonidine, were rarely used in this cohort, and were not analysed. For appendectomy, regional analgesic techniques are now increasingly used within a multimodal analgesic regimen,[14] and these might contribute to improved PROs.

One strength is that the database is derived from everyday clinical practice reflecting the care given to the majority of patients, and not in artificial study settings, where patient care may differ. Standardised questionnaires and data collection procedures were used, allowing benchmarking to distinguish between institutions.

We used a more global measure of PROs, considering pain-related functional interference instead of pain scores only. This is in line with the multidimensional characteristic of pain severity, encompassing pain intensity and pain-related functional interference.[5,6,43] PRO scores can be regarded as an attempt to develop a more comprehensive assessment of children's pain experience using a single variable. A future consensus on a core outcome set of paediatric pain-related PROs would be helpful.

## Conclusions

Adequate dosing of non-opioid analgesics and dexamethasone, and lower opioid doses were associated with favourable patient-reported outcomes in children undergoing appendectomy and tonsillectomy. Timely administration of adequate doses is easy and cost-effective. Improvements require interdisciplinary concepts, education of staff, and measures of quality control that consider processes and pain-related patient-reported outcomes.

## Authors' contributions

Study conception and design: US, TL, FS, WM
Acquisition of data, analysis and interpretation of data: US, KB, KBJ, SS, MH, TL, FS, WM
Drafting the manuscript and revising it critically: KB, US, TL, KBJ, MH, 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.

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## Declarations of interest

WM received payments for advisory boards and talks outside of the submitted work from Mundipharma, Grünenthal, Ethypharm, Spectrum Therapeutics, Septodont, and Northern Swan. US received payments for lectures outside the submitted work from Sanofi Aventis, and Grünenthal, Switzerland, paid to her institution. The other authors declare that they have no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.09.028.

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**Supplementary Content**

**Methods: Calculation of full daily doses of non-opioid analgesics**

For the **"conservative approach",** the following doses were considered as one full daily dose: Acetaminophen i.v., rectal or oral 60 µg $kg^{-1}$; metamizole (dipyrone) i.v. or oral 60 µg $kg^{-1}$; ibuprofen 30 µg $kg^{-1}$; diclofenac 3 µg $kg^{-1}$; ketorolac: 1.5 µg $kg^{-1}$.
Examples: If a patient had received i.v. acetaminophen 40 µg $kg^{-1}$ and diclofenac 2.5 µg $kg^{-1}$, this referred to a daily dose of acetaminophen 0.67 and diclofenac 0.83, with a total of 1.5 full doses of non-opioid analgesics.
If a patient had received p.r. acetaminophen 30 µg $kg^{-1}$ and metamizole i.v. 30 µg $kg^{-1}$, this referred to a daily dose of acetaminophen 0.5 and metamizole 0.5, with a total of 1.0 full doses of non-opioid analgesics.
If a patient had received i.v. acetaminophen 60 µg $kg^{-1}$, i.v. metamizole 60 µg $kg^{-1}$ and p.r. ibuprofen 20 µg $kg^{-1}$ this referred to a daily dose of acetaminophen 1.0, metamizole 1.0 and ibuprofen 0.67, with a total of 2.7 full doses of non-opioid analgesics.

For all children weighing ≥50 kg, the adult maximum daily doses of 4000 mg acetaminophen and 4000 mg metamizole were considered as one full daily dose. For Etoricoxib this was 60 mg, for Ketoprofen 100 mg.

The alternative **"liberal approach"** is based on published papers and recommendations using higher daily doses for acetaminophen and metamizole:
Paracetamol p.r. 90 µg $kg^{-1}$, paracetamol p.o. 80 µg $kg^{-1}$ and metamizole 75 µg $kg^{-1}$.

