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Original article

Efficacy of tobramycin aerosol in nasal polyposis

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ABSTRACT

Context: Treatment of infected nasal polyposis.
Material and methods: Multicenter interventional prospective double-blind randomized study with matched groups: treatment with tobramycin aerosol versus isotonic saline aerosol. The study population included 55 patients: 23 receiving isotonic saline aerosol and 32 receiving tobramycin. A novel device (Easynose®) was used with an original principle limiting pulmonary deposition and ensuring homogeneous peripheral deposition in the nasal cavities.
Objectives: The principal objective was to compare bacteriological eradication between tobramycin 150 mg/3 ml versus isotonic saline, both administered by nebulization via the Easynose® device.
Results and conclusion: Tobramycin aerosol administered via the Easynose® device showed significantly better bacteriological eradication than isotonic saline.

1. Introduction

Nasal polyposis (NP) is a chronic inflammatory disease of the sinonasal mucosa, with prevalence of about 4% [1]. It is characterized by essentially bilateral ethmoid and nasal cavity polyps [2].

The few bacteriological studies of NP are concordant, showing 70–80% of cultures pathogen-positive [3–5]. Isolates mainly comprise *Staphylococcus aureus* (40–60% of samples), *Pseudomonas aeruginosa* (approx. 5%), *Haemophilus* spp. (approx. 5%), and *Streptococcus pneumoniae* (approx. 5%) [4,5]. These rates are the same in operated and non-operated patients. The isolates are susceptible to tobramycin [3–5]. However, NP course features infectious episodes associating heightened sinus secretion and abundant purulent secretion in the nasal cavity [2,3]. These episodes are presently treated by wide-spectrum systemic antibiotics, sometimes associated to oral corticosteroids. No published studies have demonstrated the efficacy of such treatment, and there are no published guidelines.

Notably, there are no published data regarding the efficacy of any kind of nebulization aerosol therapy in rhinosinus pathologies, whether acute or chronic, despite the fact that this mode of administration seems especially well suited by virtue of the easy access to the nasal and sinus cavities [6]. It seems particularly suited to patients undergoing bilateral ethmoidectomy for NP, in view of the wide opening of the sinuses. A new device was recently developed by the Diffusion Technique Française company (Easynose®), based on an original principle (patent No. FR2938770) that reduces pulmonary deposition and ensures homogeneous peripheral deposition in the nasal cavities [7].

In the light of these data and this recent innovation, we performed a prospective multicenter study in France to assess the contribution and limitations of nebulization of tobramycin solution in infection following surgery for NP.

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2. Material and methods

2.1. Methods

2.1.1. Study design

A prospective interventional study randomized patients into two matched groups (tobramycin versus isotonic saline nebulization) in a double-blind comparative multicenter design. Randomization was balanced (ratio 1:1), based on a list comprising size-4 blocks. Patients randomly received either tobramycin (group B) or isotonic saline (group A). The local review board (*Comité de Protection des Personnes* [CPP] Île-de-France VIII) approved the research protocol on October 8, 2010.

2.1.2. Treatment

The active treatment was a solution of 150 mg tobramycin for inhalation by nebulization in a single dose of 3 ml medium (150 mg/3 ml), administered by the Easynose® mesh nebulizer. The solution was composed of tobramycin 150 mg, water for injection qs 3 ml, and NaCl. The isotonic saline solution comprised the excipient of the active treatment. Active treatment or saline was administered twice daily for 7 days. Long-course corticosteroid therapy was allowed on condition that there had been no change in dosage for at least 1 month before inclusion. For the duration of the study, patients were not to have any nose-wash with physiological saline, antibiotherapy or systemic corticotherapy.

2.1.3. Study objectives

The principal study objective was to compare bacteriological eradication efficacy between tobramycin 150 mg/3 ml solution versus isotonic saline, both prepared for inhalation by aerosol nebulization using the Easynose® device.

