Effect of dexamethasone on postoperative morbidity after dental rehabilitation in children

Effet de la dexaméthasone sur la morbidité postopératoire après restauration dentaire chez l'enfant

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Abstract

Purpose *Dexamethasone reduces postoperative morbidity after adenotonsillectomy, strabismus surgery, and third molar extraction. Our hypothesis was that dexamethasone would reduce pain and other morbidity in children undergoing dental surgery for up to 24 hr postoperatively.*
Methods *A triple-blinded, randomized, controlled trial was carried out on 200 children undergoing prolonged dental rehabilitation under general anesthesia. Subjects were randomized into two groups: group D, given dexamethasone 0.3 mg·kg⁻¹; group S, given normal saline. The primary outcome measure was pain over 24 hr as evaluated by a parental 0-10 numerical rating scale (NRS). Key secondary outcomes included oral intake on a four-point*

scale at 24 hr and the overall incidence of postoperative vomiting (POV). Analysis for the primary outcome consisted of comparison of means in the NRS with the Wilcoxon rank sum test and for occurrence of POV with Fisher's test.

Results *After eliminating 22 subjects for protocol violations and withdrawals, 178 subjects were analyzed. There was no significant difference in pain scores (NRS) at 24 hr or the worst NRS experienced over the preceding 24 hr. There was no difference in the quality of oral intake between the groups. There was a significant difference in the percentage of patients who vomited during the first 24 hr: eight of 91 in group S and one of 87 in group D. Therefore, 7.74% more vomited in group S ($P = 0.045$), with a 95% confidence interval of 0.32 to 15.16 for the difference in percentages.*

Conclusions *Dexamethasone, 0.3 mg·kg⁻¹, did not reduce pain over 24 hr in healthy children undergoing dental rehabilitation under general anesthesia. The quality of oral intake was also unaffected by dexamethasone at 24 hr. Dexamethasone did produce a significant reduction in postdischarge vomiting, beyond the incidence found with ondansetron alone.*

Author contributions *Rebecca E. McIntyre was involved in the study design, study implementation, manuscript preparation, and abstract presentation. Christina Hardcastle was responsible for study implementation, manuscript presentation, and abstract presentation. Reuben L. Eng was involved in study implementation and abstract presentation. Alberto Nettel-Aguirre, Kristine Urmson and David R. Lardner were involved with study design and study implementation. Meggie Livingstone was involved with study implementation. Alastair Ewen participated in study design and manuscript review. Robin G. Cox is principal investigator and was involved in study design and manuscript preparation.*

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Résumé

Objectif *La dexaméthasone diminue la morbidité postopératoire après une intervention chirurgicale pour adéno-amygdalectomie, strabisme et extraction de la troisième molaire. Nous avons formulé l'hypothèse que la dexaméthasone pouvait diminuer la douleur et d'autres morbidités chez des enfants subissant une chirurgie dentaire jusqu'à 24 heures après l'intervention.*

Méthodes *Une étude randomisée, contrôlée, à triple insu a été menée chez 200 enfants subissant une restauration*

dentaire prolongée sous anesthésie générale. Les patients ont été randomisés en deux groupes : le groupe D a reçu 0,3 mg/kg de dexaméthasone; le groupe S a reçu du sérum physiologique. Le critère d'évaluation principal était la mesure de la douleur au cours des 24 heures au moyen d'une échelle d'évaluation numérique (EEN) de zéro à dix à l'usage des parents. Les critères d'évaluation secondaires incluait l'alimentation par la bouche dans les 24 heures sur une échelle à quatre points et l'incidence globale des vomissements postopératoires (VPO). L'analyse du critère d'évaluation principal a consisté en une comparaison des moyennes de l'EEN par le test de la somme des rangs de Wilcoxon et de la survenue de vomissements postopératoires par le test de Fisher.

