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Broncho-Vaxom® in Children with Rhinosinusitis: A Double-Blind Clinical Trial

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Abstract. Fifty-one children aged 4–12 years, presenting with an acute epidose of chronic rhinosinusitis, were treated for 6 months with either Broncho-Vaxom® (BV; marketed in Yugoslavia under the trade mark of Broncho-Munal®) or placebo under double-blind randomized conditions. The efficacy of BV was assessed on the basis of clinical symptoms (cough, nasal discharge, congestion of nasal mucosa), number and duration of concomitant treatments (antibiotics, secretolytics, antitussives), number and duration of acute episodes during the trial and serum IgA levels. In BV treated patients the incidence and duration of infectious episodes and the number and duration of concomitant treatments decreased significantly in comparison with the placebo group, and the clinical response correlated positively with an increase in the serum levels of IgA. The results of treatment of acute episodes of chronic rhinosinusitis in children demonstrated the curative and prophylactic efficacy of BV.

Introduction

Impairments of both mucosal and systemic immune responses have been described in patients with respiratory tract infections which include humoral and cellular immunity [1].

Bacterial extracts have been proposed for many years to enhance the responsiveness of the immune system and to secure protection against infections.

Broncho-Vaxom® (BV; marketed in Yugoslavia under the trade marke of Broncho-Munal®) is a lyophilized bacterial lysate containing fractions of the following bacteria: *Haemophilus influenzae, Diplococcus pneumoniae, Klebsiella pneumoniae* and *ozaenae, Staphylococcus aureus, Streptococcus pyo-*

genes and *viridans, Neisseria catarrhalis.* It acts by stimulating the body's natural defense mechanisms.

It has been shown in several clinical trials that BV decreases the frequency and the duration of infections in children [2, 4, 6–11], reduces the intensity of symptoms and shortens the duration of antibiotherapy. It also improves the immunological parameters [3, 5, 10, 12, 13].

This study was therefore designed to investigate the curative and prophylactic efficacy of BV in pediatric patients with acute exacerbation of chronic rhinosinusitis in comparison with the placebo and to assess its tolerance.

Patients and Methods

Fifty-five patients aged 4–12 years, presenting with an acute episode of chronic rhinosinusitis, were selected for treatment with either BV for children, containing 3.5 mg of the lyophilized bacterial lysate or the placebo under double-blind conditions according to the following therapeutic scheme: 1-month curative treatment phase involving the administration of one capsule daily of BV or placebo during 30 consecutive days. After 1 month without treatment a 3-month prophylactic treatment phase was started involving the administration of 1 capsule/day of BV or a placebo for the first 10 days of each of three consecutive months; this was followed by 1 month of observation without treatment.

The attending physician was asked to record the patient's condition at baseline and to enter any changes observed at control visits on day 15 and at the end of each month of treatment as well as to carefully record any concomitant therapy prescribed (antibiotics, secretolytics, antitussives).

The efficacy of treatment was assessed on the basis of laboratory analyses (serum IgA levels, leukocyte counts, erythrocyte sedimentation rates, ESR), sinus X-rays and clinical parameters (cough, nasal discharge, congestion of nasal mucosa). The data were submitted to statistical analysis using Student's t test and Person's variability coefficient and the analysis of variance.

Table I. General patient characteristics during the 12 months preceding the trial

Characteristics	Broncho-Vaxom (n = 29)	Placebo (n = 22)	p
Age, years	6.53 ± 0.96	6.81 ± 0.80	n.s.
Sex (male/female)	15/14	13/9	n.s.
Duration of disease, years	2.31 ± 0.33	2.34 ± 0.37	n.s.
Recurrence rate of disease, n	6.72 ± 1.21	5.59 ± 1.22	n.s.

Results

Of the 55 patients who initially entered the trial, 29 patients in the BV group and 22 in the placebo group were eligible for statistical analysis.

At the beginning of the trial there were no statistically significant differences between the BV- and the placebo-treated groups with respect to general patient characteristics (age, sex, body weight and frequency of contact with other children) and medical history (diagnosis, previous duration of disease, annual recurrence rate, concomitant diseases, concomitant therapy) during the preceding 12-month period (table I).

