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Review article

Effectiveness of hyaluronic acid in post-tonsillectomy pain relief and wound healing: A prospective, double-blind, controlled clinical study

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ABSTRACT

Objectives: To find the effectiveness of hyaluronic acid in post-tonsillectomy pain relief and wound healing.
Methods: Fifty patients were included in this prospective, double-blind, controlled clinical study (20 males, 30 females mean age of 13.56 years). Hyaluronic acid was applied to one side and the other side was used as a control during tonsillectomy. Therefore, the same patient evaluated and scored the post-tonsillectomy pain, excluding individual bias.
Results: Results indicated that patients had significantly lower pain scores for hyaluronic acid treated side ($p < 0.001$). At the end of two weeks follow-up period, the wound in the hyaluronic acid side was almost completely healed, indicating that the healing was faster with hyaluronic acid compared to control side ($p < 0.001$).
Conclusion: Hyaluronic acid could be recommended as an effective treatment for the management of post-tonsillectomy pain and wound healing.

Contents

1. Introduction

Tonsillectomy produces an open wound, therefore, associated with significant postoperative pain which can last up to 14 to 21 days with a 2–4% risk of immediate or delayed hemorrhage [1,3–8]. The morbidity rate caused by postoperative pain and secondary bleeding was reported to be one in 35,000 [5,9]. Little is known about the real cause of post-tonsillectomy pain; however the main reasons of this prolonged moderate to severe pain were described to be related with the sensitivity of tonsillar fossae to tissue damage, the disruption of mucosa, the pharyngeal muscle spasms and glossopharyngeal and/or vagal nerve fiber irritation causing inflammation [5,6,9].

Oral opioids such as codeine and nonsteroidal anti-inflammatory drugs are usually used to manage pain after tonsillectomy [2,7]. It was well reported that respiratory depression, sedation and bleeding resulted from the unpredictable metabolism of opioids were one of the reasons of morphine toxicity causing morbidity

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and life-threading post-tonsillectomy complications [2,5,10]. Therefore, the use of safer opioid and non-opioid analgesics as an alternative approach to relieve the pain caused by tonsillectomy is getting more important. The American Academy of Otolaryngology—Head and Neck Surgery (AAO—HNS), for example, currently recommends the routine use of ibuprofen for pain relief after tonsillectomy [4,5,11].

Hyaluronic acid is a linear, hydrophilic, high molecular weight glycosaminoglycan naturally found in the joint synovial fluid and in the extracellular matrix of skin in the human body [12–15]. It is naturally secreted during wound healing in proliferative phase to stimulate the migration and mitosis of fibroblasts and epithelial cells [16–18]. It was shown to reduce the levels of inflammatory mediators and, therefore, can safely be used as an anti-inflammatory agent [13,18,19]. Being a growth factor and having lubricant properties, hyaluronic acid is commonly used as a naturally biocompatible, biodegradable and non-immunogenic biomaterial in biological dressing formulations [19]. The positive effect of the use of hyaluronic acid in pain relief and wound healing in treatment of pressure ulcers [15], in management of osteoarthritis [12], in treatment of tendon disorders [12], in non-surgical treatment of deep wounds [20], in burns, epithelial surgical wounds and chronic wounds [18,21] and in vocal fold wound healing in animal models [22] were reported. However, to our best knowledge there is no study investigating the effectiveness of hyaluronic acid on the treatment of tonsillectomy.

Therefore, the aim of this prospective, double-blind, controlled clinical study was to evaluate the effectiveness of hyaluronic acid on the reduction of post-tonsillectomy pain and wound healing during the first 14 postoperative days.

2. Materials and methods

2.1. Patients and surgical procedure

Between January 2013 and March 2014, 50 patients listed for tonsillectomy were included to the study at Liv Hospital. The 50 patients were consecutive patients admitted to the clinic for tonsillectomy. There were no patients refused to participate in the study. The study protocol was approved by the Local Hospital Ethics Committee and conducted according to the Declaration of Helsinki. An informed consent was obtained from adult patients and from parents of children patients.

