LETTER TO THE EDITOR

IMPACT OF INTRANASAL NEBULIZED ECTOINE ON MORBIDITY AND SHORT-TERM QUALITY OF LIFE AFTER PEDIATRIC ADENOIDECTOMY

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To the Editor,

Adenoidectomy is the third most common pediatric procedure performed in the United States, after myringotomy with tube placement and adenotonsillectomy (1). There are several adenoidectomy techniques, however, standard adenoidectomy with adenoid curette or adenotome, remains the most common surgical procedure performed. Recovery from adenoidectomy is remarkably faster and better when compared with post-tonsillectomy, either as a single procedure or combined with adenoidectomy. Patients who undergo adenoidectomy are typically discharged the same day of surgery.

However, immediately after the procedure, children usually complain of nasal symptoms such as nasal obstruction, rhinorrhea, pharyngeal and neck pain from the surgical site and endotracheal intubation, ear pain, halitosis, scabs in the mouth and bad breath (2). After surgery, saline nasal irrigations (SNIs) of the nasal fossae and nasopharynx are frequently used. This allows the removal of secretions, crusts, and debris, which typically accumulate in the nasopharynx, promoting a rapid recovery of nasal respiration. Recently, some studies suggest that the use of a saline solution with ectoine (as a coadjutant treatment for many upper airway inflammatory diseases) significantly improves symptoms and findings of the endoscopic evaluation. Ectoine binds strongly to water molecules and forms a hydrating shield that prevents dehydration and proteins' irreversible denaturation of the tissues. It also reduces inflammatory and oxidative stress induced by exposure to polluting dust, and plays a protective and stabilizing role for many components of the cell wall (3). Recently, Moffa et al. (4) investigated the use of ectoine that was nebulized with a new nasal device called Spray-sol™, for the prevention of recurrent upper respiratory tract infections (rURTIs) in pediatric subjects. Their work showed a statistically significant reduction in the number of URTI episodes, days of absence at school, and patient compliance. Spray-sol™ is a practical nasal device that allows aerosol delivery to the middle turbinate, the osteo-meatal complex, and nasopharynx region (5, 6). The main goal of this study is to investigate the role of ectoine saline solution nebulized with Spray-sol™, as an adjuvant treatment to hasten the improvement of nasal respiration, minimizing patients' discomfort after adenoidectomy. Adherence and compliance of the medication are considered secondary objectives.

Key words: Spray-sol™; single dose vial; nasal device; ectoine; adenoidectomy; nebulization and children.

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MATERIALS AND METHODS

This prospective, observational study was carried out following the principles of the Helsinki Declaration. All parents signed an informed consent form and were provided with the relevant information regarding the trial. Forty-four consecutive patients aged 3-10 years with endoscopic diagnosis (7) of AH defined as a third or more degree, with or without otitis media with effusion (OME) were prospectively enrolled at the University of Foggia, Unit of Otolaryngology, from September 2019 to February 2020. Excluded were patients: a) less than three years of age or older than ten years; b) with rURTIs; c) with coagulopathy, or any major illness that was contraindications to surgery. All patients who underwent adenoidectomy with or without myringotomy with tube placement were included in the study. They were divided into two treatment groups:

- Ectoine group (E-group): 20 patients; 8 females and 12 male, with a mean age of 5.66 years; patients and parents were instructed to use ectoine saline solutions nebulized with Spray-sol™. The commercially available product named Isonebial Kit (Steve Jones S.R.L., Sesto Fiorentino, FI, Italy) composed of 20 singl-dose 5-ml vials with sodium chloride (0.9%) with the addition of ectoine, sodium phosphate, polyvinylpyrrolidone and water, a nasal device called Spray-sol™ and a Luer-Lock syringe of 5 ml;
- Saline group (S-group): 22 patients; 10 females and 12 males; with a mean age of 5.7 years; Patients and parents in the S-group were instructed to use 5 ml of isotonic saline solution contained in a single-dose vial.

The solutions were applied, placing half the solution into both nostrils twice/day (morning and evening) for the 14 days after surgery. Five patients (three belonging to E-group and two to S-group) who did not report for post-operative controls were excluded from the study.

