



Efficacy of Doxycycline in Treatment of Rhinoscleroma

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Abstract:

Background & Objectives: Rhinoscleroma is a chronic granulomatous disease of the nose and upper respiratory passages endemic in Egypt, this study aimed to evaluate the efficacy of Doxycycline (alone and in combination with Ciprofloxacin) as an alternative to the regular regimen in treating rhinoscleroma.

Patients and methods: A prospective randomized comparative clinical trial included 42 Rhinoscleroma cases, 21 cases treated with Doxycycline and 21 cases treated with a combination of Doxycycline and Ciprofloxacin. This study was conducted in Otorhinolaryngology department at Assiut University Hospital from October 2021 to October 2023. The collected data included: Age, sex and residence, pretreatment clinical symptoms/signs, posttreatment clinical symptoms/signs, posttreatment biopsy results for rhinoscleroma and follow up biopsy results for rhinoscleroma 3 months after successful treatment in the studied groups.

Results; For treatment of rhinoscleroma, it was found that doxycycline has a relatively low efficacy both clinically and histopathologically (with 28.6% remission rate) when used alone but this efficacy is significantly increased on combining the drug with ciprofloxacin (showing 57.1% remission rate).

Conclusions: The combination of doxycycline and ciprofloxacin offers a promising alternative to regular regimens used in treatment of rhinoscleroma with a shorter course, and fewer controllable side effects.

Keywords: Rhinoscleroma, Doxycycline, Ciprofloxacin, Combination, Histopathological.

Introduction

Rhinoscleroma is a chronic granulomatous disease endemic in many eastern countries, including Egypt, and also in Eastern Europe, North Africa, and parts of Central America. It exhibits an affinity for the upper respiratory tract mucosa, most commonly the nose, but it can involve the nasopharynx, oropharynx, and can also be seen in the larynx, trachea, and tracheobronchial tree. The condition was first described in 1870 by Von Hebra and was histologically described with its foam

cells by Mikulicz in 1876. Its causative agent is a gram-negative bacillus, *Klebsiella Rhinoscleromatis*.¹

Rhinoscleroma predominantly affects young adults but can occur at any age and has been seen equally in both sexes with no racial difference. Low socioeconomic populations are the most affected.²

There are four known stages of the lesion. The first of which is the 'Catarrhal stage' presented with purulent rhinorrhea and usually missed until

proceeding to the 'Atrophic stage' with a picture similar to that of non specific atrophic rhinitis, the next is the 'Hypertrophic' or 'Granulomatous' stage where there are bluish-red rubbery nodules in any part along the distribution of the disease, and eventually the 'Fibrotic' or 'Sclerotic' stage with stenosis, deformity, and loss of function of the affected parts, it is to be noted that more than one stage can exist in the same patient.²

The diagnosis after clinical suspicion is confirmed by biopsy taken for histopathological examination and for culture on blood or MacConkey agar.³

Histologically, there is an accumulation of plasma cells, lymphocytes, eosinophils, and scattered among these are the well-known Mikulicz or foam cells and Russell bodies.¹

The transmission of the disease from person to person is still not entirely clear, but it mostly occurs through airborne secretions and infected discharge, and requires close contact with a case of rhinoscleroma over a prolonged period to be transmitted.⁴

Treatment includes a prolonged course of antibiotics along with surgery in some cases to achieve a definite cure and avoid relapses.⁵

Examples of commonly used drugs include 'Rifampicin', 'Trimethoprim-Sulfamethoxazole', 'Streptomycin' and 'Tetracycline'.^{3,6}

Doxycycline is a commonly used second generation Tetracycline, as it has the advantage of easier dosing and better patient compliance with a shorter course (6 weeks), currently, the use of 'Doxycycline' and 'ciprofloxacin' in combination is recommended by many authors.⁷

The aim of the current study is to evaluate the efficacy of Doxycycline (alone and in combination with Ciprofloxacin) as an alternative to the

regular regimen used in the treatment of rhinoscleroma.

