Journal for Re Attach Therapy and Developmental Diversities
eISSN: 2589-7799
2023 December; 6 (10s(2): 2412-2416

Effects Of Low-Dose Versus Standard-Dose Intravenous Dexamethasone On Postoperative Vomiting, Nausea And Pain In Children Undergoing Tonsillectomy: A Randomised, Controlled, And Blind Trial

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ABSTRACT

Background: Tonsillectomy among the children is often linked to postoperative nausea and vomiting (PONV) and pain that may slow down the recovery and accelerate hospital readmissions. Dexamethasone has been proved to decrease the morbidity after surgery, but the optimal dose is still unknown. **Methods:** This is a prospective, randomized and double-blind study in which 76 children aged between 2 and 8 years undergoing elective tonsillectomy were selected to receive anaesthetic induction at intravenous dexamethasone 0.15 mg kg-1, dexamethasone 0.5 mg kg -1, and placebo. The main outcome was the occurrence of PONV, whereas additional outcomes were postoperative pain and analgesics needs. **Results:** Both dose levels of dexamethasone decreased the case of rescue anti-emetic treatment significantly when compared with placebo (P = 0.012). There were no substantial differences in the two doses of dexamethasone. The analgesic needs in the postoperative period did not differ between groups and yet the pain scores rose on the second day of postoperation in patients treated with dexamethasone. **Conclusion:** Dexamethasone at a single low dose as an IV bolus is effective in the reduction of PONV following paediatric tonsillectomy and does not increase adverse events.

Keywords: Tonsillectomy; Dexamethasone; Postoperative nausea and vomiting; Paediatric anaesthesia; Postoperative pain

INTRODUCTION

The most common type of surgery that is performed among the paediatric population is tonsillectomy. Despite the fact that it is mostly perceived to be routine, the operation has a high postoperative morbidity. Postoperative nausea and vomiting (PONV), severe pain in the throat, the threat of postoperative bleeding, and dehydration due to a decreased intake of liquids and solids are common complications[1]. Postoperative pain and PONV are the most common causes of unplanned hospital readmission in children who have undergone tonsillectomy as an outpatient procedure, and the rates of them were reported to be as high as about 14%. PONV following tonsillectomy is a multifactorial development that is inclusive of patient-related, surgical and anaesthetic factors. The incidence has been widely reported in the literature with a range of between 23% to a high of 73% being reported. In the same way, the origin of post-tonsillectomy pain is multifaceted and complex[2]. The intensity of pain is the highest in the first three days after surgery, although pain can last up to 10 days and may disrupt oral intake and the healing process. Inadequate pain management and recurrent nausea may lead to dehydration, slow recovery and healthcare overuse[3].
Corticosteroids have also been offered as an intervention to decrease the morbidity after tonsillectomy through post operative stages because of their established anti-inflammatory and anti emetic effects. Steroids could contribute to alleviating postoperative pain and reducing the rate of PONV by alleviating the inflammation of the tissues and central emetic stimulation[4]. Regardless of these possible advantages, there is still the debate on whether it should be used regularly in paediatric tonsillectomy. Among the issues are the best dosing, administration time and adverse effects of corticosteroids, dexamethasone (DEX) has received the most comprehensive investigation in terms of tonsillectomy. DEX is quite common, cheap and frequently well tolerated, and the side effects of this drug are very rare when taken as a single dosage preoperative[5]. Systematic reviews and meta-analyses have provided evidence that one intravenous dose of DEX is safe and effective in reducing morbidity in the postoperative period e.g., nausea, vomiting, and pain, after paediatric tonsillectomy. Although most have agreed that dexamethasone use must be prior to the anaesthetic induction in order to achieve maximum effectiveness, the best dose is not a definite one[6]. Varied doses have been noted in different studies and no obvious agreement on the same has been reached. Thus, the aim of the current study was to determine the efficacy of two individual doses of intravenous dexamethasone 0.15 mg/kg in decreasing

postoperative nausea and vomiting rates and also in reducing the postoperative pain in the children after undergoing elective tonsillectomy[7].

