EFFECTIVENESS OF CIPROFLOXACIN VS DOXYCYCLINE IN TREATMENT OF RHINOSCLEROMA- A CASE-CONTROL STUDY

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ABSTRACT

BACKGROUND

Rhinoscleroma is a chronic inflammatory condition in which deforming masses of tissue distend the nasal cavity. Klebsiella rhinoscleromatis is the causative agent. Antibiotic therapy traditionally consisted of streptomycin and tetracycline. But long-term therapy results in adverse side effects and poor patient compliance, hence this study to search alternative agents.

MATERIALS AND METHODS

This is a prospective study of 60 cases of rhinoscleroma visiting to the Department of ENT, KIMS, for a period of two years.

RESULTS

After 8 weeks treatment in the atrophic and granulomatous group, 6 (60%) became histopathologically negative and 4 (40%) remained histopathologically positive. The treatment was continued for another 4 weeks in positive cases and at the end of 12 weeks, 8 (80%) turned histopathologically negative, 2 (20%) remained positive.

CONCLUSION

We conclude that ciprofloxacin is a very good alternative drug compared to doxycycline in the treatment of rhinoscleroma particularly in the early stages of the disease and complete cure can be achieved by early diagnosis and treatment.

KEYWORDS

Rhinoscleroma Therapy, Ciprofloxacin, Doxycycline.

HOW TO CITE THIS ARTICLE: Kallapa S, Sarkar SR, Shankar MG. Effectiveness of ciprofloxacin vs. doxycycline in treatment of rhinoscleroma- A case-control study. J. Evid. Based Med. Healthc. 2017; 4(20), 1165-1168. DOI: 10.18410/jebmh/2017/229

BACKGROUND

Rhinoscleroma is a chronic granulomatous disease, which affects nose, but may extend into nasopharynx, oropharynx and occasionally involves larynx, trachea and tracheobronchial tree. Isolated skip lesions without affecting the nose has been reported. It was first described by Von Hebra in 1870 and was established as an inflammatory process in 1876 by Mikulicz. The causative agent, gram-negative bacillus, Klebsiella rhinoscleromatis was isolated by Von Frisch in 1882.[1,2]

Rhinoscleroma occurs at any age, predominantly affecting young adults and in both sexes. It is endemic in Eastern Europe including parts of Hungary, Poland, North Africa, Pakistan and Indonesia, India and parts of Central America. The people of any race may affect.

It affects most commonly people with poor standard of living. The disease has endemic belts in some parts of the country. Oomen found scleroma in some 20 of the inhabitants of an Indonesian village with a population of about 1,000. Most patients were relatives and he regarded a household relationship as the decisive aetiological factor. This suggests that the disease results from exposure to a common source of infection among the affected members. Although, it does not imply that infection is necessarily conveyed from person to person by contact. In spite of occurrence in the members of same family, the disease is not inherited and also not proved to be contagious always.

The concept of a bacterial aetiology for scleroma of nose is now documented and well accepted. It is caused by the 'Klebsiella rhinoscleromatis' also known as Frisch bacillus. The evidence testifying the aetiological role of Klebsiella-rhinoscleromatis exists. This includes the regular presence of this microorganism in the tissue affected, electron microscopic studies, immunofluorescence antibody studies and immune-peroxidase technique. On the other hand, scanning electron microscopic studies have revealed the presence of spores and hyphae of fungi in association with Klebsiella rhinoscleromatis on the nasal mucous membrane.

The pathology of this disease consists mainly of submucosal infiltration in the affected part. Histologically, there is an accumulation of plasma cells, lymphocytes, eosinophils and scattered amongst these are presence of Mikulicz or foam cells and Russell bodies. The Mikulicz

Financial or Other, Competing Interest: None.
Submission 21-02-2017, Peer Review 24-02-2017,
Acceptance 02-03-2017, Published 09-03-2017.
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DOI: 10.18410/jebmh/2017/229

cells have a central nucleus and largely vacuolated cytoplasm and most of the time contain 'Frisch bacillus' in them. Russell bodies, which resemble plasma cells have an eccentric nucleus and abundant cytoplasm staining with Eosin.

The clinical picture depends upon the stage, site and the extent of lesion. The first stage is known as 'catarrhal stage' and it resembles atrophic rhinitis. In the next stage, there are appearance of bluish red rubbery nodules in the anterior part of the soft tissue of nose including nasal septum and may extend posteriorly into the nasopharynx and oropharynx. The next stage is fibrosis in the lesion known as cicatrisation stage resulting in stenosis deformity with loss of functions of the parts affected. The general condition of the patient does not seem to be much affected. Another important or significant aspect of this disease is that more than one stage of the disease may be seen in the same patient.

The diagnosis depends upon the careful clinical examination and isolation of Klebsiella rhinoscleromatis from the secretion or tissue and histopathological examination of suspected lesions. Too often, the disease is first diagnosed at advanced stage with poor prognosis and difficulty in eradicating the disease, so the early diagnosis is of utmost importance to give curative treatment.

Treatment of scleroma has been tried for decades using various antibiotics and chemotherapeutic agents without much success. Only a few of these drugs have been proved to be effective to a limited degree. Different types of presentation and modalities of treatment are being reported quite often in the literature.