**Supplemental Table S1**: PRO-1 scores of the three hospital groups I, II and III and of each participating hospital.

| | | n | Mean | 95%-CI | Median (IQR) | p |
|---|---|---|---|---|---|---|
| Hospital groups | | | | | | |
| I | | 324 | 4.51 | 4.2-4.8 | 4.3 (2.7; 6.0) | |
| II | | 281 | 5.17 | 4.9-5.4 | 5.0 (3.7; 6.7) | <0.001 |
| III | | 293 | 5.66 | 5.4-6.0 | 5.7 (4.0; 7.3) | |
| Hospitals | | | | | | |
| Group I | B | 60 | 3.6 | 3.1-4.1 | 3.7 (2.0; 5.0) | |
| | A | 149 | 4.7 | 4.3-5.1 | 5.0 (3.0; 6.3) | 0.005 |
| | I | 115 | 4.7 | 4.2-5.2 | 5.0 (2.7; 6.3) | |
| Group II | G | 45 | 5.0 | 4.3-5.6 | 4.3 (3.7; 6.3) | |
| | C | 175 | 5.2 | 4.9-5.6 | 5.0 (3.3; 7.0) | 0.791 |
| | E | 61 | 5.2 | 4.8-5.7 | 5.0 (4.3; 6.3) | |
| Group III | J | 76 | 5.3 | 4.8-5.9 | 5.3 (3.7; 7.0) | |
| | F | 64 | 5.4 | 4.7-6.1 | 5.7 (3.0; 7.3) | |
| | D | 59 | 5.6 | 5.0-6.3 | 5.3 (4.0; 7.0) | 0.172 |
| | K | 54 | 6.0 | 5.3-6.7 | 5.8 (4.3; 8.0) | |
| | H | 40 | 6.3 | 5.6-7.1 | 6.2 (4.8; 8.0) | |
| All hospitals | | 898 | 5.1 | 4.9-5.3 | 5.0 (3.3; 6.7) | |

IQR: interquartile range

**Supplemental Table S2**: Results of the multinomial regression analysis with hospital group according to PRO-scores as dependent variable.

For the number of postoperative full 24 h doses, the conservative approach was used. Nagelkerke's $R^2$: 0.425.

| | | **Group III versus reference group I** | | | **Group II versus reference group I** | | |
|---|---|---|---|---|---|---|---|
| **Variables** | | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** |
| Appendectomy vs tonsillectomy (reference) | | 0.72 | 0.46-1.13 | 0.151 | 0.876 | 0.53-1.46 | 0.612 |
| Duration of surgery | minutes | 1.002 | 0.99-1.01 | 0.681 | 0.951 | 0.94-0.96 | <0.001 |
| Sex | females vs. males (reference) | 1.297 | 0.91-1.85 | 0.154 | 1.516 | 1.03-2.24 | 0.037 |
| Age | years | 1.123 | 1.02-1.24 | 0.018 | 1.205 | 1.09-1.34 | <0.001 |
| Weight | kg | 0.982 | 0.97-1.00 | 0.041 | 0.993 | 0.97-1.01 | 0.428 |
| Number of postoperative full 24 hrs doses of non-opioid analgesics (conservative approach) | | 0.307 | 0.23-0.41 | <0.001 | 0.181 | 0.12-0.26 | <0.001 |
| Opioids on the ward | ME µg $kg^{-1}$ | 1.005 | 1.00-1.01 | 0.001 | 1.002 | 1.00-1.01 | 0.184 |
| Dexamethasone | yes / no (reference ) | 0.498 | 0.34-0.73 | <0.001 | 1.137 | 0.74-1.76 | 0.561 |
| Preventive non-opioid analgesics yes / no (ref.) | | 0.395 | 0.24-0.66 | <0.001 | 1.241 | 0.65-2.36 | 0.510 |

OR: Odds Ratio; ME: morphine equivalents in µg $kg^{-1}$ body weight

**Supplemental Table S3**: Results of the multinomial regression analysis with hospital group according to PRO-scores as dependent variable for **appendectomy.** For the number of postoperative full 24 h doses, the conservative approach was used. Nagelkerke's $R^2$: 0.506.

