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ORIGINAL ARTICLE

Preoperative peritonsillar infiltration of dexamethasone and levobupivacaine reduces pediatric post-tonsillectomy pain: a double-blind prospective randomized clinical trial

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Abstract
Background Preoperative corticosteroids reduce post-tonsillectomy morbidities. The present study was performed to compare the effect of peritonsillar dexamethasone infiltration to intravenous injection together with peritonsillar levobupivacaine infiltration before tonsillectomy on postoperative pain in children.
Methods One hundred twenty children, ASA I–II, aged 6–12 years, scheduled for adenotonsillectomy were enrolled in the study. They were randomized equally into two equal groups; 60 children each. Group A received peritonsillar infiltration with dexamethasone and levobupivacaine, and group B received i.v. dexamethasone and peritonsillar levobupivacaine infiltration. Rest and swallowing pain in the first postoperative day using a visual analogue scale, time to first rescue analgesia, cumulative paracetamol dose, vomiting, and adverse effects related to both interventions during the first postoperative day were recorded. Children care givers were asked to score pain using a verbal rating scale and to disclose complications as halitosis, headache, fever and otalgia during the first postoperative week.
Results Time to first rescue analgesia was significantly longer in group A. Rest and swallowing pain in the first postoperative day, cumulative paracetamol dose, pain in the second and third postoperative days, and otalgia were significantly lower in group A. None of children developed postoperative bleeding, or complications related to dexamethasone or levobupivacaine infiltration. There was no significant difference in postoperative emesis, fever and halitosis between the groups.
Conclusion Addition of dexamethasone to levobupivacaine for preoperative peritonsillar infiltration has better postoperative analgesic effects than i.v. dexamethasone combined with peritonsillar levobupivacaine infiltration in children.

Keywords Post-tonsillectomy pain · Local anesthetic infiltration · Dexamethasone

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Introduction

Post-tonsillectomy pain constitutes a major problem for pediatric patients. It cumulates within the first 3 postoperative days and may be severe enough to delay return to regular activity, and impair swallowing leading to an increased risk of dehydration, secondary infection and bleeding [1, 2]. In order to reduce post-tonsillectomy pain, a variety of local anesthetics in different concentrations and volumes have been studied for peritonsillar infiltration as a method of preemptive analgesia [3, 4]. A systematic review of the literature by the Cochrane Institute found no evidence that the use of perioperative local anesthetics in adult patients undergoing tonsillectomy improves postoperative pain control [3]. In another review by Grainger and Saravanappa [4]; local anesthetics showed to provide a modest reduction in post-tonsillectomy pain.

Levobupivacaine, the S-enantiomer of bupivacaine, is an appropriate choice for this purpose in children. It has a

prolonged duration with lesser cardio- and neurotoxicity compared to bupivacaine [5]. However, only few studies investigated the effects of levobupivacaine for peritonsillar infiltration [6–9]. An overview of these studies suggests that levobupivacaine alone is not sufficient for control of post-tonsillectomy pain.

Dexamethasone is an inexpensive synthetic glucocorticoid of powerful anti-inflammatory effect as well as analgesic property and has a long half-life of 36–72 h. Intravenous dexamethasone (0.15–1.0 mg/kg) has been found to improve postoperative analgesia following tonsillectomy in children [10]. Furthermore, addition of steroid to local anesthetic for peritonsillar infiltration has been advocated with promising results [11]; though other studies found no benefits of peritonsillar dexamethasone infiltration [12, 13].

The present study was performed to compare the effects of local infiltration and intravenous injection of dexamethasone together with peritonsillar levobupivacaine infiltration before tonsillectomy on postoperative pain in children.

Methods

The study was approved by the Research Ethics Committee of Tanta Faculty of Medicine, Egypt. After obtaining a parental written informed consent and assent of children; 120 children, ASA I–II, aged 6–12 years who scheduled for adenotonsillectomy due to recurrent or chronic tonsillitis were enrolled in the study. The criteria for exclusion were coagulation disturbances, acute pharyngeal or respiratory tract infection, diabetes, cardiac disease, liver or kidney disease, hypersensitivity to levobupivacaine, regular use of analgesics within a week of surgery, or inability to understand the visual analogue scale (VAS).