Ciprofloxacin is one such drug, which attains good tissue levels and can be used in the treatment of rhinoscleroma. Two features of rhinoscleroma might appear to support the use of ciprofloxacin. First, since the disease is generally limited to the tissues of the upper respiratory tract, clinical efficacy maybe dependent on the antibiotic levels that can be achieved in nasal secretions. Ciprofloxacin, a fluoroquinolone, has the ability to concentrate in these secretory fluids and eradicate susceptible pathogens in the nasopharynx. Second, histologic examination of the tissues involved in rhinoscleroma characteristically shows large numbers of bacteria within Mikulicz cells. This intracellular localisation may help to explain the need for prolonged courses of antibiotic treatment. The well-recognised ability of ciprofloxacin to concentrate and kill organisms within macrophages may offer a special advantage in the treatment of rhinoscleroma. There has been no previous detailed study using ciprofloxacin as therapeutic agent and hence we conducted the above study.

AIM

To study the effectiveness of ciprofloxacin in the treatment of rhinoscleroma.

MATERIALS AND METHODS

It is a prospective study of 60 cases of rhinoscleroma attending to the Department of ENT, KIMS, for a period of two years. The cases were followed up for a period of 15 years.

Inclusion Criteria

1. Patients were included after confirmation by histopathological examination.
2. Patients presented in any stage of disease were included.
3. Patients were between 15-70 yrs.
4. Patients with any isolate from upper airway and digestive tract.

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 below 15 years and above 70 years.
3. Biopsy-negative cases.

A detailed history including presenting complaints, past family, personal and social history was taken, followed by detailed ENT examination, routine blood investigation, histopathological examination, bacterial culture.

Patients were divided into 2 groups of 30 each. In the control group, patients were given cap.doxycycline 100 mg once a day (OD) for 8 weeks only. In the study group, patients were given ciprofloxacin 250mg (up to 50 mg/kg body wt.) twice a day (BD) for period of 4 weeks only. The patients were followed up at weekly interval throughout the treatment period noticing the therapeutic effects and side effects if any.

The cases were followed up for 6 months interval for first two years and then yearly for next 8 years.

The results of treatment were graded into 3 groups- Good, satisfactory and poor depending on symptom relief of patient and clinical findings.

Statistical Analysis Used- Chi-square test.

RESULTS

Number of Patients	Stage	Good	Satisfactory	Poor
8	Atrophic and granulomatous	6	2	-
18	Granulomatous	14	4	-
4	Cicatricial	-	-	4

Table 1. Showing Clinical Response of Patients Treated with Ciprofloxacin

In the study group of 30 patients treated with ciprofloxacin 250mg (10 cases) or 500mg BD (20cases) showed the following results-

1. Atrophic and granulomatous stage-6 of 8 patients (75%) response was good and in 2(25%) response was satisfactory.
2. Granulomatous stage- 14 of 18 patients (77%) response was good and in 4 (33%) response was satisfactory.
3. Cicatricial stage -Both patients had poor response.

Out of 30 patients in the study group, 8 were atrophic and granulomatous, 18 granulomatous and 4 cicatricial. After 4 weeks treatment in the atrophic and granulomatous group 6(75%) became histopathologically negative and 2(25%) histopathologically positive for whom the treatment was continued for another 4 weeks following which he became histopathologically negative. At the end of 8 weeks, all patients in this subgroup were histopathologically negative.

9 patients in granulomatous stage- 4(33%) were histopathologically positive and 14(77.7%) were histopathologically negative at 4 weeks; for the 2 patients, treatment was continued for another 4 weeks; at 8 weeks, 2 were histopathologically negative, 1 was histopathologically positive. Therefore, at 8 weeks, 16 of 18 (88.88%) were histopathologically negative and 2(11.22%) histopathologically positive.

4 cicatricial patients who were histopathologically positive even after 8 weeks of treatment. They were treated surgically by canalisation and oral ciprofloxacin 500 mg twice a day for 4 weeks. No recurrence was noticed in the follow up period.

Number of Patients	Stage	Good	Satisfactory	Poor
10	Atrophic and Granulomatous	2	6	2
16	Granulomatous	8	4	4
4	Cicatricial	-	-	4

Table 2. Showing Clinical Response of Patients Treated with Doxycycline (Control) for 8 Weeks

In the control group, 30 patients treated with doxycycline 100mg O.D. for 8 weeks, following was the pattern of response.

1. Atrophic and granulomatous stage-2 of 10 patients (20%) response was good, 6(60%) response was satisfactory and 2(20%) response was poor.
2. Granulomatous stage- 8 of 16 patients (50%) response was good, in 4(25%) response was satisfactory and in 4(25%) the response was poor.
3. Cicatricial stage -Both patients had poor response.

Out of the 30 patients in study group, 10 were atrophic and granulomatous, 16 granulomatous, 4 cicatricial. After 8 weeks treatment in the atrophic and granulomatous group, 6(60%) became histopathologically negative and 4(40%) remained histopathologically positive. The treatment was continued for another 4 weeks in positive cases and at the end of 12 weeks, 8(80%) turned histopathologically negative, 2(20%) remained positive.