METHODS

This is a prospective randomized and blind study, approved by the Institutional Ethics Committee and the written informed consent of all participants was obtained either through the parents or legal guardians. The sample size was 76 children aged 2 to 8 years were all electively scheduled to undergo tonsillectomy with or without adenoidectomy[9]. Surgical indications were obstructive sleep apnoea due to hypertrophy of tonsils, frequent tonsillitis, which is an abscess more than four episodes in two consecutive years, or tonsillar abscess. Children were not included in case they had active infection, diabetes mellitus, sickle cell disease, known coagulation abnormalities, or had been administered anti-emetic, corticosteroids, and analgesics before surgery. The participants were randomly divided into three groups: dexamethasone 0.5mg/kg -1 (maximum dose 15mg), dexamethasone 0.15mg/kg -1 (maximum dose 8mg), or equal volume of the placebo 0.9% sodium chloride solution. Children above 30 kg were eliminated to prevent overdose of dexamethasone. Randomization was done using sealed envelopes with each block having the same number of allocations in all the treatment groups[10]. The randomization and preparation of the study medication was conducted by an anaesthesiologist who was not involved in data collection. Blinding was done to all clinical team members and outcome assessors on group allocation.

Anaesthetic protocol was standardized in all children. In children aged less than 4 years, premedication was given by rectal midazolam (0.5 mg kg -1) 30 minutes before induction, whereas in older children midazolam was administered orally 45 minutes before induction. Intraoperative therapy encompassed pulse oximetry, electrocardiography, non-invasive blood pressure, rectal temperature and end-tidal carbon dioxide[11]. Sevoflurane was used in combination with oxygens and nitrous oxide to induce anaesthesia. After accessing the intravenous route, fentanyl (2 µg kg -1), paracetamol (15 mg kg -1), tramadol (2 mg kg -1), and the assigned study drug were intravenously induced[12]. Fluid therapy was based on maintenance paediatric standards. Sevoflurane in 50 percent oxygen and 50 percent nitrous oxide was used as a form of anaesthesia. The tonsillectomy was done with dissection technique and in case of necessity, electrocoagulation was used. Patients were completely awake at the end of surgery and were ventilated and sent to the post-anaesthesia care unit (PACU).

Trained nursing personnel measured postoperative nausea and vomiting (PONV) and pain. PONV was managed using intravenous alizapride, and tropisetron was used when necessary[13]. The measurement of pain was done using age-specific validated pain scales and rescue analgesia was given accordingly. The PACU had discharge criteria of stable vital signs, good pain management, no bleeding, and the ability to consume oral food. The most important outcomes were the PONV incidence and postoperative pain severity. Time to PACU discharge and postoperative bleeding requiring re-exploration were the secondary outcomes[14]. The severity of pain was treated on a dichotomous scale between significant and non-significant. Non-parametric tests were used to perform the statistical analysis at the P value of less than 0.05.

RESULTS

There were a total of 76 children that were then analyzed and distributed fairly across the 3 study groups: placebo (n = 25), dexamethasone 0.15 mg kg -1 (n = 26), and dexamethasone 0.5 mg kg -1 (n = 25). Table 1 shows the baseline demographic and surgical characteristics. The groups did not have statistically significant differences in terms of age or body weight. The three groups had a median age of 45-48 months and a median body weight by 16-17kg, which depicts a similar paediatric population. Children who received a combination of tonsillectomy and adenoidectomy represented a high proportion and did not vary significantly under all groups (96100 percent). Similarly, the application of electrocoagulation in the operating room also showed no significant differences between groups, as it proved that there is homogeneity in terms of surgical method. Table 2 presents the need of postoperative analgesic and anti-emetic drugs. The decrease in the necessity of anti-emetic treatment by alizapride was critical in children who were undergoing dexamethasone administration. The administration of alizapride had the highest number in the group that was administered the placebo, with almost half of the patients (48%) in the placebo arm having to undergo treatment of postoperative nausea and vomiting. Conversely, patients under DEX 0.15 (15 percent) and DEX 0.5 (24 percent) were alizaprid-bound and this is a significant difference between groups (p = 0.012). The implication of this finding is that both doses of dexamethasone were effective in reducing the occurrence of postoperative nausea and vomiting with the lower dose being the most effective.