Surgical procedure

Transoral cold curettage adenoidectomy was performed with a McIvor mouth gag and Beckmann adenoid curette size 0-5, depending on the characteristics and necessity to reach the rhino pharynx with the instrument. Adenoid tissue was excised by transoral cold curettage. Hemostasis was achieved thought compression with a tampon soaked with hydrogen peroxide; electrocautery was not used. Digital hand check visualization was performed to ensure the removal of the adenoid and rhino pharyngeal permeability. For the children with a history of OME, an operating microscope was used to visualize the tympanic membrane where myringotomy was performed, the fluid was suctioned and the ventilation tube was placed at the site of the incision.

Evaluation

On enrollment, the following baseline parameters were obtained: sex, age, AH degree, OME, and history of allergy. The assessment was performed on day 1 (T1) and day 14 (T2) of the postoperative period, and recollection of data of upper airway symptoms, side effects, compliance to the treatment, difficulties/unpleasantness experienced during administration and adherence to the assigned treatment was achieved by the physicians as indicated below:

- *Upper Airway Symptoms Score.* Parents were asked to complete a daily diary to estimate the severity of the main symptoms complained of by their children in the postoperative period. The main symptoms evaluated were nasal dryness, nasal obstruction, runny nose, epistaxis, itchy nose, snoring, post-nasal discharge, sore throat, ear pain, and halitosis. Each symptom score ranged from 1 (no symptoms) to 10 (severe symptoms) and were grouped in the Global Symptoms Score (GSS). Our research group created this questionnaire as it brings together and highlights the most common clinical symptoms typically referred by children and parents following adenoidectomy.
- *Concomitant medication use*. No restrictions were placed on the use of concomitant medication during any acute ailment. Both groups received standard treatment during the acute stage if any complication occurred during the study period and included: antipyretics, mucolytics, nasal decongestants, and systemic antibiotics.
- *Complications* such as hemorrhage.
- *Compliance with the treatment.* Patients with their parents were evaluated for their attitude concerning tolerability during and after application using a standard 10 cm Visual Analog Scale (VAS) ranging from 0 (not comfortable) to 10 (very comfortable).
- *Adherence to the assigned treatment* was evaluated by counting the number of dispensed and returned Isonebail Kits and single-dose vials.

- *Difficulties/unpleasantness experienced during administration.* Complaints of itch/pain/discomfort, medication flowing down throat/nose, struggling away, experiences of fear/anxiety/cries, flat refusal, unpleasant after taste, only allowing the application of 1 nostril, nostril dryness, and epistaxis.

Statistical analysis

All qualitative parameters were converted to a numeric scale for evaluation purposes. The results were collected and stored in a Microsoft Excel spreadsheet. Statistical analyses were performed using the statistical package STATA version 13 (StataCorp LP, College Station, TX, USA). Graphs were prepared using GraphPad Prism 6.0 for MacOS (GraphPad, La Jolla, CA, USA). The results are expressed as mean and SD. Non-parametric Mann-Whitney test for non-paired data was used to compare different values. Our criterion for statistical significance was set at p values of less than 0.05 (2-tailed).

Table I. *Demographic characteristics of study participants*

	E-group (20 patients)	S-group (22 patients)
Mean age (yr)	5.66	5.70
Male	12 (60%)	12 (54.4%)
Female	8 (40%)	10 (45.5%)
Weight (kg)	24	25
Height (cm)	119.35	120.20
III degree of AH	6 (30%)	8 (36.36%)
IV degree of AH	14 (70 %)	14 (63.64%)
Recurrent OME	8 (40%)	10 (45.54%)

RESULTS

Forty-four patients were analyzed in the study (Table I). No uncontrolled bleeding was observed during or after the surgical procedure.

Upper airway symptoms score

At the beginning of the treatment (T1), the GSS in the E-group was 30.65±4.5, while in S-group was 30.86±3.87 ($p > .05$). At the end of the treatment (T2), in the E-group the GSS was 12.6±5.7, while in the S-group the GSS was 17.1±4.9, with a mean reduction of 18.05±7.7 and 13.77±5.7 respectively ($p = 0.01$). All the specific nasal symptoms assessed showed a greater severity reduction in case of E-group (Table II). In particular, nasal dryness (E-group: 3.0±1.4, S-group: 1.9±1.4; $p = 0.02$), nasal obstruction (E-group: 2.5±1.4, S-group: 1.6±0.96; $p = .03$), runny nose (E-group: 2.5±1.7, S-group: 1.5±1.5; $p = .04$), and post-nasal discharge (E-group: 2.75±0.9, S-group: 1.7±1.5; $p = 0.001$) showed a statistically significant difference between groups, while snoring (E-group: 2.5±1, S-group: 1.8±1.6; $p = 0.08$) was not significantly different.