Patient and methods:

Study design: A prospective randomized comparative study conducted on forty two patients diagnosed with rhinoscleroma, scheduled for treatment and divided into two groups with twenty one cases each, (Group A cases were treated with doxycycline 100mg tab once daily for 8 weeks and Group B cases were treated with both doxycycline 100mg tab once daily and ciprofloxacin 250mg tab twice daily for 8 weeks).

Study site: Assuit University Hospitals (AUHs) main hospital, at Otorhinolaryngology department. This study was conducted in the period from October 2021 to October 2023.

Study participants: The study included adult patients with confirmed diagnosis of rhinoscleroma presented to Otorhinolaryngology outpatient clinic, Assuit University Hospitals.

Inclusion criteria:

- 1 Acceptance of the patients to participate in a research process.
- 2 Patients were included after confirmation by histopathological examination.
- 3 Patients presented in active stages of the disease.
- 4 Patients` age > 18 years.

Exclusion criteria:

- 1 Any granulomatous lesion or features suggestive of rhinoscleroma associated with any other nasal lesions like syphilis, leprosy and tuberculosis were excluded.
- 2 Patients <18 years and >70 years.
- 3 Biopsy-negative cases.
- 4 Inactive disease.
- 5 Contraindication to the treatment or known hypersensitivity to the drugs used.

6Refusal of enrollment in a research process by the patient.

Data collection: The data was collected by clinical assessment of patients at the Otorhinolaryngology Outpatient Clinic and reassessment was done after completion of treatment. A structured questionnaire was designed and filled in by personal interview with the patients in addition to biopsy results pre and post-treatment from the pathology lab at Assiut University Hospital.

The collected data included: Socio-demographic data (Name, Age, Sex and Residence), clinical data; including clinical manifestation as nasal obstruction, crustations, offensive nasal discharge, anosmia/hyposmia, epistaxis, dysphonia and difficulty of breathing and histopathology biopsy results. Clinical evaluation was aided by Karl storz (Germany) endoscopes grade 0 for nasal examination and grade 70 for laryngeal examination.

Assessment of therapeutic effect in the studied patients was done by comparatively evaluating the clinical manifestations of the disease pre and post treatment in both groups and by histopathology biopsy results after completion of treatment and three months later after successful treatment.

Statistical analysis:

All statistical calculations was done using SPSS (statistical package for the social science; SPSS Inc., Chicago, IL, USA) version 26. Data were statistically described in terms of mean \pm standard deviation (\pm SD), or median and range when not normally distributed, frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables was done using Mann Whitney U test as the data was not normally

distributed. For comparing categorical data, Chi square (χ^2) was used or Fisher Exact test instead of Chi square (χ^2) when the expected frequency was less than 5. Correlation between various variables was done using Pearson correlation test. P-value is always 2 tailed set significant at 0.05 levels.

Ethical Considerations:

The study was consistent with the declaration of Helsinki for medical research.

Results

Patients' demographics:

In our study the age range was from 18 to 60 with mean age was (33.93 \pm 12.96), also the disease was more common in females 27 (64.3%) than males 15(35.7%),as for residence 21.4% were urban residents, while 78.5% were rural residents.

A total of 10 patients (23.8 %) in both groups recalled having a positive family history of similar conditions.

Results of clinical evaluation:

Regarding nasal obstruction (illustrated in chart 1), when the two groups of treatment were compared together, there was a statistically significant difference between them showing better results in group B compared to group A (p-value 0.043), as in Group A none of the 14 cases with nasal obstruction showed improvement after treatment, while in Group B, there was statistically significant difference pre and post treatment, 7 of the 15 patients with nasal obstruction in this group improved with (P value 0.018).

Also on comparing patients with nasal crustations in both groups there was a statistically significant difference between the two groups showing better results in group B compared to group A (p value was 0.037), this data is well illustrated in the following chart (2) showing that in Group A 6 out of 17

cases with nasal crustations improved after the treatment compared to 6 out of 15 patients in Group B showing improvement which was a statistically significant difference pre and post treatment in group B only (P value was 0.043).

The following chart (3) illustrates results from both groups for cases presented with offensive nasal discharge, on comparing these results between the two groups, there was a statistically significant difference between the two treatment modalities with better results seen in group B which showed improvement of 8 cases from a total of 11 cases compared to group A with only 3 cases improved out of 12 cases with offensive nasal discharge, (p value 0.04).