The rescue anti-emetic treatment using tropisetron was not common and did not have a significant difference among the three groups. The proportion of patients in the placebo group having Tropisetron was 8% and in the dexamethasone groups was 4% (P = 0.604) showing no significant change of severe/refractory nausea and vomiting irrespective of treatment assigned. Groups had similar postoperative analgesic needs. Morphine was used on 50 percent of the patients

in the placebo, 42 percent in the DEX 0.15 and 36 percent in the DEX 0.5. Even though the numerical trend was towards less opioids use in patients with dexamethasone, this was not statistically significant (P = 0.338). Likewise, the requirement of tramadol was the greatest in the placebo group (56) than the requirement of DEX 0.15 (40) and DEX 0.5 (44) groups though none of these differences was statistically significant (P = 0.356). On the whole, these findings indicate that dexamethasone appeared to have a considerable beneficial effect on the need to avoid anti-emetic treatment in the aftermath of paediatric tonsillectomy, whereas the impact of dexamethasone as an anti-analgesic medication did not produce any significant impact.

Table 1. Participant characteristics

Variable	Placebo (n = 25)	DEX 0.15 (n = 26)	DEX 0.5 (n = 25)	P-value
Age (months)	48 (40–61)	46 (38–59)	45 (36–58)	0.368
Weight (kg)	17 (15–19)	16 (14–18)	16 (14–18)	0.315
Tonsillectomy with adenotonsillectomy (%)	96	96	100	—
Use of electrocoagulation (%)	72	81	76	—

Table 2. Requirement for analgesic and anti-emetic medications

Medication	Placebo (n = 25)	DEX 0.15 (n = 26)	DEX 0.5 (n = 25)	P-value
Alizapride (%)	48	15	24	0.012
Tropisetron (%)	8	4	4	0.604
Morphine (%)	50	42	36	0.338
Tramadol (%)	56	40	44	0.356

DISCUSSION

The results of the current study prove that postoperative morbidity is considerably reduced by administration of dexamethasone (DEX) during perioperative periods after paediatric tonsillectomy[15]. Single intravenous dose of DEX administered at the time of anaesthetic induction was linked with a decrease in both early and delayed postoperative nausea and vomiting (PONV) and an improvement in the score of postoperative pain, which was recorded on the second postoperative day[16]. Further increases of dose of DEX beyond 0.15 mg kg -1 to 0.5 mg kg -1 did not lead to any further clinical effect but the study was not specifically designed or powered to show small differences in effect between the two regimens[17-18]. Many studies have been conducted to determine the effect of DEX on PONV and posttonsillectomy pain in children. Most of these studies were however constrained by small sample sizes or methodological differences like variations in anaesthetic methods, surgical methods, and rescue drug administration[19]. Also, the results of randomized placebo controlled trials of one intravenous dose of corticosteroids have been inconsistent with some studies showing definite benefits and others showing minimal or no effect. In spite of these discrepancies, the anti-emetic action of DEX has been reproducibly supported in the literature, but the specific mechanisms underlying such action are not fully understood[20]. The theories that have been suggested are inhibition of prostaglandin synthesis, alteration of serotonin pathways, and inhibition of endogenous opioid release. Although the anti-inflammatory effect of DEX is proven, its effectiveness in the postoperative pain treatment remains controversial[21]. The positive influence on pain in the current study was noticed only on the second day after operation. This delayed action is in line with the pharmacodynamics and pharmacokinetic properties of DEX since its anti-inflammatory property is usually reflected several hours after the administration of the drug. Therefore, a direct decrease in the immediate level of postoperative pain is not likely[22]. This latency of effect can be the reason behind some of the earlier studies which have not shown a significant analgesic effect during the early postoperative period. The controversy on the optimum dosing of DEX in tonsillectomy of children is still unsettled. Prior experiments that have tested very low to comparatively high doses have not been able to establish a definite dose response association to either PONV or postoperative pain. Likewise, studies that have compared moderate and higher dose levels of DEX have demonstrated that PONV is significantly reduced relative to placebo, but not significantly different between doses[23]. These findings are also supported in the current study thus indicating that the lower doses of DEX can be used to produce clinically significant effects without causing the drug exposure that is unjustified.