Indicators for tonsillectomy in this study were recurrent tonsillitis (acute tonsillitis 7 times in first year, 5 times in second year, 3 and more times in third year), tonsillar hypertrophy resulting in snoring and chronic tonsillitis which was not responding to medical therapy(beta-lactamase–resistant antibiotics), difficulty in eating and talking. The indications for antibiotic treatment in tonsillitis were history of fever, exudate, anterior servical lymphadenopathy. Exclusion criteria were bleeding disorder, having chronic or severe systemic disease like diabetes, peritonsillar abscess formation, unilateral tonsil hypertrophy, patients with obstructive sleep apnea and patients who received steroids, antiemetics, antihistamines, or psychoactive drugs within 24 h of surgery.

A prospective, double-blind study design was used in the study. Tonsillectomy was done under general anesthesia with oral intubation and with conventional dissection and snare technique performed by the same otolaryngologist. Adenoidectomy was performed for 5 patients. During surgery, a hyaluronic acid gel (Pure regen gel sinus, BioRegen Biomedical Co. Ltd Hamburg Germany) was placed to one of the randomly selected sides and both anterior and posterior tonsillar plica are sutured with 4/0 Vicril. To the other side only anterior and posterior tonsillar plica suture were performed and be used as a control. Patients and care providers (mostly parents) were blinded to the hyaluronic acid placed side. After the surgery, patients were transferred to the postanesthesia care unit. They were moved to Ear Nose Throat Ward when fully awake, stable, and comfortable. Patients who were fully awake, alert, able to drink liquids, had stable vital signs, no nausea and no bleeding were considered to be ready for discharge. All patients were discharged the day after surgery with same analgesic (paracetamol 4 × 500 mg per day for adults, 10–15 mg/kg per day) and same antibiotiotic (amoxicillin/clavulanic asid) twice daily for one week postoperatively in weight-related doses. None of the patients have received steroid and opioid analgesic treatment. All patients stayed overnight. Liquids, soft diet and activity restriction were recommended for 1 week.

2.2. Effectiveness assessments

Postoperative care was the same for all patients. All effectiveness assessments were recorded by an independent otolaryngologist blinded to the hyaluronic acid (1 ml) placed side. Post-tonsillectomy throat pain was measured twice a day (in the morning and in the afternoon) for each side during the period of 14 postoperative days using visual analog scale (VAS) on a scale of 0–10 after 2 h of analgesic intake. Wound healing was assessed by direct visual examination of the area of slough in each tonsillar fossa at 7th, 10th and 14th postoperative days and scored on a scale of 0 to 5 (0 = completely healed wound, 5 = not healed wound). The wound healing score was evaluated by the method described by the Magdy et al. [21] (Table 1).

2.3. Statistical analysis

Statistical analysis was performed by the SPSS software package for Windows (Statistical Package for Social Sciences, version 12.0, SPSS Inc., Chicago, Illinois, USA). Categorical variables were given as numbers and percentages and quantitative variables as mean ± standard deviation (SD), median, minimum and maximum values. The normality of quantitative variables were analyzed by Kolmogorov–Smirnov test and normally distributed variables were compared with Student's *t*-paired test. The level of significance was set at $p < 0.05$.

3. Results

Fifty patients were included to this prospective, double-blind, controlled clinical study on the effectiveness of hyaluronic acid in post-tonsillectomy pain relief and wound healing. There were 20 males (40%) and 30 females (60%) between 9 and 22 years, averaging 13.56 years (median age 14.02). Thirty-four patients (22 boys, 12 girls) were child. No major complications such as airway abstraction, hemorrhage from tonsillar fossae, dehydration, or anesthetic toxicity were observed.

3.1. Effectiveness of hyaluronic acid on the reduction of post-tonsillectomy pain

Results of post-tonsillectomy throat pain measured twice a day (in the morning and in the afternoon) for non-treated (control) and

Table 1
Scoring system for tonsillar fossa wound healing.

Feature	Absence	Presence	Severe
Erythema	0	1	2
Edema	0	1	
Fossa whitening	0	1	
Wound healing	1	0	