Results on studying olfactory changes (hyposmia and anosmia) showed no statistically significant difference between the two groups (p value 0.293), as all of the 3 cases (1 case in group A and 2 cases in group B) presented with hyposmia or anosmia showed no improvement after the treatment.

The same applies for cases with nasal deformity, all of the 4 cases (3 cases in group A and 1 case in group B) were not improved after treatment and so, when the two groups of treatment were compared, there was no statistically significant difference between them (p value 1.000).

On comparing cases with dysphonia in both groups, there was no statistically significant difference between the groups (p value 1.000), 2 of the 3 cases in Group A and 5 of the 6 cases in group B improved after treatment, however, both weren't statistically significant.

A total of 5 cases presented with epistaxis in both groups (11.9%), with 1 case in group A and 4 cases in group B, all cases in both groups showed improvement post-treatment, but none of this was statistically significant.

Also, all of the 3 cases with difficulty of breathing in group B were improved after the treatment, while the single case in Group A was not improved.

Post-treatment biopsy results

Chart (4) show biopsy results after treatment in both groups, there was a higher percentage of negative samples for rhinoscleroma (better results) in Group B compared to Group A however it wasn't statistically significant. In Group A, there was 6 of the 21 cases in the study with negative biopsy result after treatment (28.6%) and the other 15 samples remained positive (71.4%), in Group B the number of patients with negative biopsy samples was 12 (57.1%) compared to only 9 positive samples (42.9%) with a total number of 18 negative samples in both groups (42.9%) (P value 0.061).

After the follow up biopsy 3 months later for the biopsy negative cases, we found that in Group A the number of cases that remained negative for rhinoscleroma was five cases (83.3%) and only one case showed recurrence and turned positive (16.7%), in Group B the number of cases that remained negative was 8 cases (66.7%) and the other four cases showed recurrence and turned positive (33.3%), however, this association wasn't significant (P value 0.457).