Out of 16 patients in granulomatous stage- 6(37.5%) were histopathologically positive and 10(62.5%) were histopathologically negative at 8 weeks. Positive cases received treatment for another 4 weeks and at the end of 12 weeks, 12(75%) were histopathologically negative, 4(25%) were found positive.

4 cicatricial patients who were histopathologically positive even after 12 weeks treatment were subjected to surgical canalisation and medical treatment. No recurrence was noticed in the follow up period.

DISCUSSION

Rhinoscleroma is a chronic inflammatory condition caused by gram-negative bacilli and Klebsiella rhinoscleromatis. Clinically, rhinoscleroma begins with rhinorrhea, crusting and nasal obstruction. It differentiated from atrophic rhinitis by the presence of granulomatous nodules on the nasal septum, inferior turbinate and floor of the nasal vestibule. These nodules coalesce resulting in blocked airways.

Most cases of rhinoscleroma can be accurately diagnosed on the basis of history and clinical examination. It is endemic in Hubli-Dharwad district of Karnataka, India. Complete cure can be achieved by early diagnosis and treatment.

MayoClinic (1993) mentioned in a review of patient with rhinoscleroma that fluoroquinolones to treat as potentially deserves further study.

Johannes Borgstein et al suggested short course of ciprofloxacin is very effective in treatment of rhinoscleroma and ozena.[3]

Robin K Avery et al reported a patient with extensive nasal rhinoscleroma who achieved pathological and bacteriological resolution with oral ciprofloxacin treatment and the patient previous courses of tetracycline and trimethoprim-sulfamethoxasole.[4]

Lydia Badia et al in a case report on a young patient with nasal rhinoscleroma who achieved resolution after treatment withoral ciprofloxacin.[5]

In our study, we found that both ciprofloxacin and doxycycline were effective in the early stages of disease. However, poor response was noted for both in critical stage.

Ciprofloxacin is a convenient drug for oral administration has fewer side effects. It achieves good tissue penetration and concentrates in macrophages. Adverse effects are comparatively few and include GIT symptoms in 3%-6% of patients and uncommon central nervous system symptoms and allergic symptoms. Ciprofloxacin has the advantage of twice daily administration. Ciprofloxacin appears to be a better drug compared to doxycycline. Nasal lesions were quicker to respond, while scleroma of larynx and other sites were relatively resistant. No single antibiotic can be declared as highly effective in treating all cases of rhinoscleroma.

Hara et al and New et al reported first case of rhinoscleroma successfully treated with streptomycin. Since then, it has been employed by many workers including Quevedo Kalkar et al and propose repeated audiogram and caloric test during the treatment.

Negesh et al suggested streptomycin and chloramphenicol to be the best weapon against scleroma.

E.L. Mofty (1962) and Klassen (1965) performed in vitro sensitivity tests and postulated that chlortetracycline was the best antibiotic in their experience.[4]

According to Acuna R.T. (1973) streptomycin alone is less effective when larynx and bronchi are involved and he advised combination of antibiotics therapy in extensive involvement of the lesion.[6]

Lawrense A. Cone (1987) used Ceforanide 120 g for 2 months and results were encouraging.[7]

Banerjee (1989) used rifampicin because of its known strong bactericidal action against resistance acid fast organism like tuberculosis and leprosy.

Cost Effectiveness

Drugs	Cost of the Tab. (Rs.) (Economical Brand)	Dose	Duration of the Treatment	Total Cost of the Treatment
Doxycycline	3	OD	8 weeks	180
Ciprofloxacin	5	BD	4 weeks	300

Table 3. Comparison of Total Cost of Therapy

Klebsiella rhinoscleromatis also being problem resistant pathogen was presumed to have effect under rifampicin and it has been observed to control the disease within a very short time.

ShaerM (1981) used a new local 'acriflavine' as powerful lethal action invitro upon K. rhinoscleromatis encouraging to design the present clinical trial to assess the effectiveness in the treatment of rhinoscleroma.[2]

Gamea AM (1988) used local rifampicin in treatment of rhinoscleroma instead of using systemically and found good response to the treatment.[8]

Granulomatous and cicatricial stages require canalisation of nasal passages. A long followup is necessary to know the recurrence of the disease.

Side Effects

The side effects of the drugs in both control and study groups were similar.

Comparison of the cost of the therapy, duration of the therapy, the response of the drug and drug effects, it is evident that ciprofloxacin is more cost-effective, therapeutically efficient than drug in the control group, i.e. doxycycline.

CONCLUSION

We conclude that ciprofloxacin is a very good drug compared to doxycycline in the treatment of rhinoscleroma, particularly in the early stages of the disease and complete cure can be achieved by early diagnosis and treatment.

ACKNOWLEDGEMENT

It gives me immense pleasure to express my gratitude and respect to my beloved teacher and guide, Dr. Udayshankar, Professor, Department of ENT, KIMS, Hubli, for his priceless guidance, advice, suggestions and enduring patience, which saw me through the completion of this study. With wholehearted gratitude, I wish to acknowledge him.

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