Résultats Après l'élimination de 22 patients pour violations du protocole et sorties de l'étude, 178 patients ont pu être analysés. Il n'y a pas eu de différence significative dans les scores de douleur (EEN) à 24 h ou de l'EEN de la pire douleur éprouvée au cours des 24 h précédentes. Il n'y a pas eu de différence dans de l'alimentation entre les groupes. Il y a eu une différence significative quant au pourcentage de patients qui ont vomi au cours des 24 premières heures : huit sur 91 dans le groupe S et un sur 87 dans le groupe D. Le pourcentage de patients ayant eu des vomissements a donc été de 7,74 % plus élevé dans le groupe S ($P = 0,045$; intervalle de confiance à 95 % : 0,32 - 15,16 pour la différence en pourcentages).

Conclusions La dexaméthasone à la dose de 0,3 mg/kg n'a pas diminué la douleur au cours des 24 heures chez des enfants en bonne santé subissant une restauration dentaire sous anesthésie générale. La qualité de l'alimentation à 24 heures n'a pas, non plus, été modifiée par la dexaméthasone. La dexaméthasone a entraîné une réduction significative des vomissements après le congé allant au-delà de l'incidence constatée avec l'ondansétron seul.

Dental rehabilitation is one of the most common procedures requiring general anesthesia in children in North America. These procedures are often prolonged in nature and have the potential to cause significant morbidity from both the procedure and the anesthetic administered.^{1,2} In children undergoing tonsillectomy, dexamethasone has been shown to reduce postoperative pain and vomiting.³⁻⁶ It has also been shown to reduce pain, swelling, and postoperative nausea and vomiting following extraction of third molar teeth in adults.^{7,8} Dexamethasone has been shown to reduce postoperative nausea and vomiting in children following strabismus surgery,⁹⁻¹¹ especially in combination with ondansetron.¹² We hypothesized that a single intraoperative dose of dexamethasone would reduce postoperative pain and other morbidity in children for up to

24 hr after dental rehabilitation under general anesthesia. The primary outcome was postoperative pain, as measured by a parental numerical rating scale (NRS). The two key secondary outcomes measured were the quality of postoperative oral intake and the overall incidence of postoperative vomiting (POV). Other outcomes included the use of rescue analgesics and antiemetics and the overall parental satisfaction.

Methods

The Conjoint Health Research Ethics Board of the University of Calgary approved this study, and written consent was obtained from the parents or legal guardians of all subjects. The study population was selected from healthy children scheduled to undergo elective outpatient dental rehabilitation requiring general anesthesia scheduled for more than one hour. Required inclusion criteria were American Society of Anesthesiologists physical status I or II, age two to eight years, and at least one parent/guardian who spoke English. Exclusion criteria included any child who had an upper respiratory tract infection during the past two weeks, a history of using oral or inhaled steroids during the previous six months, significant gastrointestinal disease, or cognitive delay or who was undergoing an additional procedure other than dental rehabilitation.

Subjects recruited into the study were randomized into two groups via computer-generated randomization. To facilitate allocation concealment, the randomization sequence was created in blocks of randomized size. An independent anesthesiologist was aware of the randomization and prepared the identical study syringes, which contained either dexamethasone or normal saline; this anesthesiologist was not involved in the study following preparation of the study drugs and was responsible for concealing the randomization. Neither the investigators nor the statistician were unblinded until after the data were fully analyzed. The study was therefore triple-blinded in design. The two groups consisted of group D ($n = 87$), who received $0.3 \text{ mg} \cdot \text{kg}^{-1}$ (maximum 8 mg) of intravenous dexamethasone, and group S ($n = 91$), who received saline; both preparations were given after induction of anesthesia.

