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Effect of Systemic Ivermectin in Patients of Masal Myiasis and Diabetes

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ABSTRACT

Background: Nasal myiasis is not uncommon in a country like India, which has got multiple favourable factors for infestation by maggots. The aim of the study was to assess the effect of diabetes on clinical presentation and outcome and to assess the effect of systemic ivermectin in patients of nasal myiasis. **Methods:** This was a prospective study, 80 patients were enrolled in the study. The patients were divided into diabetics and non-diabetics (Group A and Group B). These were further randomly divided into two groups, in Group I endoscopic removal of maggots using Tilley's nasal packing forceps, after local application of chloroform and turpentine oil mixture was done. In Group II along with the endoscopic removal the patients also received two doses of oral ivermectin (6 mg). **Results:** Presence of diabetes was associated with more severe disease, in the form of septal perforation, involvement in posterior wall of nasopharynx / remnants of adenoid tissue and involvement of nasopharyngeal end of eustachian tube and fossa of Rosenmuller. Use of ivermectin along with mechanical removal was associated with significantly reduced maggot shedding time (41.23 ± 4.23 hour in mechanical removing and 24.60 ± 3.15 hour mechanical removing plus ivermectin group). **Conclusion:** Presence of diabetes is associated with more severe disease. Use of ivermectin was equally efficacious in both the diabetic and non-diabetic groups. Use of ivermectin was associated with early clearance of maggots, decreased morbidity and less hospital stay. Ivermectin use was not associated with any significant adverse events.

Keywords: Nasal myiasis, Diabetes, ivermectin, maggots

INTRODUCTION

Diabetes mellitus (DM) is one of the major evolving threats to public health in the 21st century. The number of persons with diabetes is anticipated to increase from 425 to 629 million adults between 2017 and 2045.[1] It is a widely perceived notion, by both the medical personnel and the common public, that individuals with diabetes have an increased susceptibility to develop infections.[2] The association between diabetes and infection has been attributed to a number of mechanisms, such as hyperglycemia associated impaired immune response, vascular insufficiency, sensory peripheral neuropathy, autonomic neuropathy and altered lipid metabolism.[3] Individuals with diabetes are more prone to many opportunistic infections some of which occur almost exclusively in them.[4] However the common belief of association between diabetes mellitus and enhanced susceptibility to infection is not backed by robust evidence.[5]

Myiasis is defined as the infestation of vertebrate animals and humans by the insect larvae. The term myiasis was coined by F.W. Hope in 1840. It is derived from the Greek word μυῖα (myia), which means "fly".[6] Though the term myiasis was first used in the nineteenth century, it has been recognized since ancient times. Flies responsible for myiasis are one of the world's most devastating creatures, it causes severe damage in animal husbandry leading to huge financial losses because of decreased milk production, weight and fertility issues, and detoriation in the quality of hide.[7]

Though myiasis is considered a rare disease, but scrutiny of literature shows that it is more common than expected. It is common in developing countries where sanitation is still a public health problem. It mostly it affects people in tropical countries and during summers, because the larvae needs warm and moist temperature to unincubate.[8]

Myiasis can be classified on the basis of site of involvement such as dermal, sub-dermal, cutaneous, nasopharyngeal, auricular, ocular, intestinal or urogenital.[9] It can also be classified into furuncular myiasis or secondary myiasis. The former is due to penetration of larvae to the tissue leading to furuncle formation, the latter is due to deposition of larvae into the cavities.[10]

The human invasion by these larvae leads to destruction of the host's body tissues. The gravid flies deposit their eggs into the open necrotic

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wounds, body cavities or natural orifices such as nose, ear, eye, vagina and anus. The larvae feed themselves on the host's dead or living tissues, liquid body substances or even the consumed food.[11,12] The fully grown larvae then leave the host in order to further develop into pupae [Figure 1]. Usually after 1-3 weeks, adult flies develop from the pupae.[13]

The clinical presentation depends on the tissues or organs involved. Nasopharyngeal myiasis presents clinically with pain, epistaxis, foul smelling discharge, swelling of the mid face region (lower lids, nose, upper lip), or passage of maggots from the nose. The old aged, immobile, debilitated, or comatose patients, mentally retarded people, and drug addicts are more susceptible to infestation by the flies.[14]