Children were randomized equally using computer generated random number into two groups. Group A ($n = 60$) received preincisional peritonsillar infiltration with a mixture of dexamethasone sodium phosphate [(dexamethasone, Amriya. Pharm. Ind, Egypt; 4 mg/1 ml) (0.5 mg (0.125 ml)/kg; maximum 8 mg)] plus levobupivacaine HCL [(Chirocaine®, Abbot Laboratories; 5 mg/ml) (1 mg (0.2 ml)/kg; maximum 25 mg)] plus normal saline to form a solution containing 0.25 % levobupivacaine. They, also, received *iv* placebo (2 ml normal saline). Group B ($n = 60$) received preincisional peritonsillar levobupivacaine infiltration [1 mg (0.2 ml)/kg; maximum 25 mg] diluted in normal saline to form 0.25 % levobupivacaine solution; in addition to *iv* dexamethasone (0.5 mg/kg diluted in 2 ml normal saline; maximum 8 mg). Randomization and preparation of the study medications was performed by an anesthetist not involved in administration of anesthesia or patients' assessment. The anesthesiologist, otolaryngologist, subjects, their parents, observers and data collectors were blinded to treatment group.

Patients were instructed how to use a 0–10 VAS (0: no pain–10: worst pain). They received midazolam 0.3 mg/kg orally; 20 min before transference to the operating room. Monitoring included pulse oximetry, electrocardiogram, noninvasive arterial blood pressure and end-tidal CO_2. Anesthesia was induced by sevoflurane 8 % inhalation followed by propofol 1 mg/kg and fentanyl 1 μg/kg after obtaining an intravenous access. Oral endotracheal intubation was done without muscle relaxants and ventilation was manually assessed to maintain the end-tidal CO_2 between 30 and 40 mmHg. Anesthesia was maintained with 1–2 % sevoflurane adjusted to maintain heart rate and blood pressure values within 20 % of baseline values. Intravenous fluids were given in the form of ringer's solution (10 ml/kg) during the operation.

Before surgery, the otolaryngologist infiltrated the study medications superficially into the peritonsillar fossae using the aspiration injection technique at the lower pole, upper pole, anterior pillar, posterior pillar and subcapsular plane (3–5 ml/tonsil) using a straight 23-G needle. Adenotonsillectomy was performed, 5 min after injection, by curettage for adenoidectomy and electrocautery dissection technique for tonsillectomy by the same surgeon. After surgery, patients were observed in the post anesthesia care unit (PACU) for 30 min, at least, before transference to the ward. Patients were discharged 24 h postoperatively.

A senior anesthesia resident who was blind to the treatment groups assessed all the patients postoperatively. Rest pain at 15, 30 min, 2, 6, 12, and 24 h postoperatively and swallowing pain (during drinking or eating) at 2–6, 6–12 and 12–24 h postoperative periods were evaluated by the VAS. If patients were sleeping, evaluation of VAS was delayed till they waked up. Rescue analgesia was paracetamol (Perfalgan, Bristol Myers Squibb, Egypt) 15 mg/kg *iv* repeated every 6 h as necessary if rest pain score was > 3. Time to first rescue analgesia measured from time of extubation, and cumulative dose of paracetamol during the first postoperative 24 h were recorded. Adverse effects including bleeding, arrhythmia, allergic reaction, difficulty in swallowing due to sensory, motor or mass effect of injectate, and vomiting (more than one episode) were recorded. Metoclopramide 0.5 mg/kg *iv* was given for treatment of vomiting.

During the first postoperative week, analgesia was given in the form of Ibuprofen 50 mg/kg/day and children care givers were daily contacted by telephone and asked to score pain during the previous 24 h using a verbal rating scale (VRS) (0: no pain–100: worst pain) and to disclose complications as halitosis, headache, fever and otalgia.

Statistics

The primary endpoint was the time to first rescue analgesia. Sixty patients were required per group to determine that infiltration with levobupivacaine and dexamethasone would increase the duration of absolute analgesia by 25 %, based on a pilot study, with 95 % power ($\alpha = 0.05$) in comparison with levobupivacaine infiltration and i.v. dexamethasone. Data were analyzed using SPSS (version 16), and are presented as mean ± SD, or number (%) as appropriate. Student's *t* test was used to compare the mean value of quantitative data between the two groups. Fishers' exact test was used for comparison of gender and percentage of postoperative complications. VAS pain scores were compared between groups with Mann–Whitney *U* test. A *P* value < 0.05 was considered statistically significant.

Results

Age, gender, weight, time of surgery and time to extubation were almost equivalent similar in both groups ($P > 0.05$). Time to first rescue analgesia was significantly longer in group A than B ($P < 0.001$) and the cumulative dose of paracetamol was significantly lower in group A than B ($P < 0.001$) (Table 1).