Chart (1): Effect of both regimens on nasal obstructions

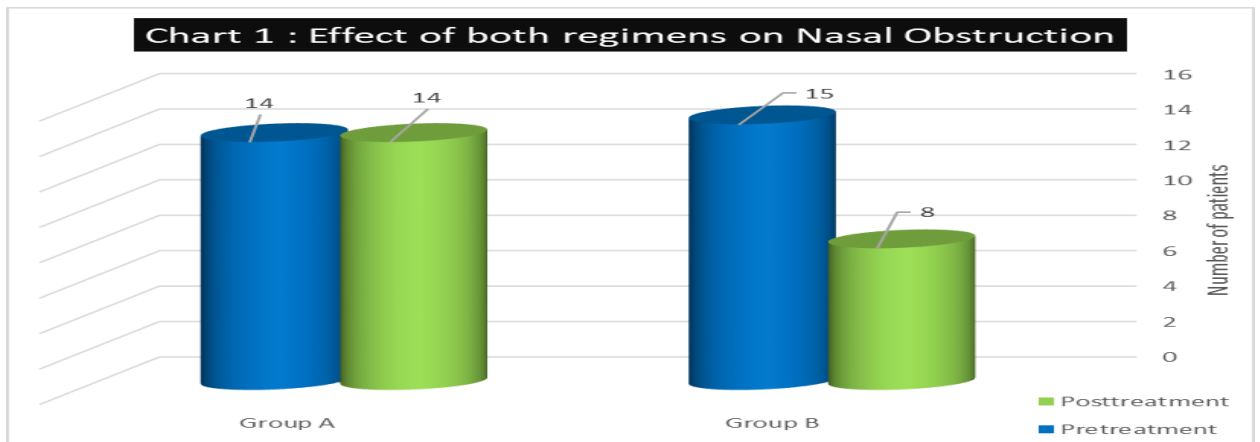


Chart (2): Effect of both regimens on nasal crustations

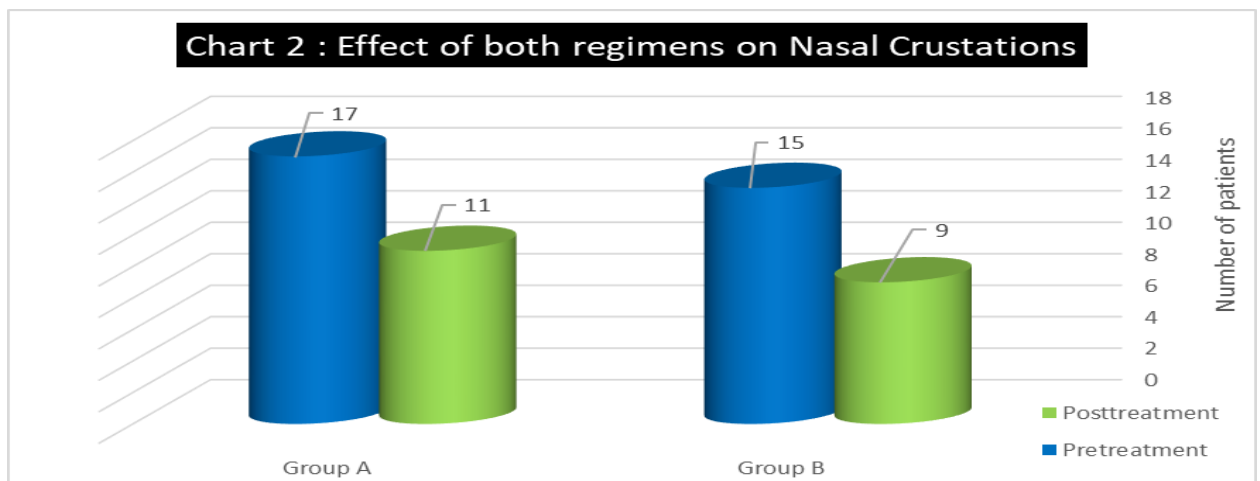


Chart (3): Effect of both regimens on offensive nasal discharge

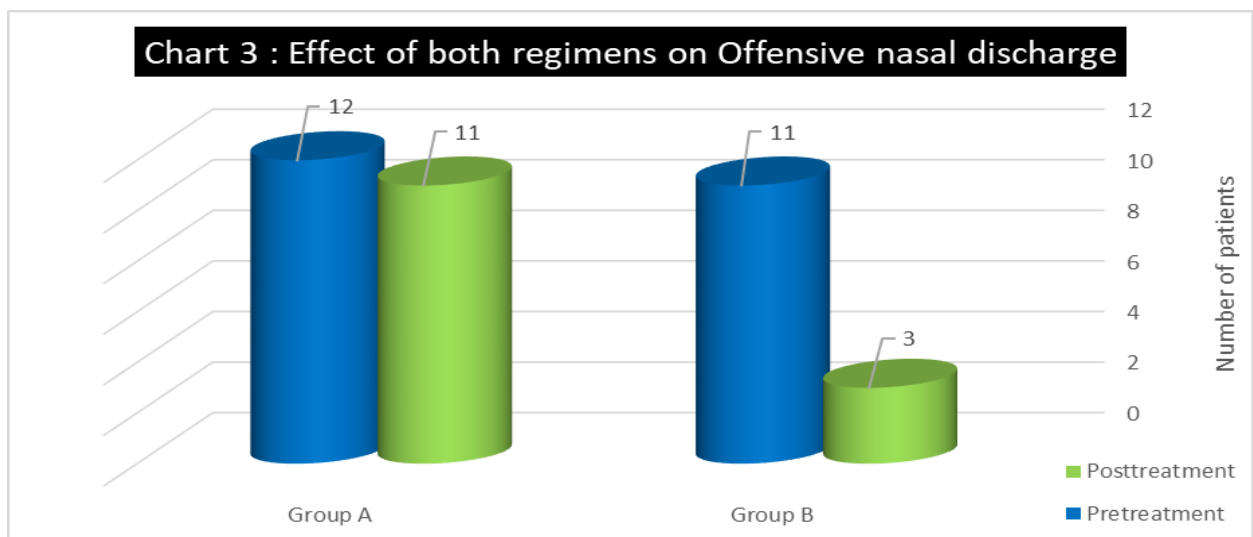
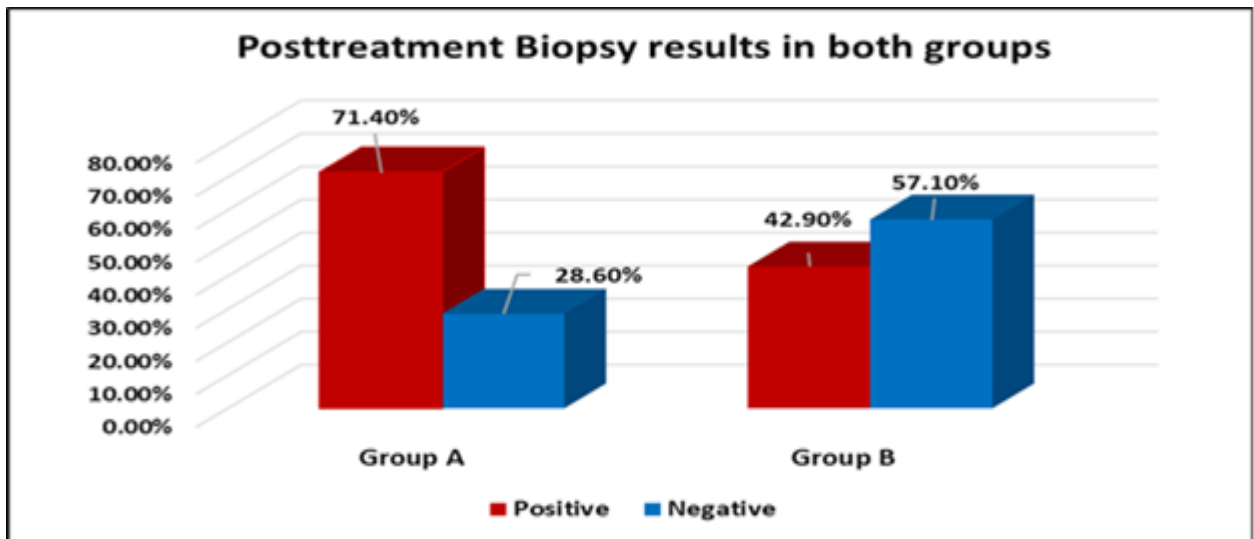


Chart (4): Post-treatment biopsy results in both groups



Discussion:

Rhinoscleroma is a chronic granulomatous infectious disease that affects the nose and other parts of the respiratory tract. It is caused by the Gram negative bacterium *Klebsiella pneumoniae* subsp. *Rhinoscleromatis*.⁸

Diagnosis is mainly histopathologic and depends on the identification of the pathognomonic Mickulicz cells (MCs) which are prominent during the granulomatous phase but scanty or absent during catarrhal or sclerotic phases of the disease⁸, any delay in the diagnosis can lead to complications such as physical deformity, upper airway obstruction, and sepsis.⁵

Treatment includes a prolonged course of antibiotics along with surgery in some cases to achieve a definite cure and avoid relapses.⁵ Various antibiotics are found to be effective in the treatment of rhinoscleroma.⁹ Ciprofloxacin was proved to be one of the most effective due to their increased penetrance⁸, doxycycline on the other hand, has shorter response time and has the advantage of easy dosing and hence, better compliance, many authors

recommend the use of both doxycycline and ciprofloxacin in combination for better results.⁷

Discussion of the clinical data

According to **Quevedo, 1949**¹⁰ rhinoscleroma has a specific locality in each region in which the disease is endemic that appears to be the nucleus of that region where most of the cases are found, in our study most of the cases were from rural areas (78.5%), however none of these areas was found to be a specific nucleus of the disease.

A wide age range has been observed with the disease and the mean age in the present study was (33.93 ± 12.96) , this can be explained by the chronic prolonged nature of the disease with the relative long latent period.

