



# Effect of Amphotericin B on Treatment of Chronic Rhinosinusitis: A Double-blind Randomized Clinical Trial

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## Abstract

**Background:** Chronic rhinosinusitis (CRS) is the inflammation of paranasal sinus mucous membranes. Considering the influence of fungi on chronic rhinosinusitis and different results concerning the effect of Amphotericin B on improvement of this condition; this study aimed to determine the effect of topical Amphotericin B on improvement of the symptoms in patients with CRS.

**Methods:** In this double-blind randomized clinical trial, 80 patients with chronic rhinosinusitis who visited the allergy clinic of Baqiyatallah Hospital from June to October 2014 were randomly allocated to two groups; the first group received 10 cc topical lavage of Amphotericin B (5 cc each nostril for every 12 hours) and the second group received placebo for three months. Symptoms, nasal mucosa smear, serum level of inflammatory cytokines, CT scan and rhinoscopy score changes were evaluated in both groups after three months.

**Results:** Fifty-five male and 25 female patients were evaluated in two groups. The mean age was  $26.1 \pm 2.36$  and  $27.9 \pm 1.59$  years in intervention and control groups respectively ( $P = 0.08$ ). There were no significant differences in demographic data between the groups ( $P > 0.05$ ). Nasal obstruction, post nasal drip (PND), reduced sense of smell, quality of life, CT scan and rhinoscopy scores were not significantly different between the two groups after intervention ( $P > 0.05$ ). Facial pain severity score was significantly more reduced in intervention group in comparison with control group ( $P < 0.01$ ).

**Conclusions:** We concluded that application of Amphotericin B as an adjunctive medication to other common treatments, does not seem to be an efficient method for improvement of CRS symptoms.

**Keywords:** Quality of Life, Symptoms, Chronic Rhinosinusitis, Amphotericin B, VAS Score

## 1. Background

Chronic rhinosinusitis (CRS) is defined as the inflammation of paranasal sinus mucous membranes lasting more than 12 weeks (1, 2). Facial pain, feeling of facial fullness, nasal congestion or discharge, reduced or lack of sense of smell, acute fever, postnasal discharge, headache, fever in non-acute type, fatigue, toothache, coughing, and feeling of pressure or fullness in ear are the clinical symptoms of this disease (1). Without treatment, CRS could lead to major complications such as periorbital abscess, cellulitis and meningitis (3, 4). CRS is one of the most common chronic diseases in the United States of America affected 29.2 million adult patients (14.2% of population) (5). Medical treatments including broad-spectrum antibi-

otics along with antihistamines, nasal decongestants, and mucosa solvent drugs as well as surgery and nasal irrigation are used to treat this disease (6-8). Surgery, with high expense and enduring complications, is the treatment of choice in case of unsuccessful or delayed medical treatment and presence of complication (1, 9-14).

Fungi spores are one of the constituent elements in the breathing air and are commonly found in respiratory system; therefore, their impact on CRS has been confirmed (15-18). Previous data have demonstrated the therapeutic effects of Amphotericin B against fungi (19). Studies investigating the effects of Amphotericin B on improvement and treatment of CRS have shown different and even controversial results (20-22). Therefore, the present study aimed

to determine the effect of topical Amphotericin B on improvement of the symptoms in patients with CRS.

## 2. Methods

This double-blind randomized clinical trial was approved by ethics committee of Baqiyatallah University of Medical Sciences, Tehran, Iran (reference code: IR.BMSU.REC.1392.68). [Figure 1](#) shows a flowchart of the trial. Based on the previous studies and Cochran's sample size formula, a total of 40 patients with chronic rhinosinusitis were needed for this evaluation. According to the discrepancy between the current study and other similar studies in receiving placebo and drug and also the possibility of some participants leaving the study, 100 patients who visited the allergy clinic of Baqiyatallah hospital from June to October 2014 were enrolled in the present study without any age and gender limitations. A written informed consent was obtained from all the participants.

To confirm the eligibility of patients, those who had the conclusive diagnostic criteria of CRS were complied with the definition of rhinosinusitis task force (RSTF), proposed by the American academy of otolaryngology-head and neck surgery (AAO-HNSF) in 1996, and entered the study. The main inclusion criterion was the inflammation of nasal and sinuses mucosa with at least two major criteria and/or one major criterion together with two minor criteria that lasts 12 weeks ([23, 24](#)).

