

## Effect of dexamethasone on nausea, vomiting, and pain in paediatric tonsillectomy

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### Editor's key points

- Paediatric tonsillectomy is associated with significant postoperative nausea, vomiting, and pain.
- A prospective randomized controlled trial tested the effects of a single dose of dexamethasone at the induction of anaesthesia on postoperative nausea, vomiting, and pain in children after tonsillectomy
- Dexamethasone reduced the incidence of postoperative nausea, vomiting, and pain in children at both doses tested.

**Background.** The efficacy of dexamethasone (DEX) to reduce morbidity after paediatric tonsillectomy remains controversial. We evaluated the effect of 0.15 and 0.5 mg kg<sup>-1</sup> DEX on the incidence of postoperative nausea and vomiting (PONV) and on pain intensity after paediatric tonsillectomy.

**Methods.** A total of 147 children aged 2–8 yr undergoing elective tonsillectomy were included in this prospective randomized double-blind study. At the induction of anaesthesia, subjects received 0.15 mg kg<sup>-1</sup> (DEX 0.15), 0.5 mg kg<sup>-1</sup> (DEX 0.5) DEX, or an equivalent volume of saline solution (placebo). Anaesthetic and surgical techniques were standardized. The incidence of PONV and the need for anti-emetic drugs and additional analgesia (tramadol and/or morphine) were recorded. Postoperative pain was assessed using the Children's Hospital of Eastern Ontario Pain Scale, the visual analogue scale, and the postoperative pain measure for parents.

**Results.** The incidence of early PONV (primary outcome variable) was lower in both DEX groups (DEX 0.15: 21%; DEX 0.5: 22%; placebo: 49%;  $P=0.001$ ). The incidence of severe pain was reduced in the DEX groups on the second postoperative day (DEX 0.15: 20%; DEX 0.5: 5%; placebo: 47%;  $P<0.001$ ). The study was not powered to assess a difference between the two DEX dose groups.

**Conclusions.** A single i.v. injection of DEX at the induction of anaesthesia was effective in reducing the incidence of early and late PONV and the level of pain on the second postoperative day. A 0.15 mg kg<sup>-1</sup> DEX dose appeared to be as effective as a 0.5 mg kg<sup>-1</sup> dose to reduce the incidence of PONV.

**Keywords:** dexamethasone; nausea/vomiting; paediatric; pain; tonsillectomy

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Tonsillectomy is one of the most frequently performed surgical procedures in children.<sup>1</sup> It remains associated with a high morbidity related to postoperative nausea and vomiting (PONV), pain, risk of bleeding, and dehydration due to impaired oral intake.<sup>2</sup> In children undergoing ambulatory tonsillectomy, PONV and pain are responsible for a hospital readmission rate of 14%.<sup>3</sup>

PONV is of multi-factorial origin, with a reported incidence ranging from 23% to 73%.<sup>4 5</sup> Post-tonsillectomy pain is also multi-factorial; it is more intense within the first three post-operative days, but can persist until day 10.<sup>6</sup> Steroids can have beneficial effects on post-tonsillectomy morbidity due to their anti-emetic and anti-inflammatory properties; however, there is still no consensus on whether they should be used routinely after tonsillectomy. The most studied steroid for this purpose is dexamethasone (DEX), which is inexpensive and largely devoid of side-effects. A recent Cochrane meta-analysis concluded that 'a single

i.v. dose of DEX is an effective, safe and inexpensive treatment for reducing morbidity from paediatric tonsillectomy'.<sup>7</sup> The general consensus among authors is that DEX must be administered at the induction of anaesthesia to be effective, but the optimal dose is still debated. The aim of the present study was to evaluate the efficacy of two single i.v. doses of DEX, 0.15 and 0.5 mg kg<sup>-1</sup>, on the incidence of PONV, and on pain intensity after elective tonsillectomy in children.

### Methods

The Institutional Ethics Committee approved this study, and informed parental written consent was obtained. One hundred and forty-seven patients, aged 2–8 yr, undergoing elective tonsillectomy with or without adenotonsillectomy, were included in this prospective randomized double-blind study (EUDRACT number: 2006-005789-38). Indications for tonsillectomy were obstructive sleep apnoea syndrome with tonsil hypertrophy, recurrent infections (more than four

episodes within two consecutive years) or tonsillar abscess. Exclusion criteria included active infection, diabetes mellitus, sickle cell disease, known coagulation disorders, and pre-operative treatment with anti-emetics, steroids, or analgesics.