Cough

Cough was evaluated for its presence by a 3-point rating scale: 1 = none; 2 = moderately frequent (weekly); 3 = frequent (daily). Analysis of the effects of BV on cough showed a statistically significant improvement already by the 15th day of treatment ($p < 0.01$). In the placebo group, the reduction in the incidence of cough observed after 15 days of

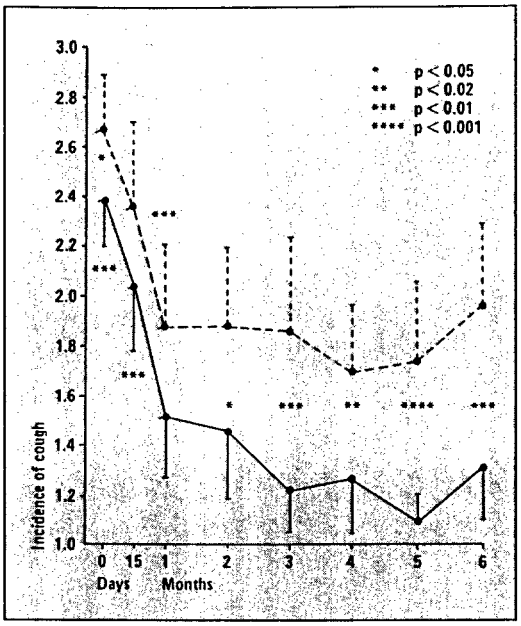


Fig. 1. Mean incidence of cough during BV (——) and placebo (– – –) treatment.

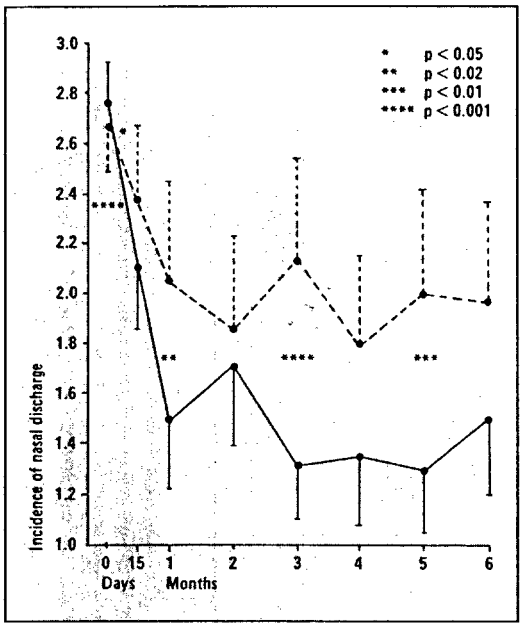


Fig. 2. Mean incidence of nasal discharge during BV (——) and placebo (– – –) treatment.

treatment was not statistically significant (fig. 1).

Subsequently the decrease in cough incidence was much more pronounced in the BV group where it had virtually disappeared by the 5th month of treatment, to rise only very slightly during the 6th month, i.e. 1 month after termination of treatment. In the placebo group, the incidence of cough, after a significant drop at 1 month, remained unchanged throughout the observation period, its presence being estimated as 'frequent'.

Comparative evaluation of cough incidence between BV and placebo indicated a statistically significant difference in favor of the BV-treated group in month 2 ($p < 0.05$), month 3 ($p < 0.01$), month 4 ($p < 0.02$), month 5 ($p < 0.001$) and month 6 ($p < 0.01$) (fig. 1).

Nasal Discharge

Nasal discharge was evaluated for its presence by a 3-point rating scale: 1 = none; 2 = moderately frequent (weekly); 3 = frequent (daily). Analysis of the effects of BV on nasal discharge indicated a statistically significant decrease by the 15th day of treatment ($p < 0.001$) and this downward trend continued till the end of the study (fig. 2). In the placebo group nasal discharge significantly improved by the 15th day of treatment ($p = 0.05$) but there was no further change during the rest of the study period. Comparative analysis of the effects of BV and placebo on nasal discharge demonstrated a statistically significant difference in favor of BV at month 1 ($p < 0.02$), month 3 ($p < 0.001$) and month 5 ($p < 0.01$) (fig. 2).