Patients under treatment for CRS or those taking antibiotics, positive history of prior surgery or allergy to Amphotericin B, evidences of immune system deficiency or being under treatment with immunosuppressive drugs, positive culture for Mycobacterium, osteoporosis, liver and kidney disorders, and also pregnant or lactating women and patients not willing to participate were excluded from the study.

To prepare Amphotericin B solution, an ampoule product from Indian company Cilpa was solved in sterilized water to provide a 200 microgram per millilitre solution. In addition, the storage conditions of Amphotericin B (temperatures between 2 to 6°C, keeping it away from light and shaking the solution before use) were taught to patients.

Patients were randomized into two groups using random-number table: The intervention group was treated with Amphotericin B and the control group was assigned to placebo (10 cc topical lavage, 5 cc each nostril for every 12 hours). Amphotericin B or placebo was administered using syringe. Then patients underwent follow-up and treatment for three months. Nobody was aware of the drugs ingredients and how the patients were divided except the supervisor and data analyst of the study. Coronal CT scan was performed for all the patients in order

to obtain adequate evidence from bone composition and mucosal exposure, anatomical structure, mucosal thickness and bone alteration. Also air-fluid level was investigated and the patients were evaluated based on the quintuple criteria of Lund and MacKay scoring system ([23](#)). MRI imaging was performed as well to distinguish fungal inflammation from viral and bacterial inflammation.

The patients were evaluated for rhinoscopy score (scored based on Lund and Mackay system), symptoms (nasal congestion, post-nasal drip, reduction in the sense of smell and facial pain) severity score (visual analogue score [VAS] score = 0 to 10), quality of life score (applying validated Persian Rhinosinusitis Outcome Measure 31 [RSOM-31] questionnaire), blood levels of interleukins 4, 5, and 13 effective in allergic fungal process (by ELISA assay) and level of blood IgE (by N-phlometry method), nasal local smear, CT scan and MRI results ([25-27](#)).

### 2.1. Statistical Analysis

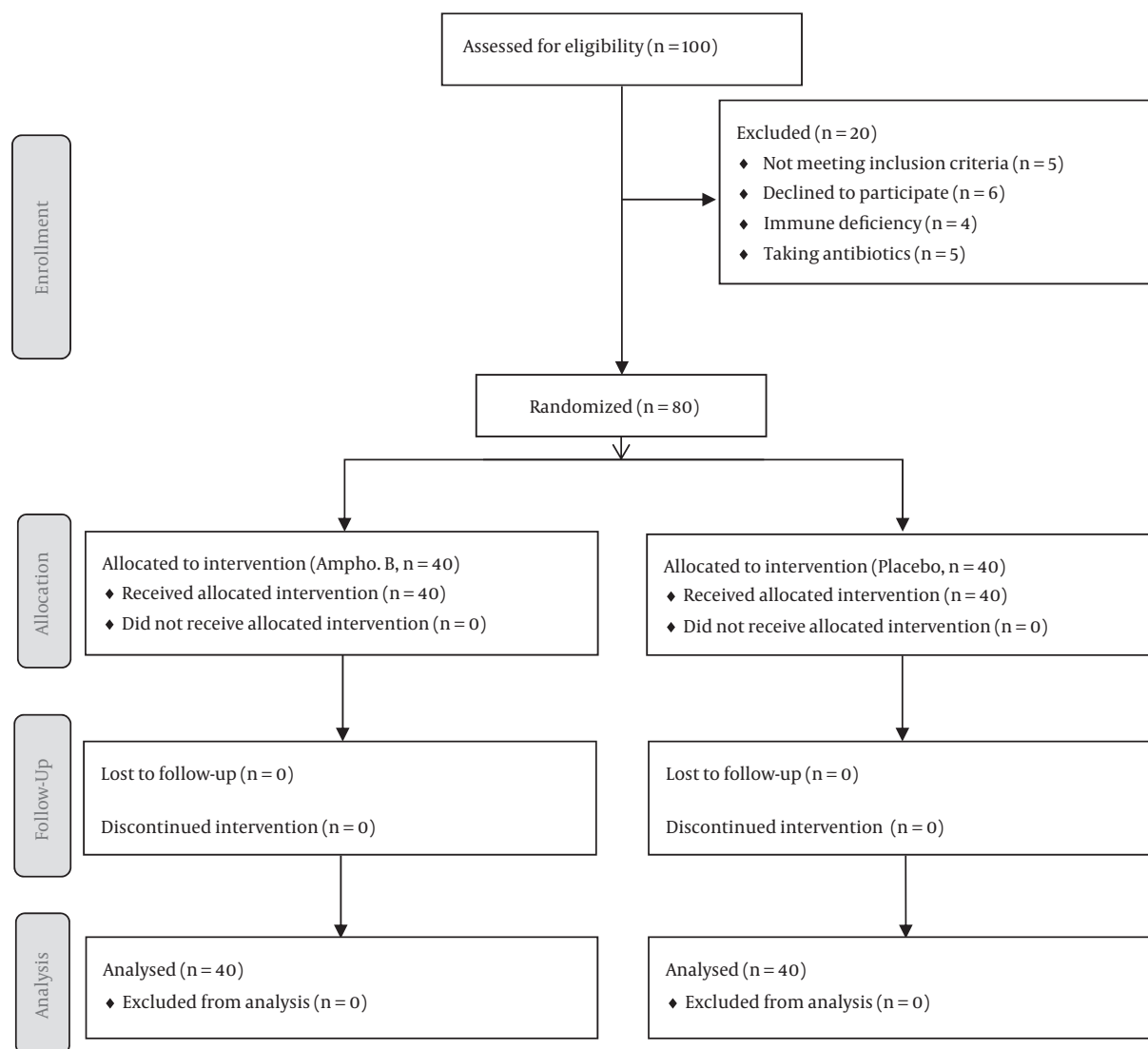
Data were analyzed using SPSS software version 20 (SPSS Inc., Chicago, IL). Normal distributed variables (approved by 1-sample Kolmogorov-Smirnov test) were compared using independent sample t test between the groups and paired sample t test within the groups. The chi-square test was used to compare categorical variables in two groups. A p value of less than 0.05 was considered as statistically significant.

