

INHALED THIAMPHENICOL AND ACETILCYSTEINE IN CHILDREN WITH ACUTE BACTERIAL RHINOPHARYNGITIS

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Antibiotic abuse for treating rhinopharyngitis induces the occurrence of resistant bacteria. As topical drugs might reduce this phenomenon, the aims of our study are to evaluate inhaled thiamphenicol associated with acetylcysteine in children with acute bacterial rhinopharyngitis and to compare it with the use of saline solution. The trial was conducted as randomized, parallel group, and single blind. Children, aged 3-6 years, with acute bacterial rhinopharyngitis were treated with aerosolized thiamphenicol associated with acetylcysteine (250 mg: ½ vial in the morning and ½ vial in the evening) (Group A) or saline solution twice daily (Group B), both of them for 5 days. Both treatments were administered using a new device: Rinowash. The following parameters were assessed: nasal obstruction, mucopurulent rhinorrhea, post-nasal drip, cough, sore throat, fever, and cultures. Of 104 patients screened, 90 children, median age 3.7 years (44 females and 46 males), completed the study: 60 in Group A and 30 in Group B. Actively-treated children achieved a significant improvement of all parameters, but fewer than the control group. In conclusion, inhaled thiamphenicol associated with acetylcysteine may represent a valid treatment for acute bacterial rhinopharyngitis in children, as it is effective, safe, economic, and simple to use.

Rhinopharyngitis is a common disorder in children (1) and frequently causes complications, including otitis media, rhinosinusitis, and lower respiratory tract infections (2). Even though upper respiratory infections (URIs) are usually sustained by viruses, they represent the leading reason for antibiotic prescription in children in U.S.A. (3). Antibiotic abuse often modifies normal saprophytic flora in rhinopharynx (4), thus inducing the occurrence of resistant bacteria (5). In this regard, long-term courses of antibiotics are the first cause of selecting resistant strains (6).

Intranasal inhalatory therapy satisfies the requirements for restoring the patency and the drainage of OMC and RP. As a matter of fact, it allows to achieve higher local drug concentrations, to consequently use lower drug dosage, to exert prompt activity, to remove secretions by the watery solution, to increase tolerability (particularly suitable for children), and to reduce the occurrence of antibiotic resistance. In this regard, several studies highlight the effectiveness of inhaled antibiotics in treating bacterial respiratory infections (7-12). Very recently, we provided evidence that inhaled

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tobramycin was more effective than amoxicillin clavulanate in treating children with acute bacterial rhinopharyngitis (13).

Moreover, the treatment of acute bacterial rhinopharyngitis may be "empirical" or "rational": the first based on generic antibiotic prescription, the second based on cultures but awaiting results. However, empirical prescription may easily induce abuse of antibiotics and consequent resistance. Thus, the aims of our study are to evaluate inhaled tiamphenicol associated with acetylcysteine in children with acute bacterial rhinopharyngitis and to compare it with saline solution.

MATERIALS AND METHODS

Study design

The trial was conducted as randomized, parallel group, and single blind. Inclusion criteria were based on a documented diagnosis of acute bacterial rhinopharyngitis (positive culture for bacteria) and validated parameters. Children (aged 3-6 years) had to present at least 5 of these 7 parameters: nasal obstruction, mucopurulent rhinorrhea, post-nasal drip, cough, sore throat, fever, and positive culture according to previous study (13).

Exclusion criteria were anatomic anomalies (septal deviation, choanal atresia, etc), hypersensitivity to tiamphenicol and acetylcysteine, respiratory allergy, cystic fibrosis, renal failure, use of antibiotics and/or corticosteroids in the last 30 days, and negative culture.

All parents of the enrolled children provided informed written consent. The study was approved by the Institutional Review Board.

An adaptive randomization procedure was used to assign patients in a 2:1 ratio to receive tiamphenicol associated with acetylcysteine or hypertonic solution.

Cultures

Nasal swab was performed in rhinopharynx using a sterile silicon-covered pad with the tip extracted close to the exudate. Nasal swabs were plated onto the following media: blood-agar plate, CNA blood-agar, chocolate-agar plus isovitalax, (OXOID, Italy), Mac-Conkey agar, and Brain-Heart Infusion agar. All plates were incubated for 24 h at 37°C. Bacteria were identified by conventional techniques such as Gram stains; catalase and oxydase tests. Species identification was accomplished by API methods (BioMérieux, Marcy L'Étoile, France). As numerous species were identified, also in the same patient, to simplify results the data were expressed as positive culture number, without quantifying and qualifying bacteria.

Drugs and monitoring

The treatment regimen consisted of 250 mg of aerosolized tiamphenicol associated with acetylcysteine (1/2 vial in the morning and 1/2 vial in the evening) (Group A) or saline solution twice daily (Group B), both for 5 days.

