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Topical Mitomycin-C can help as an adjunct to alkaline nasal wash and rifampicin in primary atrophic rhinitis

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ABSTRACT

Purpose: Primary atrophic rhinitis (PAR) is a well-known old disease characterized by a roomy nose and extensive crustations. This study was designed to investigate the effect of topical Mitomycin-C as an adjunct to medical treatment with respect to objective and subjective improvement in patients treated with PAR.

Material and methods: This prospective randomized controlled study was conducted in a tertiary referral hospital in January 2016 and March 2018. Fifty adult patients aged 18 to 45 with PAR were randomly divided into 2 groups. Study group: treatment with Mitomycin-C dissolved in an alkaline wash plus rifampicin and control group: only treated with rifampicin and alkaline nasal wash. Subjective scores for the following symptoms: After 12 weeks of treatment, foul smell, anosmia, crusting, epistaxis, and nasal blockade, an objective score of crusting, the status of nasal mucosa, nature of the secretions and condition of nasal cavity were compared between the two groups.

Results: The degree of crustations ($P < 0.0001$) and the severity of epistaxis ($P < 0.0001$) were significantly improved in patients treated with Mitomycin-C dissolved in an alkaline wash (i.e. the study group), and the secretions returned significantly to normal ($P < 0.0001$). Both groups had significant improvements in both subjective and objective parameters of the assessment.

Conclusions: In patients with primary atrophic rhinitis, the use of Mitomycin-C dissolved in an alkaline nasal wash as an adjunct to oral rifampicin can produce a beneficial result than rifampicin and alkaline nasal wash alone.

1. Introduction

Primary atrophic rhinitis (PAR) is a well-known disease that was first described by Fraenkel in the literature of the 19th century [1,2]. Other names for PAR include dry rhinitis, rhinitis sicca, open nose syndrome or ozena [3,4]. PAR is characterized by a sclerotic change in the mucous membrane of the nose and by abnormal patency of the nasal passages due to atrophic changes in the mucosa and underlying bone [5]. The disease is also characterized by thick, viscous secretions that, when dried, can cause a peculiar foul smell. The smell makes the patient rejected in society. Atrophic changes in turbinates and nasal bones produce a large nasal cavity and atrophy of the olfactory nerve causes anosmia. Miles and Taylor [6] have extensively studied the pathology of PAR. They found that chronic rhinitis causes endarteritis and periarteritis of the terminal arterioles, leading to atrophic pathology with infiltration of chronic inflammatory cells, mainly lymphocytes, and fibrosis in about 23.5% of PAR cases.

However, the etiology of PAR remains ambiguous; many theories are postulated in the explanation. The factors that may cause the genesis of PAR are Coccobacillus, Bacillus mucosus, Diphtheroid bacillus, Klebsiella ozaennae, chronic infection of the sinuses, autoimmunity, hormonal imbalance, malnutrition, heredity, and iron deficiency anemia [7,8]. The theory of chronic persistent infections and autoimmunity has the biggest supporter [9]. Uncertain PAR etiology makes its definite treatment difficult to achieve. A variety of medical treatments for managing PAR, such as a nasal wash with anhydrous glucose in glycerin or chloromycetin in the nasal drop and systemic administration of hormones, placental extract, streptomycin, vitamins, and minerals. The surgical treatment is to narrow the nasal passages, such as submucosal stitches, lateral displacement of the nasal wall or elevation of the floor or the sides of the nose, using dermal flaps, placental tissue [10] or injecting Teflon cream, hoping to reduce the space of the nasal cavity with variable degrees of success.

Mitomycin-C is a natural antibiotic derived from Streptomyces

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caespitosus. The antibacterial effect of mitomycin C was first reported in 1956 [12]. Mitomycin-C has the ability to crosslink and alkylate between DNA chains and has been used as a chemotherapy for the treatment of various solid tumors such as the bladder, gastric cancer, and colorectal cancer. Some studies have evaluated the effects of Mitomycin-C on postoperative scar formation, such as airway restoration, choanal atresia repair, esophageal stricture, and endoscopic sinus surgery [13–16]. In the field of Otolaryngology, the data about Mitomycin-C is inconclusive, and the use of Mitomycin-C is still at the research level. The purpose of this study was to evaluate the topical use of Mitomycin-c dissolved in an alkaline nasal wash as an adjunct to continued medical treatment of PAR patients to assess the degree of subjective and objective improvement.