Properties of Nasal Discharge

The properties of nasal discharge were assessed at each control visit using the following 4-point rating scale: 0 = none, 1 = clear, 2 = mucoid, 3 = purulent. Nasal discharge significantly improved under BV when compared to the placebo already after the first month of treatment (table II).

Congestion of Nasal Mucosa

Congestion of nasal mucosa was evaluated according to its frequency and intensity as: Severe congestion: 1 = none; 2.5 = moderately frequent (weekly); 3 = frequent (daily); Mild congestion: 1 = none; 1.5 = moderately frequent (weekly); 3 = frequent (daily).

Analysis of the effects of BV on the congestion of nasal mucosa revealed a statistically significant improvement by the 15th day of treatment ($p < 0.05$), continuing in the same direction at an even higher rate until the end of the curative treatment period ($p < 0.001$) and then at a somewhat slower rate till the end of the study (fig. 3).

In the placebo group, nasal congestion remained unchanged during the first 15 days and then gradually decreased, reaching statistical significance by the end of the curative treatment period ($p < 0.05$). During the remaining observation period it showed a slight but statistically nonsignificant decline (fig. 3).

Comparative analysis of the effects of BV and placebo on the congestion of nasal mucosa revealed statistically significant differences in favor of BV at month 1 ($p < 0.001$), month 3 ($p < 0.001$), month 4 ($p < 0.05$) and months 5 and 6 ($p < 0.01$) (fig. 3).

Acute Episodes

This clinical parameter was evaluated according to (a) duration (days) of acute exacerbations during the 6-month observation period and (b) number of acute exacerbations during the same period.

The mean duration of acute episodes per patient for BV and placebo was 2.17 ± 1.54 and 7.96 ± 4.11 days, respectively, yielding a statistically significant difference in favor

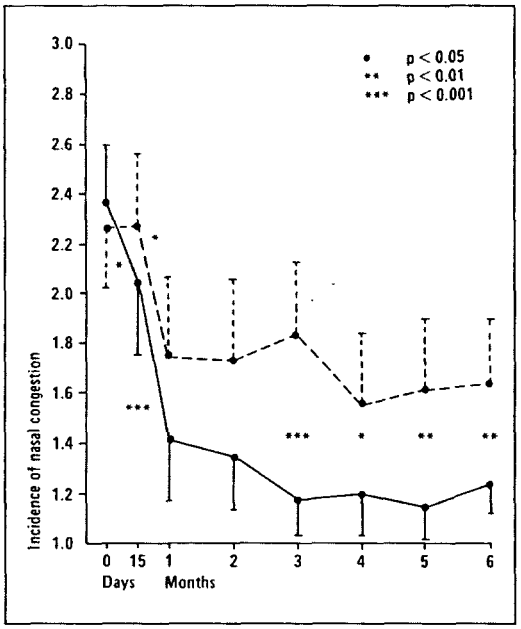


Fig. 3. Mean incidence of nasal congestion during BV (——) and placebo (– – –) treatment.

Table II. Comparison of Broncho-Vaxom and placebo with respect to the properties of nasal discharge

Control	Broncho-Vaxom/placebo		
	difference	t	p
Baseline	0.03	0.2015	>0.05
Month 1	0.98	3.1818	<0.01
Month 6	0.85	2.1981	<0.05

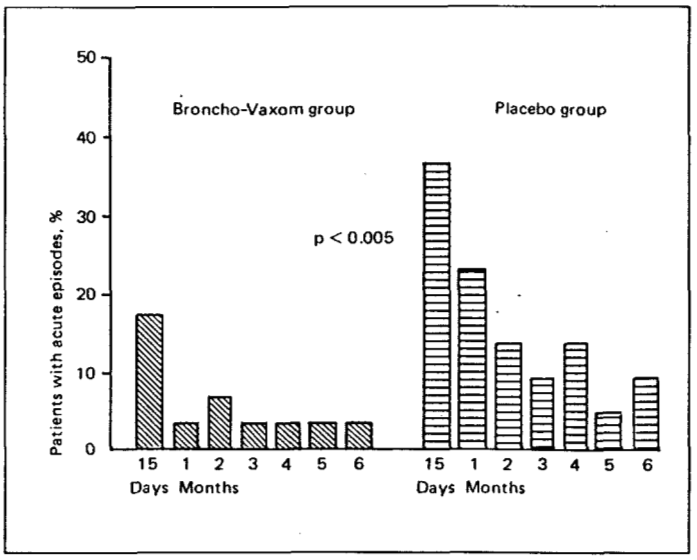


Fig. 4. Number of patients in percent with acute episodes at different times of BV and placebo treatment.