Tiamphenicol associated with acetylcysteine solution for inhalation (Zambon S.p.A., Italy) was a sterile, pH-buffered solution containing 250 mg of tiamphenicol associated with acetylcysteine to be diluted in 4 mL of saline solution. Both treatments were administered by the nasal device Rinowash (Markos-Mefar S.p.A., Italy) and an aerosol nebulizer with pneumatic compressor (1.5 bar per 5 L/min) (Moby-neb by Markos-Mefar S.p.A., Italy). As modern therapeutic strategies involve the use of a device able to administer a correct aerosol therapy, Rinowash is a device specifically designed to administer correct endonasal therapy, and proves particularly effective in the treatment of the upper respiratory ways (URW). Rinowash selectively treats the osteomeatal complex and the rhino-pharynge thanks to the dimension of the nebulized particles (13). The mass median aerodynamic diameter (MMAD) of the particles is greater than 10 micron, in accordance with the European Respiratory Society Guidelines.

During the study, the patients were visited at baseline (V1-the start of the trial) and after 5 days (V2-the end of the treatment). Nasal swab, clinical evaluation, fiberoptic endoscopy, were performed at each visit.

The following parameters were assessed: nasal obstruction (graded as absent, continuous-daily, or periodic), mucopurulent rhinorrhea (evaluated as absent, reduced or unchanged after treatment), post-nasal drip (evaluated as absent, reduced or unchanged after treatment), cough, and fever according to validated methods (14), and culture positivity.

The drugs were administered to the children by the parents, who instructed the children to perform normal tidal breathing during aerosol-therapy. No other drugs were permitted during the study.

Statistical analysis

The statistical analysis was carried out using the program Statistic '98 Edition, StatSoft, Inc. The comparison between the proportions was computed under the approximation of normal distribution and testing the null hypothesis.

For each symptom the efficacy of the two drugs was analysed evaluating the reduction of the positive cases. A p value lower than 0.05 was considered as significant.

RESULTS

Baseline evaluation (day 0)

Of 104 patients screened, 94 met the eligibility

criteria and received study drugs; 63 patients received thiamphenicol associated with acetylcysteine (Group A) and 31 received hypertonic solution (Group B). Ninety patients, median age 3.7 years (44 females and 46 males), completed the study: 60 in Group A and 30 in Group B. The two groups were similar with respect to randomization strata. There were no significant differences in baseline parameters: nasal obstruction, rhinorrhea, post-nasal drip, cough, fever, and cultures between the two groups. Thus the two groups were statistically homogeneous.

After-treatment evaluation (day 5)

Compliance, as monitored by phial and tablet count, was similar in the two groups: 90% of doses for Group A and 87% for Group B. Treatments were substantially well tolerated in both groups without significant adverse events.

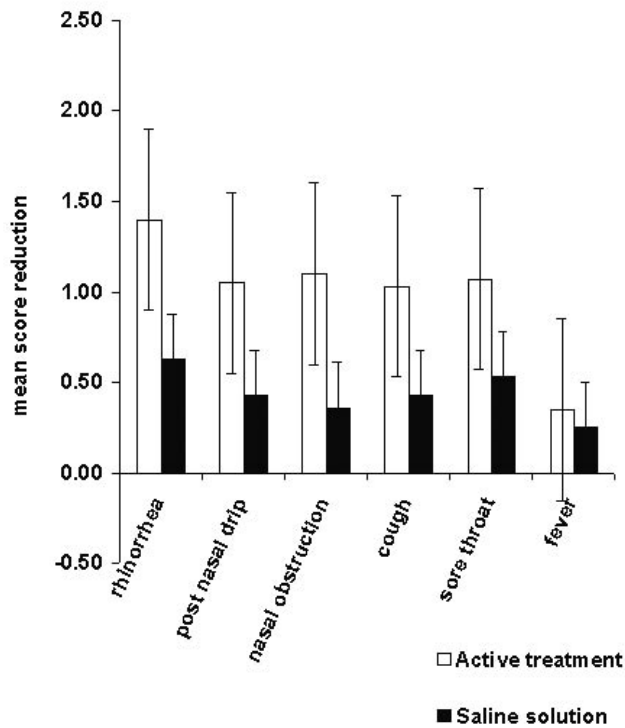


Fig. 1. Reduction of mean score for each parameter at visit 2 (end of the treatment). In group A, inhaled thiamphenicol associated with acetylcysteine induced a significant reduction in rhinorrhea ($p<0.001$), post nasal drip ($p<0.005$), sore throat ($p<0.001$) and fever ($p<0.005$).