Subjects were randomized to three groups to receive 0.5 mg kg<sup>-1</sup> DEX up to a maximum of 15 mg (DEX 0.5), 0.15 mg kg<sup>-1</sup> DEX up to a maximum of 8 mg (DEX 0.15), or an equivalent volume (0.5 ml kg<sup>-1</sup>) of NaCl 0.9% (placebo). Patients weighing more than 30 kg were excluded in order not to exceed the maximum dose of DEX. Bloc randomization was performed using an envelope system. Each bloc included 15 subjects, five in each treatment arm. On the morning of the procedure, an anaesthesiologist who was not involved in the study drew an envelope indicating the treatment allocation. Every 15 enrolled subjects, a new bloc of 15 envelopes was created. The treatment solution was prepared by the anaesthesiologist who performed the randomization and was handed to the anaesthesia team in charge of the subject. Those team members were blinded to treatment allocation.

A standard anaesthetic technique was used in all children. Premedication consisted of 0.5 mg kg<sup>-1</sup> midazolam rectally 30 min before induction for children under 4 yr old or orally 45 min before induction for children 4 yr old and older. Monitoring of subjects during the procedure included pulse oximetry, heart rate (ECG), non-invasive arterial pressure, rectal temperature, and end-tidal CO<sub>2</sub>.

Anaesthesia was induced with sevoflurane and 50% nitrous oxide in oxygen. After insertion of the i.v. line, children received 2 µg kg<sup>-1</sup> fentanyl, 15 mg kg<sup>-1</sup> paracetamol, 2 mg kg<sup>-1</sup> tramadol, and the randomized treatment solution (DEX or placebo) i.v. All subjects received lactated Ringer's solution after the 4/2/1 rule.<sup>3</sup> After tracheal intubation, anaesthesia was maintained with sevoflurane in a mixture of nitrous oxide and oxygen (50/50). Tonsillectomy was performed using the dissection technique combined with electrocoagulation when judged necessary by the surgeon. At the end of surgery, subjects were extubated when awake and transferred to the post-anaesthesia care unit (PACU).

Each subject was assessed by trained nurses on the PACU. PONV was defined as vomiting and/or retching without expulsion of gastric content and was treated with i.v. alizapride (1 mg kg<sup>-1</sup> maximum every 8 h) followed, if necessary, by tropisetron (0.1 mg kg<sup>-1</sup> maximum every 12 h). Pain was assessed using the Children's Hospital of Eastern Ontario Pain scale (CHEOPS).<sup>8</sup> If the CHEOPS score was >7, i.v. morphine was titrated with a bolus of 25 µg kg<sup>-1</sup> that was repeated every 5 min when necessary. On the ward, pain assessment was performed using the CHEOPS for children aged 2–5 yr and the visual analogue scale (VAS) for children aged 6–8 yr.<sup>9</sup> Postoperative analgesia consisted of paracetamol (15 mg kg<sup>-1</sup>) every 6 h and, if necessary (CHEOP>7 or VAS≥3), tramadol (2 mg kg<sup>-1</sup>) every 8 h. All agents were given i.v. in the PACU and on the ward until the venous line was removed. Criteria for discharge from the PACU included full consciousness, adequate pain control (CHEOPS≤7), no bleeding, stable vital signs, and no vomiting for at least 1 h

after the children were capable of ingesting ice cubes without significant pain or PONV.

The following parameters were observed and recorded: incidence of PONV and need for treatment (alizapride and tropisetron); postoperative pain in the PACU until discharge to the ward, in the evening after surgery, and on the following day before discharge from the hospital; time to discharge from the PACU; and incidence of surgical re-exploration for bleeding. On the second postoperative day, the incidence of PONV and pain severity were evaluated by a phone call to the parents. Assessment of postoperative pain was performed using the postoperative pain measure for parents (PPMP) scale.<sup>10</sup> Because three different scales were used to evaluate postoperative pain, analysis of pain severity was dichotomously assessed as the presence of significant pain (CHEOPS>7, VAS≥3, PPMP>6) or no significant pain.