Case reports of nasal myiasis have also been described in patients of cancer and intubated patients.[15] But the association of nasal myiasis with diabetes has been till now limited to case reports only.[16] One of the largest studies published till date by Sharma et al. consisting of 252 patients did not mention diabetes as a risk factor for the development of nasal myiasis.[17] Diabetes mellitus, owing to its immunocompromised state is an important predisposing factor for myiasis, more so in elderly patients with low nutritional state and people living in poor hygienic conditions.[18]

The traditional treatment of myiasis involves removal of all the larvae manually, either directly or by endoscopic assistance.[18] The larvae are photophobic, they burrow themselves into the cervices of nasal cavity mucosa. Removal can be aided by the local instillation of mixture of chloroform and turpentine (1:4), ethylene chloride, irrigation on the area with naphtha, ether and cocaine. Use of these local agents leads to asphyxiation of larvae, and encourages the larvae to exit on its own.[19]

Ivermectin is produced from an insecticide Avermectin B, which is used for crop management. Ivermectin is now widely used to treat a wide spectrum of parasitic infestation.[20] It acts via activation of glutamate-gated chloride channels, which are exclusively found only in invertebrates. The activation of these channels leads to paralysis of the parasite.[21] The evidence of systemic ivermectin use in nasopharyngeal myiasis is limited to the case reports only.[15] To the best of our knowledge this is the first study to assess the effect of systemic ivermectin in a randomised trial.

This study was originally aimed at establishing the effect of systemic ivermectin in treatment of nasal and nasopharyngeal myiasis, during recruitment most of the patient was found to have diabetes, therefore data was collected with special attention to the diabetic status of the affected individuals. The data was also analyzed to describe the role of diabetes in the course of disease and management in such patients.

MATERIALS AND METHODS

The study was prospective study performed at a tertiary level hospital in northern India. The study subjects included a total of 80 patients, both male and female, between 30-60 years of age. Ethical clearance was obtained from the institutional ethical committee. The data obtained was analyzed for the prevalence of diabetes in patients with nasal myiasis. Effect of diabetes on clinical presentation and outcome was assessed. The effect of systemic ivermectin in patients of nasal myiasis was also analyzed.

Inclusion criteria:

- All patients of nasal and nasopharyngeal myiasis with and without diabetes.

Exclusion criteria:

- Children < 5 years
- Pregnant women

The patients with nasal myiasis were divided into diabetics and non-diabetics (Group A and Group B). These were further divided into two groups using a periodic random number. In first group (Group I) endoscopic removal of maggots using Tilley's nasal packing forceps, after local application of chloroform and turpentine oil mixture (in the ratio of 1:4) was done. In the second group (Group II) along with the endoscopic removal after the local application of chloroform and turpentine oil mixture, the patients also received two doses (24 hours interval) of oral ivermectin (6 mg each). The patients were advised to record the time when they noted shedding of larvae either spontaneously or while sneezing, and also note whether they were alive or motionless. Endoscopic removal of the maggots using Tilley's nasal packing forceps was repeated after 24 h (II sitting) and 48 h (III sitting) of the initial removal (I sitting).

The clinical presentation of patients included pain, epistaxis, oedema over mid face (lower lids, nose, upper lip), headache and worms coming out of nostrils while sneezing. A thorough history was obtained and general examination, systemic examination and local examination of ear, nose, paranasal sinuses, pharynx and larynx was performed. 00, 4 mm, rigid endoscope was utilized for endoscopic examination, and the findings were documented with special importance on extent of the disease, condition of septum, turbinates, nasopharynx and soft palate. Routine blood examination was done including complete blood count, absolute Eosinophil Count (A.E.C.) and blood sugar fasting, post prandial, and HbA1c, in every

patient. Other comorbidities were also noted like history of rhinitis.

All patients received supportive treatment in the form of analgesics, antibiotics and systemic decongestants. Patients were discharged from the hospital after the third sitting of larvae removal. Alkaline nasal pack consisting of sodium bicarbonate, boric acid and sodium chloride was given to patients. They were advised to keep good personal hygiene and use mosquito nets. Diabetes was managed with insulin injections with the aim of keeping blood sugar within acceptable limit. Most of the patients were discharged 48 hours after admission. All patients were reassessed after one week with repeat nasal endoscopy to ascertain maggot clearance and the degree of healing.

Statistical Analysis:

The data was analysed by unpaired t test for mean maggot shedding time between the two groups. The endoscopic clearance of the nose and nasopharynx between the two groups was compared by chi square test.