2. Material and methods

This prospective randomized study was conducted between January 2016 and March 2018 and was approved by the Egyptian Medical Research Ethics Committee, 2017 NBA6742817. All patients signed a written consent form prior to inclusion in the study.

2.1. Patient population

Fifty adult patients were sent to the Otorhinolaryngology, Head, and Neck Surgery Department at Minia University Hospital in Minia, Egypt and Minia Medical Insurance Hospital. No pharmaceutical company sponsored the research or contributed to the research design, evaluation or writing of the research.

We included patients, according to the following inclusion criteria: (1) patients older than 18 years, (2) patients with typical features of atrophic rhinitis in terms of symptoms and clinical examination, and (3) patients with bilateral disease. We excluded patients with the following criteria: (1) patients with a history of nasal surgery, (2) patients with previous nasal trauma or irradiation, and (3) patients with characteristic systemic or nasal granulomatous disease known to affect the nasal mucosa leading to secondary atrophic rhinitis, (4) pregnant and lactating female patients and (5) patients lost to follow-up.

Patients were randomized into 2 groups: A control group (25 patients), treated with oral rifampicin (10 mg/kg weight) once daily in the morning before the meal, accompanied by a nasal douche containing warm water (200 cc glass) and sodium bicarbonate (1 teaspoon), table salt (1/2 teaspoon) and sugar (1/2 teaspoon); 3 times a day for 3 months [16]. Study group (25 patients) treated with oral rifampicin (10 mg/kg by weight) once a day in the morning before the meal, supplemented with a nasal douche with 5 cm dissolved Mitomycin-C (supplied as a sterile lyophilized powder; 20 mg vials dissolved in 100 ml saline solution (0.2 mg/ml) in warm water (200 ml glass) containing sodium bicarbonate (1 teaspoons), table salt (1/2 teaspoon), sugar (1/2 teaspoon), 3 times daily for 3 months.

Mitomycin-C is an antineoplastic drug that requires special handling for its disposal to reduce any potential risk to staff, patients and the environment. We had the following steps for safe handling according to published guidelines [17]:

1- Dissolved Mitomycin-C prepared by a well-trained nurse wearing double gloves with powder-free latex and a disposable gown during the Mitomycin-C preparation process.
2- The dissolved Mitomycin-c is placed in a properly labeled container and administered to the patient.
3- Patients should wear double gloves when using the solution and place used syringes in a puncture-resistant container.

2.2. Patients assessment

Patients underwent a complete medical history examination, with special emphasis on the duration of the main symptoms; other nasal, pharyngeal or laryngeal symptoms; Drug history (Study patients received intermittent empirical medications in the form of various antibiotics (rifampicin and ciprofloxacin), alkaline nasal douches, and multivitamins for 1 to 6 weeks prior to inclusion in the study) and the history of the operations of the head and neck. In addition, all patients were screened for diabetes mellitus and human immunodeficiency virus. The basic radiograph included a paranasal sinus scan ordered for all patients.

All patients had the following evaluation parameters at 2 fixed points: (1) just before starting treatment and (2) at the end of 3 months of treatment. The scores at the beginning and at the end of the therapy; (at 12 weeks) were compared statistically.

Patients' assessment included the following parameters.

2.2.1. The subjective scores

The score was evaluated for the most common presenting symptoms of PAR (foul odor, anosmia, crusting, epistaxis, and nasal blockage)). The symptoms were assessed on a scale of 1 to 10, with 1 being the worst score and 10 the best score [18]. The average score for each symptom in each group was calculated and compared.

2.2.2. Endoscopic scores

A diagnostic nasal endoscopy performed for all patients using a 0° endoscopic lens with a diameter of 4 mm while the patient was under local anesthesia (lidocaine 10%). According to the four objective variables described by Jaswal et al. [18], the results indicated: crustation (gross = 1, minimum/nil = 2), status of the nasal mucosa (congested = 1, normal = 2), the nature of the secretions (thick = 1, thin = 2) and the condition of the nasal cavity (spacious = 1, normal size = 2). The average of 2 nasal cavities in each patient in each group was calculated and compared.