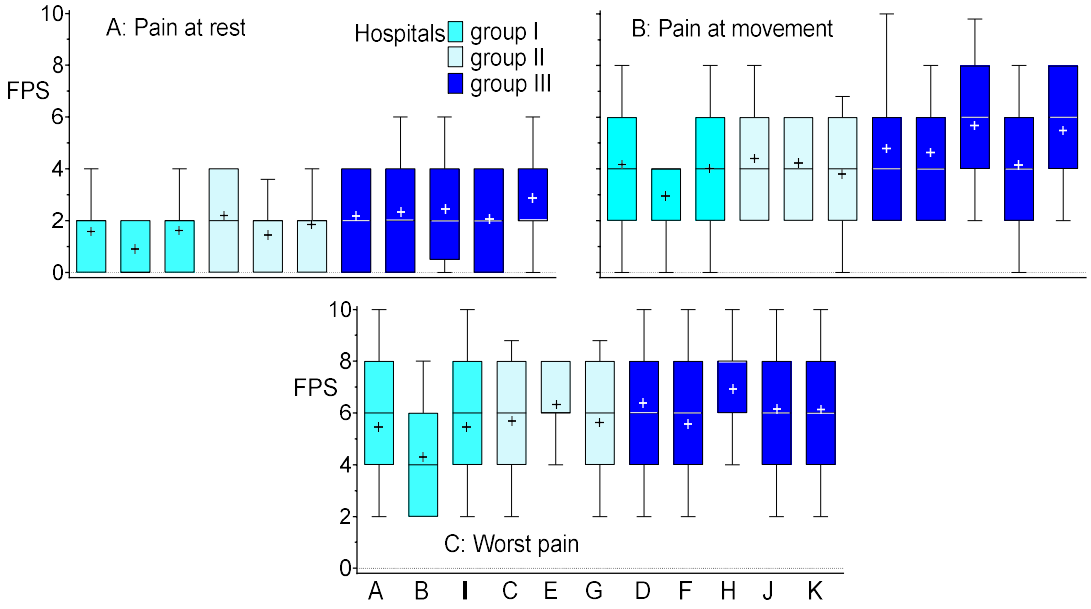
| | | **Group III versus reference group I** | | | **Group II versus reference group I** | | |
|---|---|---|---|---|---|---|---|
| **Variables** | | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** |
| Duration of surgery | minutes | 1.010 | 1.00-1.02 | 0.092 | 0.963 | 0.95-0.98 | <0.001 |
| Sex | females vs. males (reference) | 0.809 | 0.48-1.36 | 0.422 | 1.108 | 0.62-1.99 | 0.733 |
| Age | years | 1.153 | 1.01-1.32 | 0.034 | 1.079 | 0.93-1.26 | 0.329 |
| Weight | kg | 0.967 | 0.97-0.99 | 0.003 | 0.981 | 0.96-1.01 | 0.139 |
| Number of postoperative full 24 hrs doses of non-opioid analgesics (conservative approach) | | 0.138 | 0.08-0.23 | <0.001 | 0.037 | 0.02-0.08 | <0.001 |
| Opioids on the ward | ME µg $kg^{-1}$ | 0.994 | 0.99-1.00 | 0.039 | 0.998 | 0.99-1.00 | 0.551 |
| Dexamethasone | yes / no (reference ) | 0.292 | 0.17-0.51 | <0.001 | 0.461 | 0.24-0.89 | 0.022 |
| Preventive non-opioid analgesics | yes / no (ref.) | 0.342 | 0.17-0.68 | 0.002 | 0.642 | 0.29-1.45 | 0.285 |