The rest pain VAS scores (Table 2) did not differ significantly between groups at time points 15 and 30 min postoperatively ($P = 0.828$ and 0.585 respectively). At 2, 6, 12 and 24 h postoperatively, the mean values of VAS of rest pain were significantly lower group A compared to group B ($P < 0.001$ for all comparisons). The swallowing VAS pain scores (Table 3) were significantly lower in patients received levobupivacaine and dexamethasone infiltration compared to patients received levobupivacaine infiltration and *iv* dexamethasone ($P < 0.001$ for all comparisons). All children care givers were contacted postoperatively. They reported less pain in the 2nd and 3rd postoperative days, using VRS, in group A compared to group B ($P < 0.001$ for both comparisons) (Table 4).

There was no significant difference in postoperative emesis between groups ($P = 0.414$). Otalgia was significantly lower in group A than in group B ($P = 0.018$). Headache occurred less frequently in group A compared to B; but it did not reach the statistical level ($P = 0.07$). Fever and halitosis were comparable in both groups ($P > 0.05$) (Table 5). No patients developed postoperative bleeding or complications related to dexamethasone or levobupivacaine.

Table 1 Patients data

Variable	Group A	Group B	*P*
Age (years)	7.88 ± 1.73	7.41 ± 1.73	0.143
Gender (M/F)	24/36	28/32	0.581
Weight (kg)	29.28 ± 6.83	30.23 ± 4.93	0.385
Time of surgery (min)	30.75 ± 2.61	31.56 ± 2.72	0.096
Time to extubation (min)	4.86 ± 1.12	4.99 ± 1.04	0.530
Time to first rescue analgesia (h)	10.52 ± 3.27*	6.22 ± 1.06	<0.001
Paracetamol (g)	0.62 ± 0.33*	1.11 ± 0.28	<0.001

* Significant difference ($P < 0.05$)

Discussion

Preoperative administration of corticosteroids alone or in association with local anesthetics infiltration have been shown to reduce post-tonsillectomy morbidities [10, 11, 14], with few contradictory results [12, 13]. Kaygusuz et al. [11], compared dexamethasone, lidocaine and bupivacaine infiltrations before tonsillectomy. They showed a significant reduction of postoperative pain after dexamethasone infiltration compared to placebo. The analgesic effect of dexamethasone, lidocaine and bupivacaine infiltrations were comparable in the first postoperative day. Also, Mohamed et al. [15] reported that intravenous dexamethasone together with bilateral glossopharyngeal nerve block reduced pain significantly after electrocautery tonsillectomy in children compared to each of them separately. Other studies [12, 13] found no significant effect of dexamethasone infiltration. Indeed, comparison of infiltrated to intravenous dexamethasone in association with a local anesthetic to relieve post-tonsillectomy pain has not been investigated.

The present study showed that peritonsillar infiltration with dexamethasone and levobupivacaine before tonsil-

Table 2 VAS scores for rest pain

	15 min	30 min	2 h	6 h	12 h	24 h
Group A	0.58 ± 0.56	0.61 ± 0.55	1.08 ± 1.01*	1.7 ± 1.07*	1.93 ± 0.88*	2.03 ± 0.84*
Group B	0.63 ± 0.66	0.71 ± 0.71	2 ± 0.9	2.9 ± 0.98	4.4 ± 0.90	4.5 ± 0.94
P	0.828	0.585	<0.001	<0.001	<0.001	<0.001

* Significant difference compared to group B ($P < 0.05$)

Table 3 VAS scores for swallowing pain

Time	2–6 h	6–12 h	12–24 h
Group A	0.6 ± 0.58*	0.88 ± 0.66*	1.10 ± 0.57*
Group B	3.88 ± 0.84	4.23 ± 0.78	4.48 ± 0.7
P	<0.001	<0.001	<0.001

* Significant difference compared to group B ($P < 0.05$)

Table 4 VRS score for postoperative pain

Time	2nd day	3rd day	4th day	5th day	6th day	7th day
Group A	34.58 ± 9.53*	37.33 ± 9.54*	41.16 ± 6.66	40.5 ± 7.05	30.41 ± 4.62	29.16 ± 5.38
Group B	59.83 ± 10.08	63.53 ± 10.93	42.41 ± 4.82	40 ± 6.17	32.33 ± 6.20	29 ± 5.73
P	<0.001	<0.001	0.242	0.680	0.058	0.870

* Significant difference compared to group B ($P < 0.05$)

Table 5 Postoperative complications

Variable	Group A (%)	Group B (%)	*P*
Vomiting	14 (23.3)	19 (31.7)	0.414
Otalgia	4 (6.7)*	15 (25)	0.011
Headache	13 (21.7)	23 (38.3)	0.072
Fever	13 (21.7)	11 (18.3)	0.820
Halitosis	6 (10)	7 (11.7)	1.000

* Significant difference ($P < 0.05$)

lectomy significantly reduced both rest and swallowing pain during the first postoperative 24 h, prolonged absolute analgesia, and decreased additional analgesic consumption compared to levobupivacaine infiltration alone together with IV dexamethasone. The analgesic effect of the mixture lasted a full 3 days after surgery and was associated with a less incidence of otalgia.