The first investigator (O.G. Awad) carried out endoscopic follow-up at 12 weeks, who was blinded to the randomization process and did not know which patient was in the study or control group.

2.3. Statistical analysis

The Statistical Package of Social Science version 15.0 (SPSS, Chicago, Illinois, USA) was used for data analysis. The quantitative data were presented by the mean, median, and standard deviation. The *t*-test was applied to compare the groups with respect to the continuous variables. Fisher's exact test was used to find the differences in the level of compliance. The probability of < 0.05 was used as the threshold for all significant tests.

3. Results

3.1. Patient characteristics (Table 1)

A total of 50 patients (40 women and 10 men) with PAR completed their follow-up visits and were included in this study. 10 patients did not complete their follow-up and were excluded. The overall mean age of the patients was 28.15 ± 2 years with a range of 18 to 45 years. The mean age of the patient in the control group was 23.2 ± 2 years versus 25.3 ± 6 years in the study group, with no statistically significant difference between age and sex between the 2 groups. Fifteen patients (30%) were farmers. Twenty-five patients (25%) lived in rural areas and 2 patients (4%) lived in urban areas. The comorbidities are presented in Table 1. Thirteen patients (26%) had a positive family history of PAR in one of their family members. The duration of the patient's symptoms ranged from 4 to 20 years, with an average of ± 12 years. At the beginning of the study, there was no significant difference between 2 groups for subjective and endoscopic cores (Table 2).

Table 1
Preliminary assessment of the study patients.

Variables	Value
Age, y	
Mean	28.15 ± 2.6 years
Minimum, maximum	18, 45 years
Sex, no. (%)	
Male	40 (80%)
Female	10 (20%)
Comorbidities, no. (%)	
Diabetes mellitus	5 (10%)
Anemia	22 (44%)
Presentation symptoms	
Foul smell	45 (90%)
Anosmia	49 (98%)
Crusting	50 (100%)
Epistaxis	36 (72%)
Nasal blockade	45(90%)

Table 2
Comparison between 2 groups at the start of study.

Variable	Group		P-value
	Study (mean ± SD)	Control (mean ± SD)	
Symptom scores			
Foul smell	2.3 ± 1.23	2.6 ± 1.34	P = 0.413
Anosmia	3.3 ± 1.22	3.8 ± 1.56	P = 0.212
Crusting	2.4 ± 1.12	2.1 ± 1.23	P = 0.371
Epistaxis	2.8 ± 1.02	2.0 ± 1.22	P = 0.550
Nasal blockade	2.7 ± 1.27	2.4 ± 1.19	P = 0.393
Endoscopic scores			
Crusting	2.4 ± 0.52	2.6 ± 0.34	P = 1.000
Congestion of nasal mucosa	2.2 ± 0.63	2.8 ± 0.42	P = 0.195
Nature of secretions	2.6 ± 0.21	2.6 ± 0.24	P = 0.093
Condition of nasal cavity	2.4 ± 0.52	2.6 ± 0.434	P = 1.000

Mc-Nemer test for comparing clinical variables. Symptoms assessed over a scale of 1–10; 1, the worse score and 10, the best score. Crusting, (gross = 1, minimal/nil = 2); status of nasal mucosa, (congested = 1, normal = 2); nature of secretions, (thick = 1, thin = 2) and condition of nasal cavity, (roomy = 1, normal size = 2).

Table 4
Comparison between 2 groups at the end of the study (presented by mean scores).

Variable	Group		P value
	Study (mean ± SD)	Control (mean ± SD)	
Symptom scores			
Foul smell	5.1 ± 2.34	4.9 ± 2.45	P = 0.671
Anosmia	5.1 ± 2.32	4.6 ± 3.23	P = 0.362
Crusting	7.2 ± 3.56	4.2 ± 2.01	P < 0.0001*
Epistaxis	6.4 ± 3.22	4.0 ± 2.03	P < 0.0001*
Nasal blockade	4.7 ± 2.43	4.0 ± 1.90	P = 0.100
Endoscopic scores			
Crusting	3.8 ± 0.91	3.0 ± 0.65	P < 0.0001*
Congestion of nasal mucosa	3.4 ± 0.62	3.2 ± 0.56	P = 0.07
Nature of secretions	3.6 ± 0.73	3.0 ± 0.45	P < 0.0001*
Size of nasal cavity	2.6 ± 0.52	2.7 ± 0.47	P = 0.92

Mc-Nemer test for comparing clinical variables. Symptoms assessed over a scale of 1–10; 1, the worse score and 10, the best score. Crusting, (gross = 1, minimal/nil = 2); status of nasal mucosa, (congested = 1, normal = 2); nature of secretions, (thick = 1, thin = 2) and condition of nasal cavity, (roomy = 1, normal size = 2).