## 3. Results

Eventually, a total of 80 patients in two groups of intervention (26 males and 14 females) and control (29 males and 11 females) underwent analysis. Patients had a mean age of  $26.1 \pm 2.36$  and  $27.9 \pm 1.59$  years in intervention and control groups respectively ( $P = 0.08$ ). There was no significant difference between the two groups in terms of gender distribution ( $P = 0.4$ ).

The patients' characteristics are shown in [Table 1](#). There was no significant difference between the two groups in terms of nasal polyps ( $P = 0.2$ ), mean years of diagnosed rhinosinusitis ( $P = 0.32$ ) and smoking history ( $P = 0.5$ ). A history of asthma and allergy was recorded in 25 (62.5%) patients of intervention and 32 (80%) patients of control groups ( $P = 0.07$ ).

The mean VAS score for nasal obstruction decreased  $0.3 \pm 0.13$  units in Amphotericin and 0.3 units in the control groups in comparison with the baseline amount. Changes in nasal obstruction severity score were not significantly different between intervention and control groups ( $P = 0.671$ ). Mean of post nasal drip (PND) VAS score decreased  $2.27 \pm 0.18$  units in Amphotericin and  $1.78 \pm 0.15$  units



**Figure 1.** Study Flowchart

in control groups in comparison with baseline amount. Changes in post nasal drip severity score were not significantly different between intervention and control groups ( $P = 0.432$ ). The mean VAS score for reduced sense of smell decreased  $0.04 \pm 0.07$  units in both Amphotericin and control groups in comparison with baseline amount. Improvement in sense of smell score was not different between the two groups. Facial pain severity score decreased  $1.08 \pm 0.33$  units in Amphotericin and 1.55 units in control groups in comparison with baseline amount. Changes in facial pain severity score was not significantly different between the two groups ( $P = 0.526$ ). Mean VAS scores of the patients' signs and symptoms, prior to and after interven-

tion, are summarized based on the variables comparison in [Table 2](#) and based on the group comparison in [Table 3](#).

Quality of life score was  $42.9 \pm 9.4$  in Amphotericin and  $40.6 \pm 7.6$  in control groups prior to intervention ( $P = 0.22$ ). After intervention, mean of quality of life score was  $40.97 \pm 8.4$  ( $P = 0.03$ ) in Amphotericin and  $37.85 \pm 7.8$  ( $P = 0.04$ ) in control groups. Changes in quality of life score were not significantly different between the two groups ( $P = 0.854$ ).