OR: Odds Ratio; ME: morphine equivalents in µg $kg^{-1}$ body weight

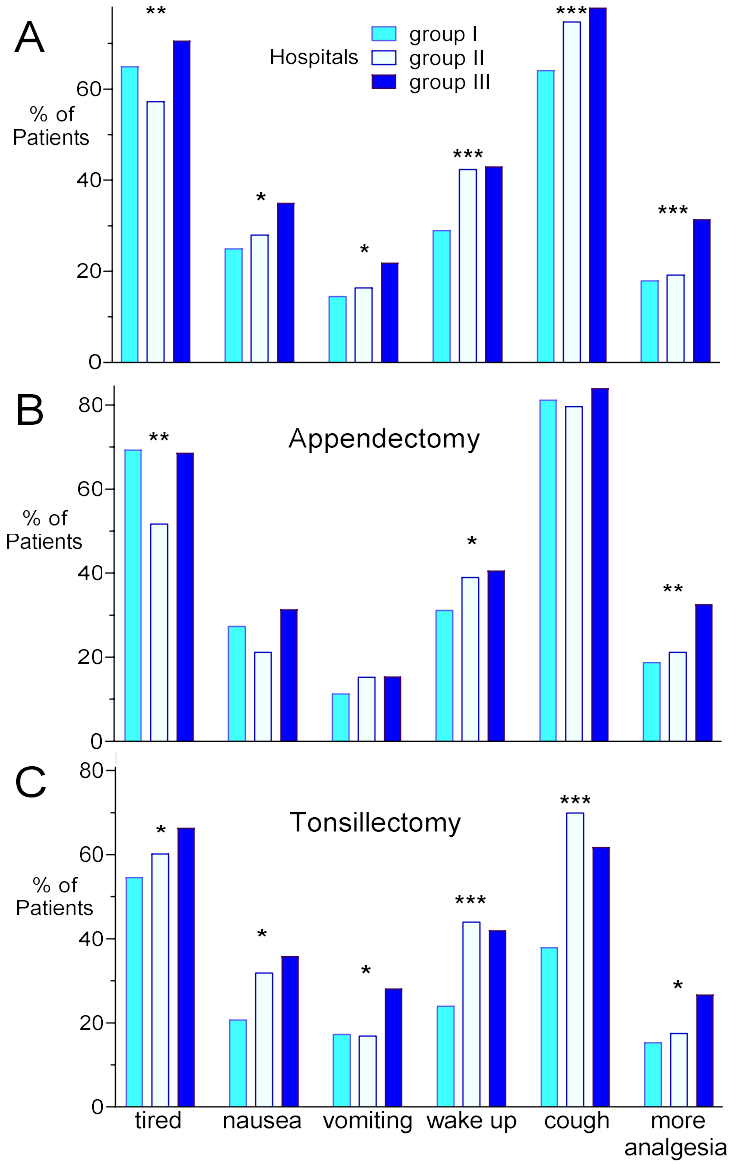
**Supplemental Table S4**: Results of the multinomial regression analysis with hospital group according to PRO-scores as dependent variable for **tonsillectomy.** For the number of postoperative full 24 h doses, the conservative approach was used. Nagelkerke's $R^2$: 0.561.

| | | **Group III versus reference group I** | | | **Group II versus reference group I** | | |
|---|---|---|---|---|---|---|---|
| **Variables** | | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** |
| Duration of surgery | minutes | 0.988 | 0.98-1.00 | 0.087 | 0.944 | 0.92-0.96 | <0.001 |
| Sex | females vs. males (reference) | 2.414 | 1.35-4.32 | 0.003 | 2.136 | 1.17-3.89 | 0.013 |
| Age | years | 0.993 | 0.83-1.19 | 0.937 | 1.249 | 1.05-1.49 | 0.012 |
| Weight | kg | 1.007 | 0.97-1.04 | 0.692 | 1.005 | 0.97-1.04 | 0.762 |
| Number of postoperative full 24 hrs doses of non-opioid analgesics (conservative approach) | | 0.464 | 0.31-0.70 | <0.001 | 0.367 | 0.23-0.60 | <0.001 |
| Opioids on the ward | ME µg $kg^{-1}$ | 1.047 | 1.03-1.07 | <0.001 | 1.039 | 1.02-1.06 | <0.001 |
| Dexamethasone | yes / no (reference ) | 0.536 | 0.30-0.97 | 0.039 | 1.900 | 0.98-3.66 | 0.056 |
| Preventive non-opioid analgesics | yes / no (ref.) | 0.411 | 0.17-0.99 | 0.048 | 15.024 | 2.68-84.17 | 0.002 |

OR: Odds Ratio; ME: morphine equivalents in µg $kg^{-1}$ body weight




**Supplemental Figure S1:** Pain scores (FPS; Faces Pain Scale revised) at rest (A), for movement-evoked pain (B) and for worst pain since surgery (C). Hospital Group I (lowest PRO-scores), Group II (moderate PRO-scores) and Group III (highest PRO-scores) are colour-coded. Box and whiskers with median, IQR, 10th-90th percentiles and mean (+).




**Supplemental Figure S2:** Percent of patients reporting side effects (being tired, having nausea, vomiting) and pain-related interference (waking up during night due to pain, pain-related interference with coughing or taking a deep breath) or liked to have received more analgesia in Group I, II and II hospitals. A: all patients, B: Appendectomy, C: Tonsillectomy; $\chi^2$ test: * $p<0.05$; ** $p<0.01$; *** $p<0.001$.