of BV ($p < 0.01$). The total duration of acute exacerbations during the 6-month observation period (63 days for BV again 175 days for placebo) was against statistically significantly longer in the placebo group ($p < 0.001$). The mean number of acute episodes per patient for BV and placebo was 0.38 ± 0.26 and 1.09 ± 0.65, respectively, yielding a statistically significant difference in favor of BV ($p < 0.05$).

Comparison of the total number of acute episodes during the 6-month trial (11 for BV against 24 for placebo) again showed a statistically significant difference in favor of BV ($p < 0.005$) (fig. 4).

Laboratory Parameters

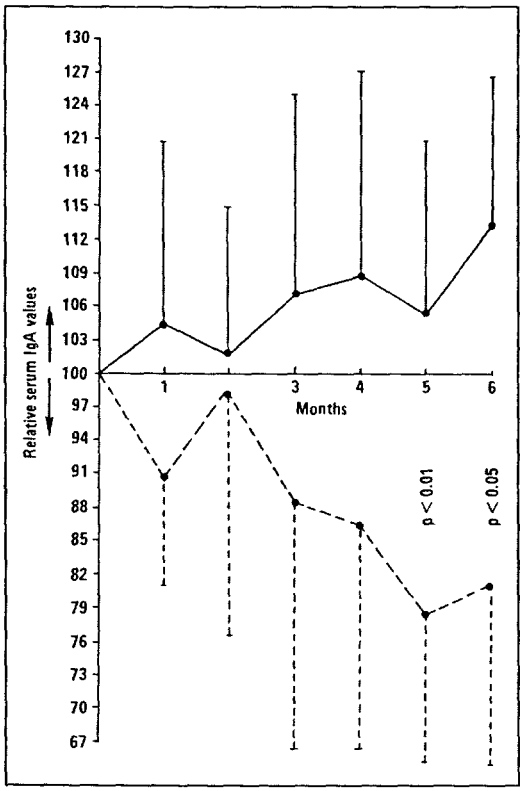
The leukocyte counts and the ESR remained within normal limits in both treatment groups throughout the 6-month observation period. However, in BV-treated patients, the ESR has significantly decreased by the end of the trial ($p < 0.05$) but still remained within normal values while in the placebo group the decrease was not statistically significant.

The mean serum IgA values were expressed as the relative changes from the baseline value which was designated as 100%.

The mean serum IgA levels during the 6-month observation period were stable under BV and tended to increase towards the end of treatment while on the contrary in the placebo group these values have steadily decreased and the differences with the BV group became statistically significant at month 5 ($p < 0.01$) and at month 6 ($p < 0.05$), as shown in figure 5.

Concomitant Therapy

With respect to cotrimoxazole therapy (sulfamethoxazole + trimethoprin), the difference between BV and placebo was not statistically significant for the number of courses but it was statistically significant in favor of BV ($p < 0.025$) for the duration of



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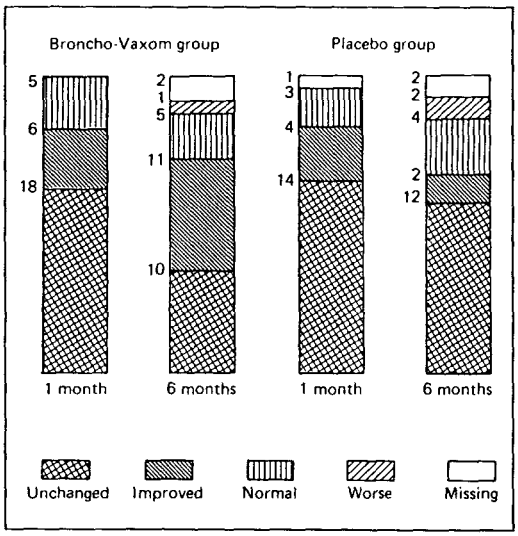

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Fig. 5. Mean serum IgA values for BV (——) and placebo (– – –) during the 6-month observation period.