Tonsillectomy induced tissue injury releases different types of inflammatory mediators such as bradykinin, serotonin and prostaglandins. Bradykinin and serotonin directly stimulate peripheral nociceptors, while prostaglandins sensitize the peripheral nociceptors to the other inflammatory mediators [15]. Continued stimulation of the peripheral nociceptors results in CNS hyperexcitable state and causes low threshold A–B mechanoreceptors to transmit painful sensations [16]. Overall, inflammation results in pain, peripheral and secondary hyperalgesia. Electrodissection tonsillectomy is well known to cause more inflammation and pain [17]. Preemptive analgesia using local anesthetic infiltration blocks nociceptors transmission and prevents CNS hyperexcitation but it does not affect inflammation that far outlasts the effects of local anesthetics. Therefore, as the effect of local anesthetic subsides, inflammatory pain is seen. In consistency, Fikret et al. [9] showed that the analgesic effect of levobupivacaine infiltration is limited to the first 30 min after electrodissection tonsillectomy. However, other studies [6–8] reported a longer postoperative analgesia varied between 16 and 24 h after levobupivacaine infiltration to peritonsillar fossae, but they did not assess pain on swallowing and performed tonsillectomy by techniques other than electrodissection. An overview of these studies elucidates the analgesic effect of dexamethasone as adjuvant to local anesthetics.

The analgesic effect of systemic steroids seems to be mediated by their anti-inflammatory effect [18–20]; whereas the role of dexamethasone infiltration is not clearly understood. However, improved pain control after dexamethasone infiltration compared to i.v. dexamethasone in the present study support the hypothesis that dexamethasone infiltration could have a synergistic effect to local anesthetic on nerve terminals in addition to the local and systemic anti-inflammatory effects [21–23].

Intravenous dexamethasone in doses ranging from 0.15 to 1 mg/kg with maximum doses ranging from 8 to 25 mg have been used in children [10]. We selected the dose of dexamethasone as 0.5 mg/kg because Kaan et al. [24] found that patients who received preoperative dexamethasone 0.5 mg/kg *iv*, compared with placebo, had significantly less pain scores, shorter time to adequate oral intake, and earlier discharge time after tonsillectomy. On the other hand, Montazeri et al. [13] infiltrated dexamethasone (0.5 mg/kg, maximum 12 mg) or an equivalent volume of saline at the peritonsillar region. They found no statistically significant difference between the two groups in post-tonsillectomy pain; but, a trend showing a reduction in pain scores in patients who received dexamethasone. In addition, these patients required less analgesia and had fewer episodes of nausea and vomiting. Egeli et al. [12] showed no difference in post-tonsillectomy pain when dexamethasone 0.5 mg/kg or placebo with lidocaine was infiltrated at the peritonsillar region which is contradictory to our results; however, their assessment of pain was based on the number of patients who received acetaminophen

postoperatively. Also, they conducted the study on adults undergoing tonsillectomy by sharp dissection and snare technique using local anesthesia. Many factor may explain these conflicting results, including the technique of tonsillectomy, use of premedication and its type, anesthetic technique, dose and volume of local anesthetic, method of local anesthetic injection, personal experience, social and ethnic factors, perceptual abilities, anxiety level, and the method of pain assessment [25, 26].

In the current study, none of patients developed complications related to peritonsillar local anesthetic infiltration as airway obstruction due to vagal or hypoglossal block, difficulty of swallowing due to glossopharyngeal block and facial nerve paralysis [27]. Also, complications related to dexamethasone as infection, delayed healing or postoperative bleeding were not encountered. Earlier concerns about increased incidence of bleeding after this operation if steroids have been administered seem to have been resolved. However, a recent meta-analysis has suggested that though the incidence is not increased, the need for operative reintervention for bleeding episodes may be higher in children receiving i.v. steroids during adenotonsillectomy [28].

This study has two limitations. Firstly: it may have been appropriate to include a control group receiving levobupivacaine infiltration alone. Secondly: though the VAS is a simple, valid and reliable method of assessing pain in children as young as 3 years, and provides reasonable trending for a given patient; a wide degree of interpatient variability exists.

In conclusion, addition of dexamethasone to levobupivacaine for preoperative peritonsillar infiltration has better postoperative analgesic effects than IV injection of dexamethasone in children. Further studies are required to explore the mechanism of action of steroids and local anesthetics mixture.

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