CT scan score was  $13.58 \pm 3.39$  in Amphotericin and  $12.90 \pm 4.02$  in control groups prior to intervention ( $P = 0.25$ ). After Intervention, this score was  $12.35 \pm 3.0$  in Amphotericin ( $P = 0.019$ ) and  $11.40 \pm 3.64$  in control groups ( $P = 0.07$ ). No significant difference was seen between

**Table 1.** Patient Characteristic<sup>a</sup>

Variables	Patients	Control	P Value
Age, y	26.1 ± 2.36	27.9 ± 1.59	0.08
Mean of years diagnosed for CRS	4.2 ± 0.88	3.4 ± 1.1	0.32
Gender (F:M)	26:14	29:11	0.4
Nasal polyp	10 (25)	6 (15)	0.2
Smokers	3 (7.5)	2 (5)	0.5
History of asthma and allergy	25 (62.5)	32 (80)	0.07

<sup>a</sup>Values are expressed as mean ± SD or No. (%).

two groups for CT scan score after intervention ( $P = 0.2$ ). Rhinoscopy score was  $5.51 \pm 0.99$  in Amphotericin and  $4.57 \pm 0.78$  in control groups prior to intervention ( $P = 0.41$ ). After intervention, this score was  $4.47 \pm 1.06$  ( $P = 0.033$ ) in intervention and  $4.40 \pm 0.84$  ( $P = 0.1$ ) in control groups. No significant difference was seen between the two groups for rhinoscopy score after intervention ( $P = 0.72$ ).

Serum level of IL-4 was  $52.11 \pm 15.3$  in intervention group prior to and  $47.4 \pm 17.2$  after intervention ( $P = 0.31$ ). IL-5 serum level was  $40.83 \pm 8.6$  prior to and  $37.92 \pm 7.9$  after intervention in this group ( $P = 0.22$ ). IL-13 serum level was  $35.75 \pm 8.1$  prior to and  $31.78 \pm 7.5$  after intervention in Amphotericin group ( $P = 0.08$ ). Also IgE serum level was  $239.41 \pm 16.9$  prior to and  $214.94 \pm 21.4$  after intervention in this group ( $P = 0.43$ ). Mean of Eosinophil count in nasal mucosa was  $9.42 \pm 5.4$  prior to and  $5.31 \pm 2.7$  after intervention ( $P = 0.03$ ).

In the control group, Mean serum level of IL-4, IL-5, IL-13, IgE and nasal mucosa eosinophil count were  $59.2 \pm 18.1$ ,  $32.17 \pm 4.3$ ,  $37.26 \pm 11.7$ ,  $192.7 \pm 20.5$  and  $7.61 \pm 3.3$  respectively prior to intervention. While they were  $54.61 \pm 22.1$ ,  $34.2 \pm 10.3$ ,  $38.53 \pm 12.6$ ,  $181.21 \pm 30.8$  and  $6.37 \pm 1.4$  after intervention. There was no significant difference in laboratory findings before and after treatment in control group ( $P = 0.345$ ).

In Amphotericin group only 5 cases of nasal mucosa irritation were reported in first month of intervention ( $P < 0.01$ ) that were reduced to 3 in third month ( $P = 0.02$ ). The complications were significantly more presented in intervention group in comparison with control group.

#### 4. Discussion

At the moment, there is no definite guideline for treatment of chronic rhinosinusitis (CRS) and patients are usually treated with frequent anti-bacterial regimens. The effectiveness of antifungal regimen has not been yet approved for management of CRS. We found that post nasal

drip and facial pain scores in both groups after intervention had significant reduction particularly in the case group. According to this result, even though topical Amphotericin B drug caused recovery in post nasal drip and facial pain and the recovery rate was higher compared with control group, but with regard to the principle of cost-benefit, this method does not seem adequate.

Ponikau *et al.* evaluating the effect of three-month treatment with topical Amphotericin B on CRS (8 milligrams daily), reported that the symptoms improved in 75% of patients and concluded the safety and effectiveness of topical Amphotericin B which is slightly different from the results of our study. These differences may be attributed to the method of their study (absence of control group), the analysis of data and dosage of the drug (24). Ponikau *et al.* have also assessed the effect of Amphotericin B, 20 milligrams twice a day, for a six-month period in a clinical trial. After intervention, they reported a decreased mucosal thickness in CT scan and an improvement in rhinoscopy score which is not in agreement with our study (20). This may be resulted from lack of any treatments in control group. In a similar study, Liang *et al.* concluded that both endoscopy and quality of life scores were improved after four-week prescription of Amphotericin B. There was also no significant difference between the two groups for rhinoscopy score (25).

Shin *et al.* have conducted a completely similar study to the present one in which the only difference is the length of treatment period. In their study, patients underwent treatment with Amphotericin B or Placebo for 4 weeks. They reported that there was no significant difference for the inflammatory cytokines between the two groups that is in concordance with the present study (26). Comparing the effect of thirteen-week Amphotericin B treatment on serum level of inflammatory markers with placebo, Ebbens *et al.* concluded that this drug has no effect on reducing inflammatory cytokines in patients with CRS that is in agreement with the present study (27).