Fig. 6. Sinus X-ray findings during BV and placebo treatment.

treatment (53 for BV against 63 days for placebo).

For the antibiotic therapy, there were no statistically significant differences between BV and placebo regarding the number of courses. However, comparison of the overall duration of antibiotic therapy in each group (179 days for BV against 191 days for placebo) showed a statistically significant difference in favor of BV ($p < 0.001$).

For the antitussive therapy, the difference between BV and placebo groups for both the number of courses (21 vs. 35) and their overall duration (156 vs. 259 days) was statistically significant in favor of BV (respectively $p < 0.05$ and $p < 0.001$).

For the secretolytic therapy, the difference between BV and placebo for both the number of courses (12 vs. 25) and their overall duration (70 vs. 182 days) was statistically significant in favour of BV $p < 0.005$ and $p < 0.001$, respectively.

Sinus X-Ray

Statistical analysis of sinus X-ray findings during the 1st month of the trial revealed no statistically significant differences between the BV and placebo-treated groups. However, improvements plus normal findings were found in 16 cases under BV and 6 cases under placebo at the 6th month ($p < 0.05$) (fig. 6).

Table III. Distribution of patients according to the physician's assessment of treatment efficacy

Results	Broncho-Vaxom				Placebo			
	curative		prophylactic		curative		prophylactic	
	n	%	n	%	n	%	n	%
Positive (evident 1 + possible 2)	17	58.6*	22	75.9**	3	13.6	5	22.7
Questionable (3)	6	20.7	1	3.4	6	27.3	6	27.3
Nil (4)	6	20.7	2	6.9	13	59.1	8	36.4
No rating			4	13.8			3	13.6

* $p < 0.005$ (BV vs. placebo) for curative.
** $p < 0.001$ (BV vs. placebo) for prophylactic.

Physician's Assessment of Treatment Efficacy

The curative and prophylactic efficacy of treatment was assessed by a 4-point rating scale: 1 = evident; 2 = possible; 3 = questionable; 4 = none.

Statistical analysis of the ratings (table III) indicated that the efficacy of BV was superior to placebo in both curative ($p < 0.005$) and prophylactic therapies ($p < 0.001$).

Tolerance

Toxicological and clinical studies [14, 15] have shown that BV does not induce hepatic, renal or hematological changes, therefore we planned to record only clinically manifested adverse reactions with the possibility, when occuring, of undertaking laboratory investigations. No side-effects were observed during the trial period in both groups. Thus further examinations regarding drug tolerance were unnecessary.

Discussion

This clinical trial has demonstrated the usefulness of BV in the treatment of rhinosinusitis in children. Cough significantly improved after 1 month of treatment with BV, practically disappearing by the end of therapy.

Nasal discharge significantly decreased by the 15th day of treatment with BV and continued to do so throughout the observation period. The physiological properties of nasal discharge (clear, mucoid, purulent) significantly improved and the difference between the two groups reached statistical significance already after 1 month of treatment.

Congestion of nasal mucosa likewise responded favorably to BV therapy. It began to improve already after 15 days of treatment, continued to decrease rapidly throughout the first month and subsided completely by the 5th month of therapy. The ESR and the leu-

kocyte counts were within normal levels at the start and they did not differ significantly between BV and placebo during the trial. BV exhibited beneficial effects on serum IgA levels, which tended to increase by the end of therapy while in the placebo group the IgA values have steadily decreased. From the 5th month of treatment, the difference between BV and placebo was statistically significant.

BV was also found to favorably influence the number and duration of acute episodes and to reduce the consumption of concomitant therapies.

Sinus X-ray revealed no statistically significant difference between the BV and placebo groups after 1 month but the difference among the improvements and normals, after 6 months, was statistically significant ($p < 0.05$) in favor of the BV group.

The results of this clinical trial have demonstrated the curative and prophylactic efficacy of BV in the treatment of acute exacerbations of chronic rhinosinusitis in children, its ability to reduce concomitant antibiotic, antitussive and secretolytic therapy, its capacity to maintain serum IgA levels within normal values and its excellent tolerance.

Acknowledgement

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