No significant differences were reported between the two groups on the use of concomitant medication such as antipyretics, mucolytics, nasal decongestants, systemic antibiotics, tranexamic acid. No side effects related to the investigated treatments were reported in either group during the study. Children using ectoine saline solution nebulized with Spray-sol™ reported higher significant compliance than those treated with saline solutions (E-group: 7.80 ±1.2; S-group: 6.10 ±1.1; $p> 0.001$) as shown in Fig. 2. During the two weeks of treatment, in the E-group the number of treatment placements was 26.40±2.82 while in the S-group were 26.55±2.52 of the 28 administrations available without significant difference. The most common problems experienced during administration were discomfort, itch or pain (E-group: 4 patients and S-group: 7 patients), and medication flowing down the nose and throat (E-group: 3 patients and S-group: 5 patients) as shown in Table III. No cases of epistaxis were described in either of the groups.

Table II. *Specific nasal symptoms*

	E-group	S-group	
Nasal dryness	3.0±1.4	1.9±1.4	$p = 0.02$
Nasal obstruction	2.5±1.4	1.6±0.96	$p = 0.03$
Runny nose	2.5±1.7	1.5±1.5	$p = 0.04$
Post-nasal discharge	2.75±0.9	1.7±1.5	$p = 0.001$
Snoring	2.5±1.0	1.8±1.6	$p = 0.08$

Table III. *Difficulties/unpleasantness experienced during administration*

	E-group	S-group
Complaints of itch/pain/discomfort	4	7
Medication flowing down throat/nose	3	5
Struggle away	2	3
Experiences fear/anxiety/cries	2	3
Flat refusal	3	4

DISCUSSION

During the first days after an adenoidectomy, patients' short-term quality of life may be compromised by edema, extensive crust formation, mucosal alterations, excessive secretions, and impaired nasal ventilation. For these reasons, clinicians nowadays are constantly searching for agents to promote the cleaning of nasal cavities and post-operative regeneration of the nasopharyngeal mucosa. In our study, at the end of the second post-operative week of treatment, the E-group showed a fast and significant improvement in the upper airway symptoms score compared to S-group with GSS evaluation, in particular for nasal dryness, nasal obstruction, runny nose and post-nasal discharge parameters. These results reflect the effects

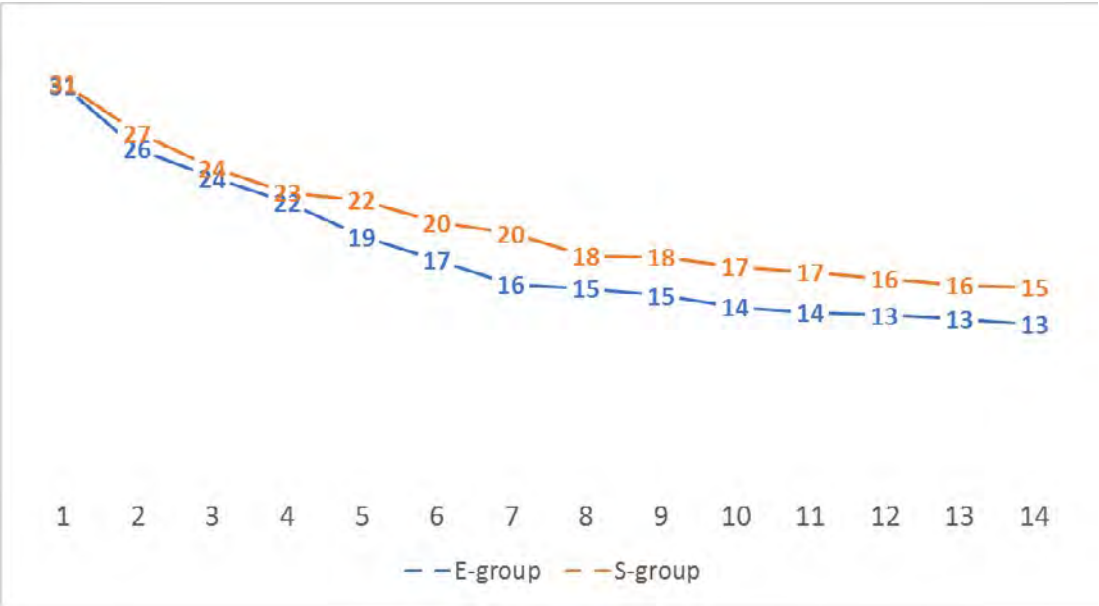

Fig. 1. *Trend of Upper Airway Symptoms in the two postoperative weeks. Ectoine with Spray-sol™ significantly and quickly improved GSS.*