### Statistical and sample size analysis

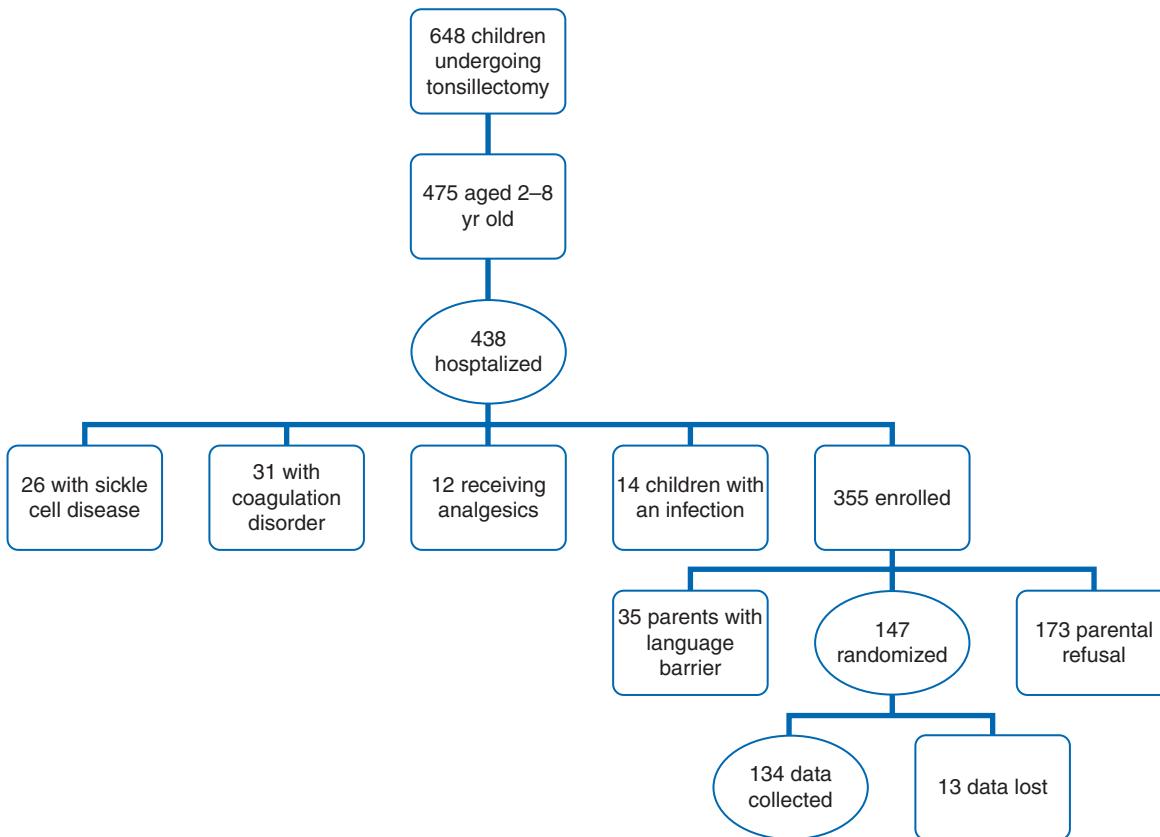
The primary outcome variable of the present study was the incidence of PONV. Previous studies<sup>3 4 11 12</sup> reported an incidence of PONV of 60 (24%) and a reduction of this incidence by about 50% with DEX. Based on these data, the present study had to include a minimum of 42 subjects in each group to have a power of 0.8 and an  $\alpha$  of 0.05. After testing for normal distribution (Kolmogorov-Smirnov test), the three groups were compared using the Kruskal-Wallis test and  $\chi^2$  where appropriate. Data are presented as median (inter-quartiles) or percentages. Randomization allocation was broken only after the statistical analysis was finalized. A P-value of <0.05 was considered significant.

### Results

From September 2005 to June 2010, 648 children undergoing tonsillectomy with or without adenoidectomy were screened for participation in the study (Fig. 1). A total of 147 children were enrolled, of which 13 were excluded because of missing data. There were thus 134 children in the final analysis. The patient characteristic and type of surgery did not differ in the three groups (Table 1). Only one subject (in the placebo group) required surgical re-exploration for significant bleeding.