* Significant difference (P-value ≤0.05).

3.2. Change of the subjective scores

As seen by the patient at the beginning and at the end of the treatment (i.e. week 12), both groups showed a statistically significant improvement in their assessed symptoms (Table 3). Patients in the study group had a statistically significant improvement in the degree of crusting and the severity of epistaxis compared to control patients; with a better improvement of anosmia, foul odor and nasal blockade with no statistically significant difference (Table 4).

3.3. Change of endoscopic findings

Comparing the four objective variables in the two groups.

3.3.1. Crustations

Both groups showed statistically significant improvements compared to pretreatment (Table 3). The study group had fewer statistically significant crusts than the control group (Table 4) (Figs. 1, 2).

Table 3
Change of assessment parameters from pre to post-treatment values in each group: (presented by mean scores).

Variable	Group					
	Study			Control		
	Pre (mean ± SD)	Post (mean ± SD)	P-value	Pre (mean ± SD)	Post (mean ± SD)	P-value
Symptom scores						
Foul smell	2.3 ± 1.23	5.1 ± 2.34	P < 0.0001*	2.6 ± 1.22	4.9 ± 2.45	P < 0.0001*
Anosmia	3.3 ± 1.22	5.1 ± 2.32	P = 0.001*	3.8 ± 1.41	4. ± 3.23	P = 0.045*
Crusting	2.4 ± 1.12	7.2 ± 3.56	P < 0.0001*	2.1 ± 1.12	4.2 ± 2.01	P < 0.0001*
Epistaxis	2.8 ± 1.02	6.4 ± 3.22	P < 0.0001*	2.0 ± 1.11	4.0 ± 2.03	P < 0.0001*
Nasal blockade	2.7 ± 1.27	4.7 ± 2.43	P = 0.0005*	2.4 ± 1.32	4.0 ± 1.90	P < 0.0001*
Endoscopic scores						
Crusting	2.4 ± 0.52	3.8 ± 0.91	P < 0.0001*	2.6 ± 0.34	3.0 ± 0.65	P < 0.0001*
Congestion of nasal mucosa	2.2 ± 0.63	3.4 ± 0.62	P = 0.001*	2.8 ± 0.42	3.2 ± 0.56	P < 0.0001*
Nature of secretions	2.6 ± 0.21	3.6 ± 0.73	P < 0.0001*	2.6 ± 0.24	3.0 ± 0.45	P < 0.0001*
Size of nasal cavity	2.4 ± 0.52	2.6 ± 0.52	P = 0.94	2.6 ± 0.43	2.7 ± 0.47	P = 0.87

Mc-Nemer test for comparing clinical variables. Symptoms assessed over a scale of 1–10; 1, the worse score and 10, the best score. Crusting, (gross = 1, minimal/nil = 2); status of nasal mucosa, (congested = 1, normal = 2); nature of secretions, (thick = 1, thin = 2) and condition of nasal cavity, (roomy = 1, normal size = 2).

* Significant difference (P-value ≤0.05).