RESULTS

Our study included 80 patients of which 53 were diabetics and 27 were non-diabetic [Table 1]. Out of these patients 34 (42.5%) were males and 46 (57.5%) were females with male to female ratio of 1:1.4. The age of the patients ranged between 30 to 60 years and the mean age of presentation was 54.3 years. The highest prevalence was seen in patients above 50 years. Most of the patients in our study were from rural population.

The clinical findings of nasal endoscopy observed in both diabetics and non-diabetics are given in [Table 2 & Figure 2].

Both diabetic and non-diabetic patients had similar incidence of turbinate destruction and septal invasion. Though the incidence of invasion of middle meatus and soft palate was more in diabetics but this was statistically non-significant. Significantly more diabetics had septal perforation, invasion in posterior pharyngeal wall and adenoid tissue remnants and invasion of nasopharyngeal end of eustachian tube and fossa of Rosenmuller as compared to non-diabetics [Table 2].

After complete evaluation, the patients were instructed to keep a record of the time when they noticed shedding of larvae either spontaneously or while sneezing, and also note whether larvae were alive or still. The last time after which there was no shedding of larva was recorded as 'shedding time'. No difference was noted in the time of recovery i.e the mean maggot shedding time and the number of patients with complete endoscopical clearance in both diabetics and non- diabetics [Tables 3,4]. But the mean maggot shedding time was significantly lower in the ivermectin group (P = 0.0001), also number of patients with complete clearance of maggot at 24 and 48 hours were significantly higher in the ivermectin group (P = 0.002 at 24 hours and 0.006 at 48 hours).

Table 1: Baseline characteristic of study population

Characteristic	N	%
Sex		
Males	34	42.50
Females	46	57.50
Age group (years)		
31-40	02	2.50
41-50	31	38.75
51-60	47	58.75
Area of residence		
Rural	74	92.5
Urban	6	7.50
Risk Factors		
Diabetes	53	66.25
Atrophic rhinitis	39	48.75
Psychiatric illness	11	13.75
Residual Paralysis	7	8.75

Table 2: Findings on nasal endoscopy

Findings	Non-diabetics (n=27)		Diabetics (n=53)		P
	Number of pts.	%	Number of pts.	%	
Destruction of turbinates	27	100	53	100	NS
Invasion of septum	25	92.6	49	92.5	NS
Involvement of middle meatus	16	59.3	33	62.3	NS
Involvement in soft palate	8	29.6	20	37.7	NS
Septal Perforation	9	33.3	30	56.6	0.04
Involvement in posterior wall of nasopharynx / remnants of adenoid tissue	1	3.7	12	22.6	0.03
Involvement of nasopharyngeal end of eustachian tube and Fossa of Rosenmuller	1	3.7	11	16.9	0.03

NS; non-significant

Table 3: Mean maggot shedding time.

	Total (n=80)	Non-diabetics (n=27)	Diabetics (n=53)	P
	Mean (hours)	Mean (hours)	Mean (hours)	
Group I	41.2 ± 4.26	40.5 ± 4.3	41.6 ± 4.2	NS*/ 0.0001#
Group II	24.6 ± 3.15	23.7 ± 3.2	25.1 ± 3.1	NS*

NS; non-significant; * P between diabetic and non-diabetic; # P: between group I and II.

Table 4: Number of patients with complete clearance

		Non-Diabetics		Diabetics		
		Number	%	Number	%	P
At 24 hours	Group I	6	46	12	44	NS*/0.002#
	Group II	11	79	21	81	NS*
At 48 hours	Group I	9	69	19	70	NS*/0.006#
	Group II	13	93	25	96	NS*

NS; non-significant; * : P between diabetic and non-diabetic; #: between group I and II.