The time (in min) until discharge from the PACU was not different in the groups [reported as median (25–75% IQ): placebo: 120 (90–180); DEX 0.15: 120 (90–150); DEX 0.5: 120 (90–157); P=0.464]. However, the incidence of PONV was significantly reduced in the DEX groups compared with the placebo group both during hospitalization and on post-operative day 2 (Fig. 2). There was no difference in PONV incidence between the two DEX groups. The use of alizapride was also lower in the DEX group than in the placebo group (Table 2). Only a few subjects received tropisetron: six in the placebo group, two in the DEX 0.15 group, and one in the DEX 0.5 group (P=0.118) (Table 2).

Administration of DEX did not reduce the number of subjects receiving morphine (PACU) or tramadol on the ward (Table 2). However, time to first dose of tramadol was

**Fig 1** Flow chart showing an overview of the study.**Table 1** Subject characteristics. Data are presented as median (inter-quartile range) or percentages.  $P<0.05$  was considered significant

	Placebo (n=44)	DEX 0.15 (n=46)	DEX 0.5 (n=44)	P-value
Age (months)	49 (39–62)	45 (37–60)	44 (35–57)	0.341
Weight (kg)	17 (15–20)	16 (14–19)	16 (14–18)	0.302
Number having tonsillectomy with adenotonsillectomy (%)	95	98	100	
Electrocoagulation (%)	74	84	76	

shorter in the placebo group [478 (376–533) min] than in the DEX 0.15 [778 (496–1180) min] and in the DEX 0.5 [555 (450–845) min] groups ( $P=0.017$ ).

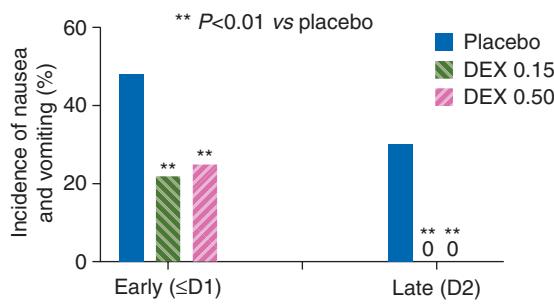
During hospitalization, the incidence of significant pain did not differ between DEX groups and the placebo group (Fig. 3). However, on postoperative day 2, the incidence of significant pain was significantly lower in the DEX groups, and there was no difference in the incidence between the two doses (Fig. 2).

## Discussion

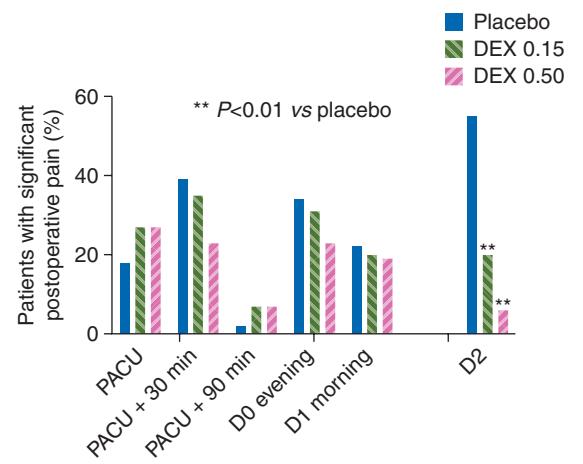
The results of the present study indicate that of DEX significantly reduces morbidity after tonsillectomy. A single dose of DEX given at the induction of anaesthesia reduced the

incidence of early and late PONV and improved pain scores on the second postoperative day. A dose of 0.5 mg kg<sup>-1</sup> DEX did not appear to be more effective than a dose of 0.15 mg kg<sup>-1</sup>, although the study was not powered for this endpoint.

Several studies have evaluated the effects of DEX on PONV and pain after paediatric tonsillectomy. They often included a limited number of patients<sup>13–16</sup> and/or did not use standardized anaesthetic techniques and rescue treatment protocols.<sup>12, 16</sup> In addition, the results of the few randomized placebo-controlled studies that evaluated the effects of a single i.v. corticosteroid administration are conflicting, in that some studies showed a beneficial effect, while others did not.<sup>4, 11, 17, 18</sup> The anti-emetic properties of DEX are well established,<sup>4, 11, 17–19</sup> but the mechanisms underlying this



**Fig 2** Incidence of early [day of surgery or postoperative day (D1)] and late (D2) PONV in the three study groups. \*\* $P<0.01$  vs placebo group.