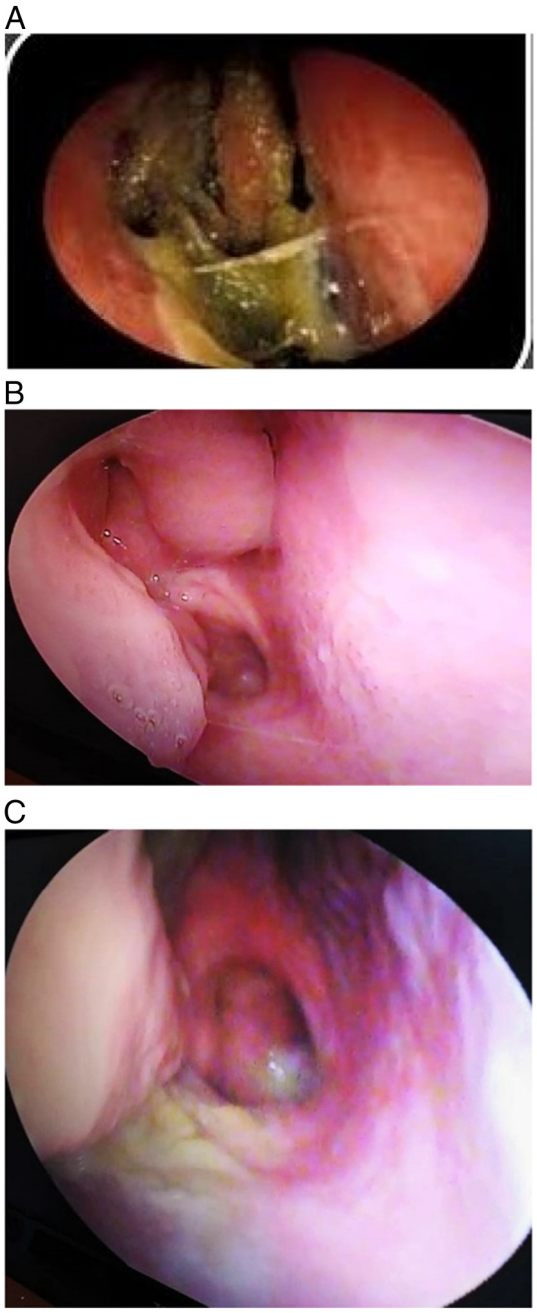

Fig. 1. (A) Right nasal cavity of 25-years old female patient with PAR showing gross crustations, roomy nose, congested mucosa and thick secretions.
(B), (C) Right nasal cavity of the same patient: 12 weeks of repeated MMC dissolved in alkaline nasal wash adjunct to oral rifampicin showing no crustations, roomy nose, normal mucosa and thin secretions.

3.3.2. Improvement in secretion from thick viscid secretion to thin normal secretion

Improvement in secretion from thick viscous secretions to thin normal secretions: Both groups showed statistically significant improvements compared to pretreatment (Table 3). The study group had a statistically significant improvement in secretion normalization compared to the control group (Table 4) (Figs. 1, 2).

3.3.3. Congestion of nasal mucosa

Significant statistical improvement was observed in both groups compared to pretreatment (Table 3). The study group had less mucosal congestion and there was no statistical difference between the two