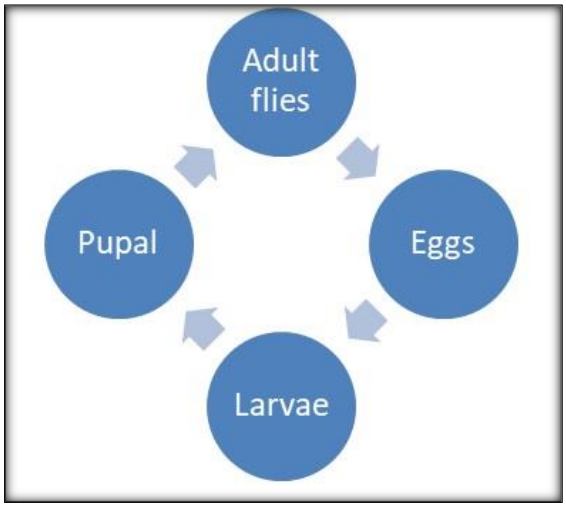

Figure 1: Lifecycle of maggots

Figure 2: Maggots and destruction of nasal septum

DISCUSSION

Nasal myiasis and nasopharyngeal myiasis are not uncommon entities, especially in tropical and subtropical countries like India.[22-24] There are various comorbid conditions that predispose to infestation by maggots, diabetes mellitus was the most common comorbidity observed in our patients (66.25%). This can be explained by the fact that there has been a global rise in the prevalence of diabetes mellitus in the last two decades.[1] Uncontrolled diabetes increases the risk of opportunistic infections like sinusitis, which together with purulent foul smelling discharge attract the flies. Since most of the patients were in the age group of 50-60 years, the mean age was 54.3 years ± 3.2 years. This finding is different from earlier studies,[25] where the most commonly affected age group was 41–50 years. This divergence can be due to increase in the life expectancy from 40 years to 69 years in 1960 and 2017 respectively and also due to the fact that the incidence of diabetes increases with age.[26]

More than 90% of the patients were from rural area, this finding is similar to previous findings.[27] Increasing prevalence of diabetes in villages, poor socioeconomic status, handling of cattle and other livestock and poor personal hygiene are the factors favouring infestation by flies.[17,28]

The incidence of diabetes is also increasing in villages, and Indian population demographics are also changing, in the form that the growth in the elderly population is higher than the general population and the difference between the two has widened over the period.[29] We can expect more patients with such infestation in future.

There was slight female preponderance with male to female ratio of 1:1.4. This can be explained by the fact that atrophic rhinitis, which is an important risk factor for nasal myiasis, is more common in postmenopausal women secondary to oestrogen deficiency. Another reason can be the fact that the elderly females in poor socio economic population are often being ignored and neglected.[30,31]

All the patients presented with complaints of pain and discomfort in the face around the nose. Apart from pain they also had complaints of epistaxis, swelling over mid face, and passage of larvae from the nose.

The larvae are voracious eaters and continue to feed on adjacent host tissues and burrow into adjacent structures like paranasal sinuses, upper lip and cheek and cause pain, nasal bleed and oedema of the face.[32]

It was found that the invasion of nasopharyngeal structures (posterior pharyngeal wall, nasopharyngeal end of eustachian tube and fossa of rosenmuller) was significantly more common in diabetics as compared to non-diabetics in whom the disease was mostly confined to nasal cavity. This clearly showed that the course of disease was more aggressive in diabetics. Thus in such patients where the larvae crawl into areas such as ethmoid air cells, maxillary antrum, eustachian tube which are inaccessible for conventional use of manual

extraction and instillation of mixture of chloroform and turpentine making it challenging to remove them. This mandates the use of a systemic and effective medication for its treatment.

Oral ivermectin was highly efficacious in clearing of maggots without any significant systemic or local side effects. There was significant difference in the maggot shedding time between both groups (41.2 hours in Group-I and 24.6 hours in group-II). This can be due to paralytic effect of ivermectin on the maggots, the paralyzed maggots tend to shed off early in group-II. Ivermectin activates the gama-amino-butyric acid (GABA) gated Cl- channels, leading to increased Cl- concentration in cells, which causes hyperpolarization, paralysis and death of parasites.[20,21] Ivermectin was equally efficacious in early clearance of maggots in both diabetics and non-diabetics, this was evident on comparing mean maggot shedding time, which was almost similar in patients of both the groups. This means hyperglycaemia per se does not have any significant effect on the action of ivermectin.

CONCLUSION

In this study we found that diabetes is an important risk factor for the development of nasal myiasis. Presence of diabetes was associated with more severe disease in the form of more involvement of nasopharyngeal structure when compared with non-diabetics. As the incidence of diabetes is increasing in India, life expectancy is also increasing, sanitation is still a big problem, so we should expect more cases of nasal myiasis in our country. Oral ivermectin was associated with early clearance of maggots without any significant adverse effect in both the diabetic and non-diabetic group.

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