All subjects received a standardized anesthetic after preoperative acetaminophen ($20 \text{ mg} \cdot \text{kg}^{-1} \text{ po}$), induction with sevoflurane and nitrous oxide in 50% oxygen, followed by propofol ($1\text{--}3 \text{ mg} \cdot \text{kg}^{-1}$) to facilitate nasotracheal intubation. Anesthesia was maintained with isoflurane and nitrous oxide in 50% oxygen, as well as ketorolac ($0.5 \text{ mg} \cdot \text{kg}^{-1}$) and ondansetron ($0.1 \text{ mg} \cdot \text{kg}^{-1}$) given ten minutes before emergence. Fentanyl ($0.5 \mu\text{g} \cdot \text{kg}^{-1}$) was permitted at the discretion of the staff anesthesiologist, and atropine ($10 \mu\text{g} \cdot \text{kg}^{-1}$) was allowed in cases of bradycardia.

Lactated Ringer's solution was infused at a rate of $20 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ for the first hour followed by $10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ thereafter. The study drug was administered immediately following induction. During the recovery period, rescue analgesia or antiemetic therapy at standard doses included fentanyl or ondansetron in the phase 1 postanesthesia care unit; in the phase 2 day surgery unit, rescue medications included codeine or acetaminophen for pain, and dimenhydrinate for vomiting. Analgesia was given at the discretion of the nursing staff, and antiemetic rescue was to be administered for one episode of retching or vomiting. At the time of discharge, parents were instructed to administer acetaminophen or ibuprofen in standard doses if they thought the child was experiencing pain at home.

Demographic and procedural data were collected on all subjects to allow comparison between the groups. They included age, weight, sex, duration of anesthesia, number of extractions and crowns, and the use of a local anesthetic.

The primary outcome measure, postoperative pain, was measured by use of a parental 0–10 NRS.^{13,14} Parents were instructed on the use of this scale prior to hospital discharge and were then contacted by a study investigator at $24 (\pm 4)$ hr postoperatively, at which time a scripted interview was conducted. An NRS score was recorded at 24 hr, and the worst NRS score was determined for the preceding 24 hr.

Secondary outcome data included the following: incidence of vomiting or retching, recorded at any time during the hospital stay and for 24 hr postoperatively; need for rescue analgesia or antiemetics over 24 hr; quality of oral intake; overall parental satisfaction. Quality of oral intake was evaluated at 24 hr and was graded on a four-point scale, where children received a score of 4 if they requested fluids, 3 if they accepted fluids when offered, 2 if they accepted fluids if coaxed, and 1 if they refused fluids.^{15,16} Finally, an assessment of overall parental satisfaction was made at 24 hr, with 4 and 3 points indicating “very satisfied” and “quite satisfied,” respectively, and 2 and 1 points indicating “quite dissatisfied” and “very dissatisfied,” respectively.

Assuming a clinically important difference of one point in the NRS, a standard deviation of 2.381, a two-sample *t* test with alpha of 0.05, and power of 80%, we calculated a need for 90 subjects in each group, with an additional ten subjects per group to allow for study violations and withdrawals, for a total of 200 subjects. After the study was complete and the results examined, the data were found to be skewed. Therefore, analysis was undertaken with the Wilcoxon rank sum test for the main outcome and a test of difference in proportions for the vomiting incidence. Analysis was by intention to treat. All statistical tests were done using a significance level alpha of 0.05.

Results

Potential subjects were identified from dental operating room lists. Parents or guardians of 200 children were approached for enrolment in the study. After eliminating 22 children for unanticipated exclusion criteria, lack of consent, protocol violations, or withdrawals, 178 completed the study and were available for analysis: 87 children in group D and 91 in group S. The Table 1 provides the characteristics of the two groups; there was no evidence of a difference in the demographics, length of procedure, or complexity of the dental surgery performed in the two groups.

Regarding the primary outcome of interest, postoperative pain, as assessed by the parental NRS, there was no significant difference between the two groups. At 24 hr, the median (interquartile range [IQR]) NRS in both groups was 0 [1]. The NRS scores at 24 hr are shown in Figs. 1 and 2. As these data were clearly skewed, comparisons were made with the Wilcoxon rank sum test, which did not demonstrate a difference between the groups ($P = 1$).