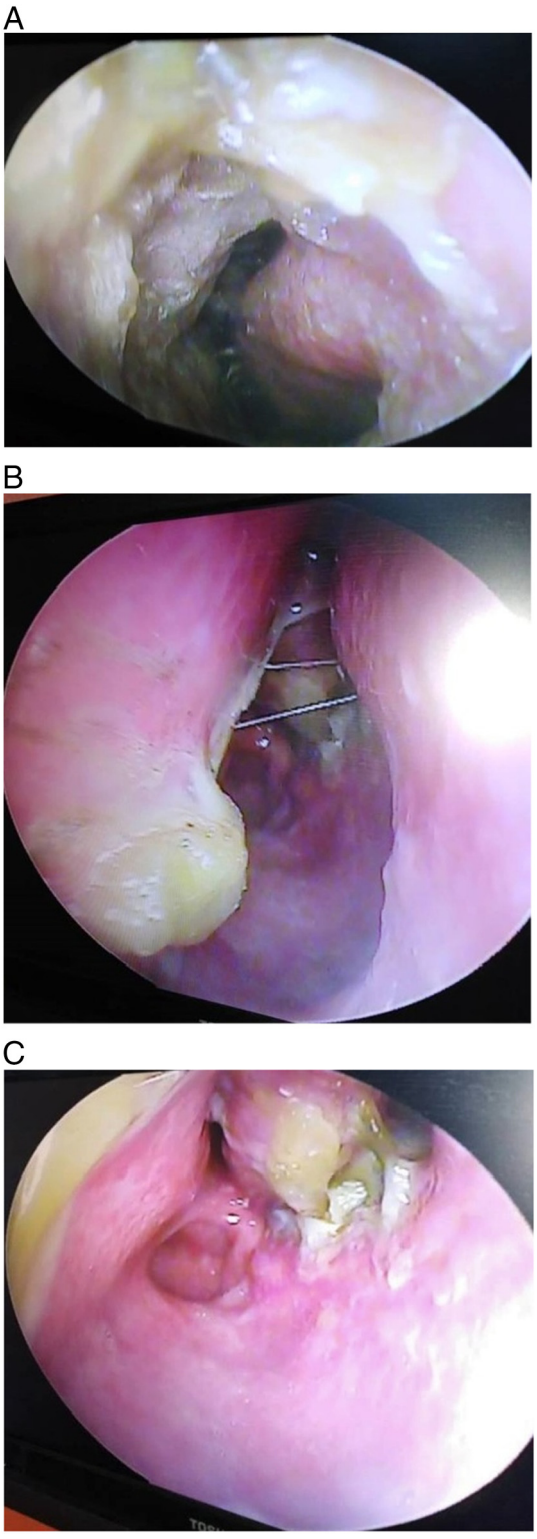

Fig. 2. (A) Left nasal cavity of 30-years old female patient with PAR showing gross crustations, roomy nose, congested mucosa and thick secretions.
(B), (C) Left nasal cavity of the same patient: 12 weeks of repeated alkaline nasal wash only adjunct to oral rifampicin showing minimal crustations, roomy nose, congested mucosa and thick secretions.

groups (Table 4) (Figs. 1, 2).

3.3.4. The size of the nasal cavity

There was no significant statistical difference observed in both

groups compared to pretreatment in the change from the wide cavity to normal size (Table 3). Also; there was no significant statistical difference between the two groups (Table 4) (Figs. 1, 2).

3.4. Complications of the procedure

During the study period, our patients did not observe complications of Mitomycin-C, signs of systemic toxicity or local toxic effects.

4. Discussion

Atrophic rhinitis is a well-known disease whose description goes back to the medical papyri of the Egyptian era. The disease was first described by Fraenkel in 1876 as a distinct clinical entity of the nose [5]. PAR is the classic form of the disease and it seems to appear from scratch. Many theories and hypotheses have been advanced in the explanation of PAR, among the various etiologies proposed, the theory of persistent chronic infection and autoimmunity have the largest supporters, with increased total protein and gammaglobulin fraction associated with the altered albumin-globulin ratio, although, it has never been proven conclusively by a lab test, this theory has many fanatical supporters [9,10,11].

The medical management of atrophic rhinitis aims to: restore nasal hydration, reduce the formation of crusts and debris and attempt to cure the disease by treating the cause. Several major classes of therapies (topical or systemic) have been used to achieve these goals. Nasal irrigation is widely used to prevent the formation of crusts. The type of irrigation used varies according to the authors and many solutions have been suggested. No evidence of the benefit of one solution over the other has been noted [1,2,19,20]. The most common type of systemic treatment is antibiotics. Oral injections of aminoglycosides and streptomycin were used in the first articles [4]. Although they have often been effective, they are not a common practice in recent years because of the toxicity of these drugs. Recently, quinolones and rifampicin have the broadest spectrum of action covering the wide variety of microorganisms extracted from cases of atrophic rhinitis [21]. Placental extract for the treatment of atrophic rhinitis was first demonstrated in 1971 by Sinha et al. [1] initiating vascularization, vasodilatation and increased host deficiency and cellular immunomodulation [9,10]. In addition, it may stimulate nitric oxide-dependent growth factors [7]. Its effect on vascularization may explain nasal mucosal congestion and normal reduction of the size of the nasal cavity towards normal at the end of the therapy in all the patients treated with placentrex. However, at the end of treatment for all patients who received placentrex treatment; the first improvement after starting treatment with placentrex either worsened at the end of treatment or did not persist after the end of treatment [10].

In our study, we used Mitomycin-C dissolved in an alkaline nasal wash as an adjuvant to oral rifampicin in the study group compared to the control group using an alkaline nasal wash alone. All variables used in the objective and subjective analyses of both groups showed continuous improvement. Similar results were reported for an early treatment regimen using rifampicin 600 mg once daily for 12 weeks, with significant changes in the normalcy of epithelial lining and glandular regeneration [18,7]. In our study, patients with Mitomycin-C dissolved in the alkaline nasal wash had a significantly improved degree of crustations, the severity of epistaxis and normalization of secretion. The other variables in the study group returned to normal with a higher degree than in the control group.