Similar wide age range was observed by **Ahmed et al. 2015**¹¹, who studied patients with age range from 12 to 72 years and a median value of 35 years, **Gaafar et al. 2011**¹² also stated that age range in their study was 13 to 73 and the highest incidence was in the third and fourth decades of life (85%), on the other hand, **Schwartz and Goriniene, 2008**¹³ had a narrower range with patients' age between 10 to

30 years, this may be due to early diagnosis and management of the disease aided by the availability of efficient health facilities for the patients in their study.

The disease showed a slightly higher incidence in females than males in our study as 27 of the included cases were females (64.3% of the cases) compared to 15 males (25.7%), similar female predominance is found with many others as **Fattah et al. 2011**¹⁴ who studied 28 females (58.3%) and 20 males (41.7%) and **Mukara et al. 2014**¹⁵ with a female percentage of 56.5% of their studied cases, on the contrary, higher male incidence was seen with **Shaw & Martin, 1961**¹⁶ who had a male predominance up to 80% of cases in their study and **de Pontual, et al. 2008**¹⁷ with 54.5% males, **Massoud and Awad, 1959**¹⁸, however, found equal incidence in both sexes, so this disparity in male/female predominance can be attributed to the presence of many other predisposing factors such as iron deficiency and immunologic/genetic factors which affect the susceptibility to the disease but generally, the condition seems to affect both sexes equally.

In 10 out of 52 patients in our study there was a positive family history of the disease, this is seen almost always with rhinoscleroma as with **de Pontual et al. 2008**¹⁷ who had nearly the same number of cases with family history as in our study (11 cases), also in an American study¹⁹, 7 cases were found in one family, this is due to the prolonged close contact between family members which is an important factor in the transmission of the disease.²⁰

Patients of rhinoscleroma can present with different signs/symptoms, nasal crustations was the most common pretreatment symptom appearing in 76.2% of patients in our study, this didn't match with the study conducted

by **Fawaz et al. 2011**²¹, where only 46% of cases presented with this symptom, while 100% of cases in their study presented with nasal obstruction which is the 2nd most common symptom in our study which was found in 69% of cases.

Effects of the two antibiotic therapy regimens

In our study both treatment regimens showed improvement in a number of cases with better results seen in patients treated with the combination of doxycycline and ciprofloxacin showing more remission rates (in 57% of cases) as proved by post treatment negative biopsy results for *Klebsiella Rhinoscleromatis* compared to 28.6% of patients treated by doxycycline alone, however, in a study by **Kallapa et al. 2017**¹ comparing doxycycline with ciprofloxacin in patients with active rhinoscleroma showed significant remission rates achieved with both ciprofloxacin alone (80% of cases) and doxycycline alone (53.3% of cases) after 8 weeks of treatment, although the study didn't evaluate the efficacy of both drugs being used in combination, it showed better results with the use of doxycycline alone than those obtained in our study given the same regimen and duration, this can be explained by many factors such as the difference in quality of the used drugs, the difference in the stage at which the patients are presented and started treatment and the difference in bacterial resistance to the used drugs, in addition, the site from which the nasal biopsy is taken and its extent may affect the result.

On the clinical aspect we found that patients treated with the combination of both doxycycline and ciprofloxacin had significant improvement compared to patients treated with doxycycline alone where the treatment had no effect on the nasal obstruction after the follow up. We also found that both groups showed

improvement of nasal Crustations and offensive nasal discharge with more significant improvement seen in patients treated with the combination.

Many authors mentioned that various antibiotics like doxycycline, tetracyclines, rifampicin, second and third generation cephalosporins, sulfonamides, clofazamine, ciprofloxacin and ofloxacin are found to be effective in the treatment of rhinoscleroma ⁹, additionally a case report on the efficacy of Doxycycline Monotherapy in Treating Rhinoscleroma by **Jage et al. 2018** ⁷ provided evidence of the drug efficacy in treating the condition, the case showed significant response after only 6 weeks of treatment with doxycycline in terms of clinical symptoms including nasal obstruction.