When the child's worst pain over the first 24 hr was evaluated, again no difference was found. Over the first 24 hr the median [IQR] NRS in group D was 3 [5], and in group S it was 2.75 [4.00]. The NRS scores over 24 hr are shown in Figs. 3 and 4. As these data were also skewed, comparisons were made with the Wilcoxon rank sum test, which did not demonstrate a difference between the groups ($P = 0.498$).

Further supportive evidence against a difference in pain between the two groups was that there was no significant difference in the amount of rescue analgesia required. The median [IQR] number of doses in group S was 1 [2], and in group D it was 1 [1].

Two key secondary outcomes were evaluated: oral intake and POV. With regard to oral intake, no difference between the two groups was found at 24 hr (Fisher's test, $P = 0.082$). Fig. 5 shows the distribution in the four categories of oral intake. Of note, only one child in each group was refusing food at 24 hr.

Postoperative vomiting was the one key outcome that showed a difference between the two groups. No child vomited in hospital in either group. By 24 hr, eight of 90 had vomited in group S (no POV data in one subject), and one of 87 had vomited in group D. Therefore, 7.74% more vomited in group S ($P = 0.045$), with a 95% confidence interval for the difference in percentages of 0.32 to 15.16.

In terms of overall parental satisfaction, there was no significant difference between the two groups (Fisher's test, $P = 0.107$), with parents reporting either being “very satisfied” or “quite satisfied” in all but four cases: three in group S and one in group D.

Table 1 Demographics and Descriptives

Variable	Group S (<i>n</i> = 91)	Group D (<i>n</i> = 87)
Mean Age (SD)	54.5 (19) months	55.7 (18) months
Mean Weight (SD)	18.1 (5.6) kg	18.4 (5.0) kg
Gender (F)	<i>n</i> = 41 (45%)	<i>n</i> = 36 (41%)
Mean Duration (SD)	74 (24) min	75 (21) min
Median Extractions (IQR)	0 (2)	0 (1)
Mean Crowns (SD)	3.6 (2.6)	4.1 (3.2)
Local Anesthesia	<i>n</i> = 32 (35%)	<i>n</i> = 32 (36%)
Median Rescue Analgesic Doses (IQR)	1 (2)	1 (1)

SD = standard deviation;
IQR = interquartile range

Fig. 1 Parental numerical rating scale (0-10) scores for the children's pain at 24 hr. Group S = saline; group D = dexamethasone

Discussion

We were unable to demonstrate a difference between the two groups with respect to pain, our primary outcome measure. Possible explanations include the following: the effect was too small to measure; our method of assessing pain was inadequate; there really was no analgesic effect. Pain scores were low in both groups, making it difficult to detect a small analgesic effect. It may be that certain procedures (e.g., crowns or extractions) cause more pain, and dexamethasone may reduce pain scores in this subgroup. Our study was not powered to stratify risk in this way, and further studies may be warranted to investigate this hypothesis. Pediatric pain scores for use by parents have been previously found to be valid and to correlate well with scores given by a medical observer.^{13,14} Parents did not seem to have difficulty learning to use the NRS and were in most cases readily able to give a number to describe their child's pain. Occasionally some prompting was required, which is also the authors' experience in using a ten-point NRS to assess adult patients' pain.

The incidence of vomiting during the postoperative period was found to be low in both groups. None of our

patients vomited, retched, or required rescue antiemetics prior to discharge. The incidence of POV on the first day after discharge was lower than expected in the saline group (8.89%), with all of our patients receiving a single dose of ondansetron intraoperatively and a minimum of 20 mL·kg⁻¹ as a fluid bolus. Adding a single dose of dexamethasone intraoperatively reduced our POV rate to 1.15%, which was a statistically significant result. We considered this result as clinically significant as well, given that any vomiting after discharge is unpleasant and, unlike pain, cannot be readily treated pharmacologically at home. A POV incidence of 1.15% over 24 hr is one of the lowest reported in the literature. Our study showed that the antiemetic benefit of dexamethasone is apparent after the child is discharged from hospital. Therefore, a strategy of antiemetic rescue during the hospital admission would not have achieved the same results. Given the typically low cost of dexamethasone, this is an inexpensive strategy to reduce postdischarge vomiting. Our results are consistent with previous studies showing a reduction in POV rates with the use of dexamethasone.