The literature has also discussed concerns over the possible adverse effects of using perioperative corticosteroids especially postoperative bleeding. Most of the studies have failed to establish a substantial growth in the complications linked to the use of DEX in children who are undergoing tonsillectomy. Even though a small study suggested the possible dose-associated increase in postoperative bleeding, the measured rates of bleeding were higher than the rates described in clinical practice. Such larger trials that have included thousands of patients have not shown an increase in

dose-dependent postoperative bleeding, even in patients receiving the higher dose of DEX, which is why its safety profile is generally not questioned. The study design has several perspectives that would be taken into account when interpreting the results. The dosage of DEX was taken at induction of anaesthesia because it has been alluded in the past that it is more effective when administered earlier rather than at the conclusion of the surgery. The age bracket was set at 2-8 years in order to maintain a consistent anaesthetic procedure through mask induction as it is usually more tolerated among younger children. Nausea is difficult to assess in very young children; thus the definition of PONV included vomiting and/or retching and the latter is an indirect measure of nausea. Age specific validated instruments, such as behavioural and self-report scale, and parental assessment following discharge were used in order to assess pain. Holding back patients in the hospital to the first postoperative day enabled greater accuracy in assessing the initial postoperative results. To conclude, the current research proves that a single dose of intravenous dexamethasone during anaesthetic induction is effective in the reduction of post-operative nausea and vomiting along with the enhancement of pain outcomes on the second postoperative day after paediatric tonsillectomy. A lower dose of 0.15mg kg -1 seems to offer similar benefits as a larger dosage of 0.5mg kg -1. Despite the obvious decrease of postoperative vomiting with dexamethasone, the studies should be furthered to establish the lowest effective dose that would maximize the efficacy and safety.

CONCLUSION

This randomized, prospective, and double-blind research study proves that perioperative dexamethasone proves to be an effective measure in the reduction of postoperative morbidity among children who are undergoing elective tonsillectomy. One IV dose of dexamethasone given on induction of anaesthesia reduced the occurrence of postoperative nausea and vomiting which is one of the most common and unpleasant side effects of paediatric tonsil operation. Dexamethasone can also help to enhance patient comfort, smooth postoperative recovery and decreased caregiver burden by decreasing the requirement of rescue anti-emetic therapy. The two doses of dexamethasone that were tested in this research, 0.15 mg/kg minus one and 0.5mg/kg minus one, both worked in reducing PONV cases compared to placebo. Notably, the higher dose did not provide any further benefit which indicates that lower dose is adequate to produce any clinically significant anti-emetic effect. The practical use of this finding is that the maximum effective dose should be utilized because it will help to limit the exposure to unnecessary drugs, yet the therapeutic effectiveness will be preserved. Despite the finding of a trend toward lower postoperative analgesic needs of patients given dexamethasone, the differences were not found to be statistically significant. However, the observation of pain outcomes on the second postoperative day is improved which suggests the possibility of delayed analgesic action in accord with the analgesic effects of dexamethasone which is an anti-inflammatory. The replication of the study also supports the safety of single dose perioperative dexamethasone among the paediatric tonsillectomy population. Any postoperative bleeding or other clinically relevant adverse events did not increase, which is consistent with current evidence that indicates that dexamethasone is favourable in this regard. The addition of dexamethasone to a standardized paediatric tonsillectomy perioperative management strategy can potentially enhance the postoperative complications, faster recovery, and possibly a reduction in unexpected hospital readmissions. Further research using more subjects might help to better understand the most appropriate dosing regimen and whether or not dexamethasone has further effects on pain control than it has on the initial postoperation. In general, this research confirms that the application of a low dose dexamethasone regimen as a component of multimodal perioperative management of children undergoing tonsillectomy is routinely applicable.

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