INTRAGROUP ANALYSIS

Rhinorrhea

In group A, inhaled thiamphenicol associated with acetylcysteine induced a significant reduction (-1.4 of mean score = -66%; $p<0.001$), whereas in group B, saline solution induced a slight reduction (-0.63 of mean score = -24%; $p=n.s.$) (Fig. 1).

Post nasal drip

Inhaled thiamphenicol reduced this symptom (- 1.05 of mean score = -62%; $p<0.005$), whereas saline solution induced slight reduction (- 0.43 of mean score = -22%; $p= n.s.$) (Fig. 1).

Nasal Obstruction

It was significantly reduced in Group A (-1.1 of mean score = -59%; $p<0.005$) and slightly in Group B (-0.36 of mean score = -14%; $p=n.s.$).

Cough

It was reduced significantly reduced in Group A (-1.03 of mean score = - 63%; $p<0.001$) and slightly in Group B (-0.43 of mean score = - 22%; $p=n.s.$).

Sore throat

It was reduced significantly reduced in Group A

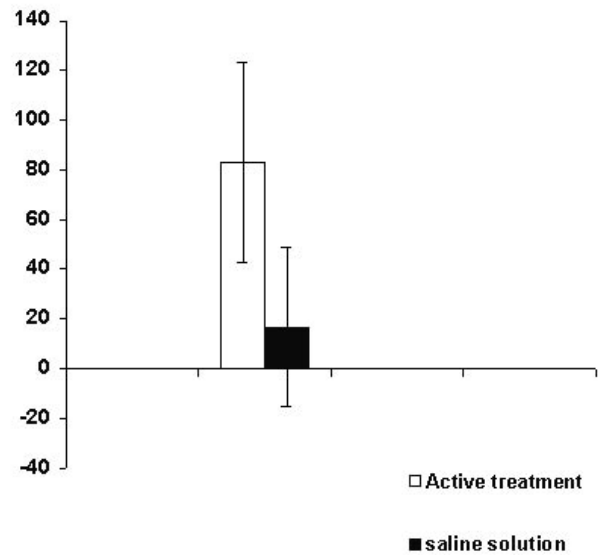


Fig. 2. Percentages of negative pharyngeal swabs at visit 2 (end of the treatment). Positive cultures were significantly reduced in Group A ($p<0.001$)

(-1.7 of mean score = - 70%; $p < 0.001$) and slightly in Group B (-0.53 of mean score = - 25%; $p = n.s.$).

Fever

Fever was significantly reduced in Group A (-0.65 of mean score = - 66%; $p < 0.005$) and slightly in Group B (-0.25 of mean score = - 29%; $p = n.s.$).

Cultures

Positive cultures were significantly reduced in Group A (85% of pharyngeal swabs were negative, $p < 0.001$), whereas slightly in Group B (17% of pharyngeal swabs were negative, $p = n.s.$) (Fig. 2).

INTERGROUP ANALYSIS

Symptoms

The active treatment induced a significantly better reduction of rhinorrhea ($p < 0.001$), post nasal drip ($p = 0.003$), nasal obstruction ($p < 0.001$), cough ($p = 0.002$), and sore throat ($p = 0.009$) in comparison with the saline solution, whereas there was no significant difference between two groups concerning fever ($p = 0.56$).

Cultures

Inhaled thiamphenicol associated with acetylcysteine induced a significantly higher number of negative cultures in comparison with the saline solution ($p < 0.01$).

DISCUSSION

This study compared two different “empirical” therapies in children with acute bacterial rhinopharyngitis: inhaled thiamphenicol (16) with acetylcysteine (nebulized by Rinowash) and saline solution. The findings showed that only the active treatment was effective. However, topical antibiotic had slight effect on fever, but this symptom was present in some patients and was usually fairly raised.

Moreover, the active drug contains acetylcysteine that exerts a mucolytic activity which may explain the effectiveness on rhinorrhea and post nasal drip improvement. Finally, inhaled thiamphenicol was well tolerated and provided a good compliance.

In conclusion, the inhaled thiamphenicol with acetylcysteine may represent a valid “empirical”

treatment, such as waiting for culture results, for acute bacterial rhinopharyngitis in children, as it is effective, safe, economic, and simple to use.

The correct application of inhaled therapy needs a specific device for upper airways and suitable drugs for nebulization (such as those with specific physical-chemical characteristics).

The abuse of systemic antibiotics for the treatment of acute rhinopharyngitis has caused and still causes antibiotic-resistance, already wide-spread in the western world. The use of topical antibiotics may prevent this occurrence.

Thus, this study provides evidence that inhaled antibiotic therapy may represent an effective treatment in children with acute bacterial rhinopharyngitis. Therefore, these findings should reduce the ostracism to therapy with inhaled antibiotics. Numerous studies have to be conducted to validate and confirm these results.

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