However, some other researches discussed the limitations and challenges of using antibiotics for treating nasal obstruction in rhinoscleroma, in a case series that discusses the challenges of treating rhinoscleroma with antibiotics by **Nayak & Shenoy, 2021** ²², they emphasize that treatment is challenging and requires a prolonged course of antibiotics to achieve a definite cure and avoid relapses, also, it was mentioned that although most patients benefit from prolonged medical treatment, surgery is warranted in cases of obstruction of the upper airway and significant nasal deformities causing nasal obstruction, this suggests that antibiotics alone may not always be sufficient to treat nasal obstruction in rhinoscleroma ⁹, which explains why the drug didn't show significant improvement of this symptom in our study.

Results of the present study have also shown that doxycycline had no effect on the olfactory changes, nasal deformity and difficulty of breathing both alone and in combination with Ciprofloxacin. While antibiotics can help manage the

infection, they may not directly improve nasal deformity or olfactory changes. ²² Other treatments, as surgery to correct deformity or to urgently manage airway obstruction and specific therapies for olfactory dysfunction, may be necessary depending on the individual case.

In the previously mentioned case series²² on rhinoscleroma reported that despite appropriate antibiotic therapy, complications can include persistent inflammation leading to physical deformity which didn't improve with medical treatment and surgery is required, also some cases with subglottic stenosis may require bronchoscopic removal of the obstructing lesions or even urgent tracheostomy to relieve severe airway obstruction ²², another research article by **Badia & Lund, 2001** ³ mentioned that rhinoscleroma is treated with long-term antibiotics and surgery in patients with symptoms of respiratory tract obstruction.

All patients presented with epistaxis and most of cases presented dysphonia showed improvement of these symptoms with doxycycline treatment alone and in combination but the total number of patients with both symptoms (5 patients with epistaxis and 9 with dysphonia) wasn't statistically significant to prove any relation to treatment.

Conclusion:

- 1 Dual therapy effectiveness: The use of both doxycycline and ciprofloxacin showed significant improvement and higher remission rates compared to doxycycline alone in terms of clinical symptoms and signs and also help overcoming bacterial resistance so improve eradication of the organism.
- 2 Symptoms not directly treated by antibiotics: such as

hyposmia/anosmia, deformity and difficulty of breathing which are often a result of the structural changes caused by the granulomas of rhinoscleroma, in such cases, additional treatments such as surgery may be required.

- 3 It is important to follow up patients after completion of treatment for early detection of relapses and prompt management accordingly

Study Strengths:

- 1 Randomized comparative study: The study design is a prospective randomized comparative study, which is a strong experimental design that can help establish causality.
- 2 Histopathological confirmation: The diagnosis of rhinoscleroma is confirmed histopathologically, which is an objective method that increases the reliability of the diagnosis and follow up of patients.
- 3 Follow-up biopsies: The study includes follow-up biopsies after treatment and 3 months later, which can help monitor the progress of the disease and the effectiveness of the treatment over time.
- 4 Use of established drugs: The study uses established drugs (doxycycline and ciprofloxacin) for treatment, which means the safety profile and side effects of these drugs are well-known.

Study Limitations:

- 1 The sample size is relatively small (42 patients), which may limit the statistical power of the study and the ability to detect significant differences between groups.
- 2 Lack of control group: The study does not appear to have a control group that received no treatment or a placebo, which could make it

harder to comparatively determine effectiveness of the treatments.

- 3 Follow-up duration: The follow-up duration after treatment is relatively short (3 months). This may not be sufficient to assess long-term outcomes and potential side effects of the treatments.

Recommendations and future work:

For health care system:

- 1 Consider dual therapy: For treating rhinoscleroma, consider using a combination of doxycycline and ciprofloxacin due to its demonstrated effectiveness in improving symptoms and achieving high remission rates.
- 2 Evaluate the importance of surgical intervention in symptoms due to granulomatous lesions untreated with medical treatment.
- 3 Explore additional treatments for olfactory changes aimed at the cause (atrophy of the olfactory mucosa).
- 4 Consider increasing the treatment duration in cases showing signs of incomplete improvement to insure good eradication of the organism.

For future research:

Future studies should be directed towards the evaluation of predisposing factors for rhinoscleroma infection and their relation to the response to the treatment.

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Conflicts of interest: No

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