The result of the study conducted by Weschta *et al.* was also similar to the present study regarding improvement of the symptoms. In this study, patients underwent treatment in two groups of Amphotericin B 4.8 milligrams and normal saline spray for 8 weeks. In accordance with Helbling *et al.* Weschta *et al.* have reported the Amphotericin B to be ineffective for treatment of CRS in the provided dose (28, 29). The symptoms severity and quality of life scores were in concordance with the present study despite differences in the control groups.

Confirming the results of the present study, Ebbens *et al.* concluded that Amphotericin B has no effect on CT scan, rhinoscopy and quality of life scores (21). In their study, patients underwent treatment with nasal Amphotericin B

**Table 2.** Mean VAS Score of Patients' Signs and Symptoms Prior to and After Intervention Based on Variable Comparison<sup>a</sup>

Variables	Groups					
	Before Intervention			After Intervention		
	Patient	Control	P Value	Patient	Control	P Value
Nasal polyp	10 (25)	6 (15)	0.2	7 (17.5)	6 (15)	0.5
	Mean in VAS			Mean in VAS		
	Patients	Control	P Value	Patients	Control	P Value
Nasal congestion	4.3 ± 1.53	3.75 ± 1.4	0.1	4 ± 1.4	3.45 ± 1.41	0.084
Post nasal drip	6.17 ± 1.48	5.70 ± 1.33	0.08	3.90 ± 1.3	3.92 ± 1.18	0.93
Decreased sense of smell	5.41 ± 1.65	5.85 ± 1.68	0.73	5.37 ± 1.58	5.45 ± 1.73	0.84
Facial pain	3.3 ± 0.98	3.65 ± 1.1	0.13	2.22 ± 0.65	2.1 ± 1.3	0.44

<sup>a</sup>Values are expressed as mean ± SD or No. (%).

**Table 3.** Mean VAS Score of Patients' Signs and Symptoms Prior to and After Intervention Based on Group Comparison<sup>a</sup>

Variables	Groups					
	Patients			Control		
	Before Intervention	After Intervention	P Value	Before Intervention	After Intervention	P Value
	No. (%)	No. (%)		No. (%)	No. (%)	
Nasal polyp	10 (25)	7 (17.5)	0.02	6 (15)	6 (15)	1
	Mean in VAS			Mean in VAS		
	Before Treatment	After Treatment	P Value	Before Treatment	After Treatment	P Value
Nasal congestion	4.3 ± 1.53	4 ± 1.4	0.2	3.75 ± 1.4	3.45 ± 1.41	0.04
Post nasal drip	6.17 ± 1.48	3.90 ± 1.3	0.01	5.70 ± 1.33	3.92 ± 1.18	0.5
Decreased sense of smell	5.41 ± 1.65	5.37 ± 1.58	0.13	5.85 ± 1.68	5.45 ± 1.73	0.02
Facial pain	3.3 ± 0.98	2.22 ± 0.65	0.008	3.65 ± 1.1	2.1 ± 1.3	0.04

<sup>a</sup>Values are expressed as mean ± SD or No. (%).

with a dosage of 100 milligrams daily for three months and control group were recipients of distilled water. Evaluating the postoperative effects of nasal Amphotericin B after endoscopic polypectomy, Gerlinger et al. achieved the same conclusions as Ebbens et al. (30).

According to the comparisons of age groups, the majority of patients with chronic rhinosinusitis are in second decade of life. Thus, improvement of quality of life and symptoms as well as patients' satisfaction is of a high importance that we were seeking in the present study by adding Amphotericin B to the treatment guideline of CRS; however, our findings do not support prescription of this drug in agreement with the previous studies.

The present study has some limitations. Relatively low sample size of the trial and difficulties in following up the patients are among the study limitations. However; using a variety of measures such as CT scan, rhinoscopy, VAS score

and quality of life for assessment of patients are among the study strengths.

#### 4.1. Conclusions

We concluded that application of Amphotericin B as an adjunctive medication to other common treatments, does not seem to be an efficient method for improvement of CRS symptoms. Slightly significant improvements after application of Amphotericin B have turned it to a possible option for management of CRS; however, it does not seem to be a beneficial method.

Further studies with a larger amount of patients and also a control group that does not receive any treatments are suggested. Also, evaluating the effect of Amphotericin B in association with other therapeutic methods may produce different results.

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