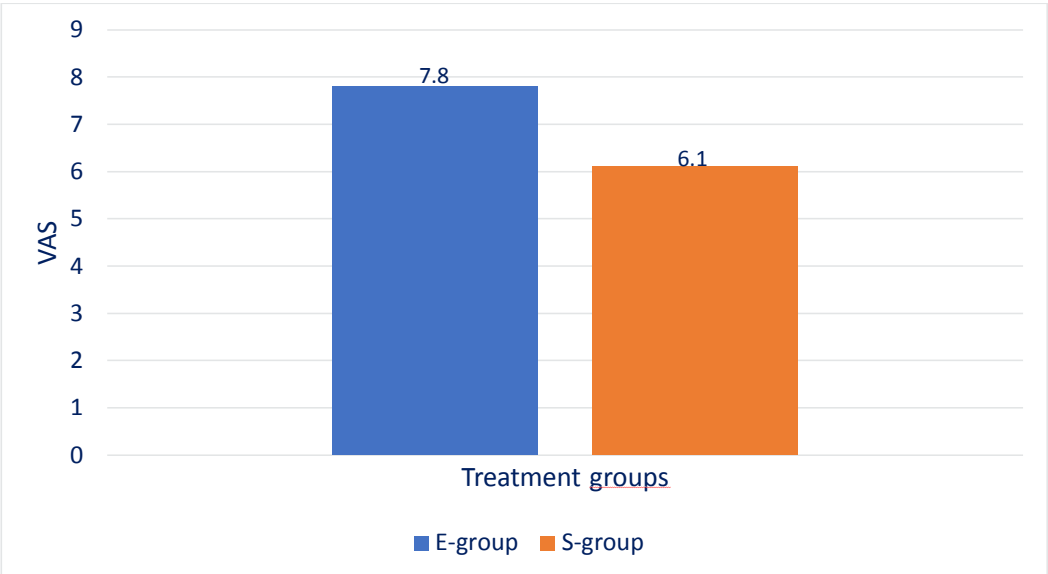

Fig. 2. *Compliance to the treatment*

of ectoine on tissue hydration, with the reduction of inflammation and secretions. Many studies showed that not all nasal devices are suitable to reach the nasopharynx region. Moffa et al. (5) showed that Spray-sol™ reached the nasopharynx region quickly in comparison with other devices, like "Rinowash" and "MAD nasal", with a statistical significance, and it could be considered a useful device for adenoiditis and Eustachian tube dysfunction therapies. Through the use of Spray-sol™, a high concentration of

ectoine solutions reached the nasopharynx region, the primary surgical site. This nasal device delivers particles with an average diameter between 10 and 20 microns, unlike "Rinowash", which has to be connected to an aerosol nebulizer with a pneumatic compressor. Spray-sol™ does not require energy, and administration time is as fast as a spray device. It allows distributions of small-diameter particles, modulation of the substance, as well as the capacity to reach all areas of nasal cavities, and the nasopharynx. Consequently, the amount of content that reaches the most posterior and upper regions of the nasal cavities is higher. Administration time (about 3-5 seconds for a complete and fine nebulization) and the ability to modulate applied forces is easy and fast. It is reusable and for a single patient. Moreover, Spray-sol™ has the advantage of delivering multiple types of saline solutions simultaneously and some drugs such as corticosteroids.

The encouraging results of this observational study have led us to investigate the potential role of ectoine saline solution in combination with Spray-sol™ in other types of acute and chronic inflammatory diseases of the upper airway. Further studies on a large scale will be needed to confirm the encouraging results obtained from the present study.

DISCLOSURE of potential conflicts of interest: M. Casale is the inventor but not the owner of B14630R/REPA/rst patent and PCT/IB2014/065121 of Spray-sol® device. All of the other authors report no conflicts of interest.

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