Nearly all patients in our study were eating and drinking well at the time of the 24-hr phone interview, with only one patient in each group refusing food. In previous studies, oral intake was improved from the preoperative status at one week following dental rehabilitation.¹⁷ Our patients were not followed after 24 hr, but we expect oral intake to have improved after this time frame.

Parental satisfaction, as reported by parents at the telephone interview, was high in both groups, again with no significant difference between the two groups. Only four (4.48%) of the parents were "quite dissatisfied," and no parent was "very dissatisfied" with their child's condition. There were no admissions to hospital for any reason during the study period. We recorded no adverse outcomes attributable to dexamethasone.

The dexamethasone dose of 0.3 mg·kg⁻¹ chosen for this study was considered an intermediate dose in comparison with previous studies, which have used anything from 0.0625 mg·kg⁻¹ to 1.0 mg·kg⁻¹. In children undergoing tonsillectomy, there appears to be no dose-escalation

Fig. 2 Distribution of parental numerical rating scale (0-10) scores for the children's pain at 24 hr. Group S = saline; group D = dexamethasone

Fig. 3 Parental numerical rating scale (0-10) scores for the children's worst pain over 24 hr. Group S = saline; group D = dexamethasone

response to dexamethasone in regard to postoperative pain reduction or preventing postoperative POV.¹⁸ An intermediate dose was thought to have the potential to exert both antiinflammatory and antiemetic effects and was in keeping with doses used routinely at our institution.

Our study was a triple-blinded, randomized, controlled trial, and our results are consistent with what previous

studies have shown in terms of the antiemetic effect of dexamethasone.⁸⁻¹² We did not stratify the risk of significant postoperative pain according to what dental procedures were performed. This may be worth investigating in future studies. However, our results suggest that dexamethasone does not have any clinically significant analgesic effect in this patient population overall.

One methodological question that arises concerns calculating the sample size, which we based on the assumption that the pain scores would be normally distributed. Once the study was completed and the data were unblinded, however, it became apparent that the data were skewed, and so nonparametric tests had to be applied. This does not diminish the validity of the sample size calculation. The correct approach to analyzing skewed data such as ours is to apply a nonparametric test (e.g., the Wilcoxon test). Randles and Wolf have shown that with normal distribution of data the *t* test is only slightly more powerful than the Wilcoxon test. In the case of skewed data, as with the pain scores we encountered, the Wilcoxon test outperforms the *t* test,¹⁹ and hence the sample size calculated under the assumption of normality satisfied the power requirements, given the distribution of the data. We believe that our overall sample size of 200 subjects was enough to provide meaningful results. The distribution of pain scores shown in Figs. 2 and 4 make it clear that there was no

Fig. 4 Distribution of parental numerical rating scale (0–10) scores for the children's worst pain over 24 hr. Group S = saline; group D = dexamethasone

Fig. 5 Quality of oral intake at 24 hr. Group S = saline; group D = dexamethasone

clinically important difference in the pain experienced between the two groups.

In conclusion, a single intraoperative dose of dexamethasone, $0.3 \text{ mg} \cdot \text{kg}^{-1}$, did not reduce pain over 24 hr in healthy children having dental rehabilitation under general anesthesia. The quality of oral intake was also unaffected by dexamethasone at 24 hr. Dexamethasone did produce a significant reduction in postdischarge vomiting—beyond the incidence found with ondansetron alone.

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Conflicts of interest None declared.

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