Since Mitomycin-C has anti-proliferative effects through its ability to inhibit fibroblast activity, the drug has been used as an anti-scaring treatment after various ophthalmologic procedures since 1980 [22]. Using Mitomycin-C after endoscopic sinus surgery can reduce postoperative adhesions [23]. In our previous study [24], we reported that repeated topical application of Mitomycin-c after removal of granulomatous tissue and lysis of fibrous adhesions in patients with rhinoscleroma with continuous medical treatment had significantly better results in granulation tissue recurrence, without complications up to 12 months of follow-up.

Sinha et al. [10] observed in their study that chronic inflammatory cell infiltration was mainly caused by lymphocytes in about 32% of cases, and fibrosis accounted for about 32.5%. Mitomycin-c has a natural anti-proliferative effect through its ability to inhibit fibroblast activity, which may explain the better results of our study group.

In our study, we did not encounter any signs of systemic or local toxic effects of Mitomycin-C. Human studies have also demonstrated the efficacy and safety of Mitomycin-C for the treatment of airway stenosis [25–27]. Veen et al. [28] concluded in their review that during topical use of Mitomycin-C, there were no systemic side effects at different parts of the aerodigestive tract and the effects that actually occur can be considered as a result of fragments of debris formed after surgery. Only 3.53% of the population surveyed had side effects due to topical use of Mitomycin-C. No side effects occurred in studies after the application site was rinsed with saline [28].

The most frequently used dosage of Mitomycin-C as a chemotherapeutic agent is 10 to 20 mg/m^2 of body surface area and is administered as an intravenous injection in a single bolus. This treatment is repeated every 6 to 8 weeks. For a person with a body weight of 70 kg and a surface area of 2.16 m^2, a single injection of 21.6 and 43.2 mg would correspond to a dose of 10 and 20 mg/m^2, respectively. Our study used only a small amount of Mitomycin-C administered topically and dissolved in 200 ml of water compared to the systemic chemotherapy dose administered to oncology patients. However; Choong et al. [29] in their study reported a transient episode of leukopenia in a dog treated with topical Mitomycin-C following the placement of an airway bypass stent. It is possible that there has been systemic absorption leading to Mitomycin-C toxicity and bone marrow suppression. This is certainly a possible side effect of topical drug application [30]. The ophthalmological literature has documented serious, vision-threatening complications after topical application of Mitomycin-C. These include severe secondary glaucoma, corectopia, corneal edema and perforation, sudden mature cataract, iritis, scleral calcification, pain and disabling photophobia [31]. Hueman et al. [32] described potentially fatal respiratory tract complications associated with the use of topical Mitomycin-C in the endoscopic treatment of laryngotracheal stenosis, they reported that airway obstruction was due to the characteristic accumulation of obstructing fibrinous exudate at the operative site in all cases and this pathological response may be caused by Mitomycin-C inhibition of fibroblast-mediated enzymatic activity, an important route in the degradation of post-surgical inflammatory fibrin exudate. They concluded that caution should be exercised when topical Mitomycin-C is used in the treatment of airway stenosis, especially when higher concentrations of Mitomycin-C (e.g. 10 mg/ml) are used [32].

Systemic absorption of Mitomycin-C and serum level monitoring are important issues that require further evaluation, which is a limitation of this study. Our study is the first study, to our knowledge, to evaluate the effects of serial topical use of Mitomycin-C with continuous medical treatment of PAR nasal lesions. This new use of Mitomycin-C has significantly reduced the degree of crustations, the severity of epistaxis and enhanced the normalization of secretion, which recommends the topical use of Mitomycin-C associated with continued medical treatment in patients with a PAR. This study is an undernourished study designed to show a significant effect of topical Mitomycin-C with respect to the histopathological changes that may occur and, therefore, a further study would be conducted to confirm or negate this effect. Although the number of patients in our study is not significant and requires short-term follow-up, other multicenter studies with longer follow-up periods will allow evaluation of the outcomes of topical Mitomycin-C in PAR and other types of atrophic rhinitis.

5. Conclusion

Repeated topical use of Mitomycin-C added to alkaline nasal wash in PAR with continued medical treatment had significantly better results regarding degree of crustations, severity of epistaxis and normalization of secretion, with no complications up to 12 weeks of follow-up.

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