Secondary objectives were:

- to compare efficacy between tobramycin 150 mg/3 ml solution versus isotonic saline, both prepared for inhalation by aerosol nebulization using the Easynose® device, in terms of clinical improvement, adverse effects and study withdrawal
- to analyze the acceptability of aerosol nebulization for the patient.

2.1.4. Study variables

To explore the principal objective, bacteriological analysis was performed on D0 and D10, following Day et al. [5], studying the presence of pathogenic strains in culture and their antibiotic susceptibility, with cytological analysis of the presence and concentration of leukocytes (D0 and D10).

Variables exploring the secondary objectives were:

- clinical: nasal congestion, anterior and posterior rhinorrhea, facial pain and heaviness, and olfactory impairment, assessed at D0, D10 and D30 on visual analog scales (VAS);
- acceptability: satisfaction in terms of ease of use of the device (preparation, inhalation) and duration of application.

Compliance was assessed in terms of failures to take treatment, reported on a self-assessment questionnaire filled out at the treatment sessions from D1 to D7, also reporting adverse effects. General clinical examination and fiberoptic endoscopy were performed at D0, D7 and D30.

2.1.5. Statistical analysis

Statistical analysis was blind, the two groups being labeled A and B (in fact, saline and tobramycin, respectively), identified only after the analysis results were in.

Table 1
Comparison of patient data per group. Differences were not significant.

	Group A Saline	Group B Tobramycin	*P*
n	23	32	
Mean age (range) in years	53 (29–70)	46 (22–70)	NS
Gender (% male)	43.48	53.13	NS
Time from NP diagnosis (years)	10	13	NS
Time from ethmoidectomy (years)	5	6	NS
% NP + asthma	17.39	28.13	
% Widal	39.13	37.50	NS

NS: non-significant.

Comparison used:

- Fisher exact test for qualitative data (gender, bacteriology);
- Student *t*-test or non-parametric Wilcoxon test for continuous quantitative data (age, time from NP diagnosis, time from last infection episode, time from ethmoidectomy, pre-treatment VAS);
- Wilcoxon test for ordinal qualitative data (bacteriological quantification of strains; cytological quantification of leukocytes).

2.2. Material

Inclusion criteria were patient:

- aged 20–70 years, with health insurance cover, consenting to the study;
- presenting with NP operated on for an episode of infection (aggravation of symptoms, with bilateral purulent secretion) within the previous 3 months;
- with fully healed total ethmoidectomy performed at least 2 months previously;
- without local or systemic antibiotherapy during the previous month;
- with NP not extending beyond the roof of the maxillary sinus.

Exclusion criteria were: pregnancy, breast-feeding, cystic fibrosis, proven ciliary dyskinesia or known immune deficiency, kidney failure and contraindications for aminoglycosides.

In all, 72 patients were randomized: 33 to group A (saline) and 39 to group B (tobramycin). Ten patients (6 in group A, 4 in group B) were excluded for negative D0 bacteriology, and 7 (4 in group A and 3 in group B) for major protocol deviation (age > 70 years, use of forbidden medication). Thus the final study population comprised 55 patients: 23 patients in group A, 32 in group B.

Table 1 presents patient data per group; characteristics were comparable ($P > 0.05$). Table 2 presents sinonasal status: symptoms, septum status, inferior turbinate status, polyposis volume, severity of purulence; characteristics were comparable.

Table 3 presents percentage positive culture per group; there was no significant difference. Table 4 presents cytologic results analyzing secretions; there was no significant difference. Table 5 presents the tobramycin susceptibility of isolates: 62 of the 70 strains were tobramycin-susceptible (88.57%), being mainly streptococci, which are naturally non-susceptible to aminoglycosides. Among the pathogenic strains, only one *S. aureus* strain had acquired tobramycin resistance.

3. Results

3.1. Compliance

Mean compliance was excellent in both groups: 98.9% in group A and 97% in group B. There were only 5 failures to take tobramycin.