**Fig 3** Incidence of severe postoperative pain during the study period in the three groups. PACU, upon arrival in the post-anaesthesia care unit; PACU+30 min and PACU+90 min, 30 and 90 min after admission to the PACU; D0 evening, the evening of the surgery; D1 and 2, postoperative days 1 and 2. \*\* $P<0.01$  vs placebo group.

**Table 2** Need for analgesics and anti-emetics. Data show the percentage of patients that received the indicated agent.  $P<0.05$  was considered significant

	Placebo (n=44)	DEX 0.15 (n=46)	DEX 0.5 (n=44)	P-value
Alizapride (%)	50	11	25	0.005
Tropisetron (%)	7	4	2	0.578
Morphine (%)	52	43	36	0.321
Tramadol (%)	52	38	40	0.331

anti-emetic effect remain largely unknown. A direct inhibition of prostaglandins, serotonin, or endorphin production has been postulated.<sup>17</sup>

Although the anti-inflammatory effects of DEX are well known, their effects on postoperative pain remain a point of debate.<sup>1 17 18</sup> We observed an effect on pain only on the second postoperative day. Based on the pharmacokinetic profile of DEX, it is expected that its anti-inflammatory effects will appear several hours after its administration. Therefore, it is not surprising that the effect of DEX on postoperative pain was observed only on the second postoperative day. This could also explain why some studies failed to observe significant pain reduction with DEX in the immediate postoperative period.

The optimal dosage of DEX is also a subject of debate. Gunter and colleagues<sup>20</sup> and Kim and colleagues<sup>21</sup> compared DEX doses ranging from 0.0625 to 1.0 mg kg<sup>-1</sup> in paediatric tonsillectomy. They did not observe a dose-dependent effect on the incidence of PONV and pain. Karaman and colleagues<sup>19</sup> compared the effects of two doses of DEX, 0.2 and 0.7 mg kg<sup>-1</sup>, with a placebo group on PONV after tonsillectomy, and observed a reduction in the incidence of PONV in the groups receiving DEX with no difference between the two doses. Our results are in line with these reports.

In most studies, administration of DEX is not associated with significant side-effects in children undergoing tonsillectomy.<sup>7</sup> Only one study reported a dose-related increase in

the incidence of postoperative bleeding.<sup>15</sup> However, this study was quite small and bleeding was far outside the generally reported range of about 1%. Moreover, a recent study in 2788 children did not observe a dose-dependent elevation of postoperative haemorrhage with perioperative DEX administration (0.5 or 1.0 mg kg<sup>-1</sup>).<sup>22</sup>

Our results should be interpreted within the context of the study design. We decided to administer DEX at the induction of anaesthesia as it was shown to be more efficacious than when administered at the end of the procedure.<sup>23</sup> We selected children between 2 and 8 yr of age in order to have a standardized anaesthetic technique based on mask induction with sevoflurane and nitrous oxide. Indeed, mask induction is often not well accepted in children older than 8 yr.

Nausea is difficult to assess in children up to 5 yr old. Therefore, we defined PONV as vomiting and/or retching without expulsion of gastric content. We still kept the term PONV instead of the term POV (postoperative vomiting) which only relates to vomiting and omits retching which can be considered as a marker of nausea.

We assessed pain severity using three scoring systems. The CHEOPS score is a behavioural observational pain score that is mostly used to assess pain severity in young children but is also applicable to older children in the immediate post-operative period (i.e. when they are still not capable of scoring pain by a VAS). The incidence of PONV and severe pain on postoperative day 2 were evaluated by a phone call to each child's parents using the PPMP scale. This scale has been validated for evaluating postoperative pain in children by the parents.<sup>10</sup> All our subjects remained in the hospital up to postoperative day 1, which allowed for a better assessment of postoperative pain and PONV.

In conclusion, a single i.v. injection of DEX at the induction of anaesthesia reduced the incidence of early and late PONV and pain severity on the second postoperative day. A DEX dose of  $0.15 \text{ mg kg}^{-1}$  appeared to be as efficacious as a dose of  $0.5 \text{ mg kg}^{-1}$ . Our results are consistent with those reported previously. The minimum dose of DEX that reduces vomiting, however, still remains undetermined.

## Declaration of interest

S.D.H. has received speaker's fees from Abbott International, Baxter International and Fresenius Belgium. P.V.d.L. has received speaker's fees and travel grants from Fresenius Kabi GmbH, Germany, and Janssen-Cilag SA, Belgium.

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