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Corneal edema due to botanical toxins

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ABSTRACT

Background: Corneal edema following contact with plant extracts occur not only with horticultural workers but also with amateur gardeners. The condition causes reasonable visual debility but is reversible and self limiting. Till date, no established therapeutic protocol exists for management of this particular condition.

Objectives: To re-examine the etiological factors behind this condition and to develop a definitive therapeutic prescript for this problem.

Materials and Methods: Forty six patients suffering from this condition were randomly divided into two equal groups. Group A was treated with topical steroids (commercially available moxifloxacin 0.5% w/v + dexamethasone sodium phosphate 0.1% w/v), whereas Group B was treated with a placebo (carboxy methylcellulose 0.5% w/v). All patients were monitored on alternate days in terms of BCVA, non contact tonometry and slit lamp examination. Pachymetry was done on arrival and after complete resolution of corneal edema.

Results: In both the groups, corneal edema resolved in all eyes by the fifth day without any residual clinical deficit. The mean pachymetry value on presentation in Group A was 626 microns and in Group B was 628 microns, and returned to 550 microns or below by day five in all patients. Visual acuity was restored to 6/9 or better in all patients of Group B and 96% (n= 22) patients in Group A, but this deficiency was not related to the disease process in question.

Conclusion: Botanical toxin induced corneal edema was self limiting and resolved in a time bound pattern without any sequel. Topical steroids neither seemed to hasten the resolution of corneal edema nor affected the final outcome of this clinical condition in any way.

1. Introduction

Calotropis gigantea, synonym *Asclepias gignatea*, also called crown flower or giant milkweed, is a native of South East Asia including India. It is a member of the family *Apocynaceae* and sub family *Asclepiadoidae*, also known as the milkweed family.[1] It is a large shrub and has clusters of white or lavender coloured flowers which have five pointed petals and a small crown rising from the centre from which it derives its colloquial name. The leaves are oval and light green in colour and have a stem which contains milky latex. It grows best in wilderness and flowers all the year round but more so in the dry seasons. It is called *madar* in Hindi and *akanda* in Bengali.

Across societies, this flower has found place in social and religious activities. In Thailand and Hawaii, it is popular for floral arrangements and ornamental garlands. In India, the fibre obtained from this plant is used to make ropes for carpets and fishing nets. The cotton obtained is used to make pillows. It has also been used in traditional Indian medicine for the treatment of respiratory and circulatory disorders since time immemorial.[2] In Hindu mythology, it is believed that crown flower is very much liked by Lord Shiva; therefore crown flower and its garland are offered to the Lord for peace, prosperity and stability in society.[2] This particular belief leads to a manifold increase in cases

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of corneal toxicity during certain festivals related to the worship of Lord Shiva, as requirement and handling of these flowers increase in the community.

Corneal toxicity usually results from accidental contact with the latex derived from stem or leaves of the plant with the ocular surface, and manifests as corneal edema and resultant visual deprivation which gradually develops within hours. This article not only tries to find a clearer understanding of this phenomenon, but also attempts to assess the existing therapeutic approaches to this condition.

2. Aims and objectives

The aims of this study were

To review the etiologic factors behind corneal edema following contact with Caloptropis plant, and

To compare the therapeutic outcomes of topical steroids with a placebo in treating this condition.

3. Materials and Methods

This study was carried out for period of approximately two years between January 2017 and December 2018 in a medical college located in rural West Bengal. All patients were explained about the disease and treatment process and inducted only after affirmation.

3.1. Inclusion criteria and evaluation

Any patient attending the eye outpatients department or the eye emergency with complaints of sudden visual loss and a history suggestive of contact with crown flower or its latex was enrolled in this study. Age, sex, caste, creed etc were not considered as a criterion for enrolment.

In all patients, a detailed history was taken regarding his/ her activity prior to the episode. This was followed by a comprehensive ophthalmic evaluation of both the eyes, which included recording of best corrected visual acuity by Sellen's chart, recording of intraocular pressure by a non contact tonometer, a thorough slit lamp evaluation of the cornea and anterior segment which also included flourescin staining to assess corneal epithelial integrity, and ultrasonic pachymetry. In all cases, the condition of the cornea during presentation precluded fundus evaluation of the affected eye.

3.2. Treatment protocol

These patients were then dissevered in two separate groups – the odd serial numbers of enrolment being designated as Group A and the even serial numbers as Group B. Patients in Group A were treated with a commercially available topical preparation of dexamethasone sodium phosphate 0.1% w/v + moxifloxacin 0.5% w/v. Group B was designated as a control group and treated with a topical preparation of carboxy methyl cellulose 0.5% w/v which acted as a placebo. The same commercial brand was used on all patients in each group to eliminate any bias whatsoever.

3.3. Follow up

All enrolled patients were followed up on alternate days. Pachymetry was done at the end of the week when there was clinical evidence of return to normalcy.

Both treatment groups were compared on the basis of time they took for complete resolution of corneal edema. The accepted therapeutic end point was a clear cornea on high magnification of slit lamp and a central corneal thickness of 550 microns or below on pachymetry.

4. Observations and Results

4.1. Demographics

Table 1 shows the quarter wise distribution of patients

Table 2 shows the age distribution of patients

4.2. Clinical features on presentation

As all the subjects in both the groups came from the same patient pool, there was no difference – clinically or statistically between the two groups on presentation. In all patients of Group A and in 91% of patients (n = 21) of Group B, the involvement was unilateral. All patients gave a history of contact with crown flower plant or its latex the previous day or a few hours back, following which the vision of the affected eye deteriorated over a period of time. Best corrected visual acuity was 6/24 or worse in all affected eyes. The mean IOP was 14 mmHg +/- 1 mmHg in both the groups. The mean pachymetry readings were 626 microns in Group A and 628 microns in Group B which had no statistical significance. Flourescin staining revealed an intact corneal epithelium in all cases. Every patient had clinical corneal edema as depicted by loss of compactness of the slit beam and folds in the Descemet membrane. Circum-corneal congestion was also universally present but no evidence of uveal inflammation like cells or flare was noted in any patient. The corneal edema precluded fundus assessment in the affected eye, but it was normal in the contra lateral eye of all patients of Group B and 96% (n=22) patients of Group A where one patient had clinical features dry age related macular degeneration. The overall impression was these were all apparently healthy individuals who had presently landed in an adverse situation following contact with a crown flower plant.

4.3. Clinical picture at the end of first week

All eyes in both groups underwent uneventful clinical resolution by fourth to fifth day. Clinical evidence of corneal edema disappeared, and pachymetry readings returned to 550 microns or below in all affected eyes. Best corrected visual acuity was restored to 6/9 or better in all eyes

except one patient in Group A who had age related macular degeneration. This however was an incidental finding and not related to the disease process in discussion in any way.

Following resolution, topical medications in both groups were discontinued and patients were advised to return to their usual activities, with an advice to report if they noticed anything unfamiliar.

Table 1: Shows the quarter wise distribution of patients

Period	Males	Females
Jan to March 2017	7	5
April to June 2017	2	1
July to Sept 2017	4	1
Oct to Dec 2017	2	2
Jan to March 2018	6	7
April to June 2018	1	1
July to Sept 2018	2	3
Oct to Dec 2018	1	1
Total	25	21

Table 2: Shows the age distribution of patients

Age	Males	Females
10 -20	2	3
21 – 30	6	6
31- 40	7	5
41- 50	7	5
51 and above	3	2
Total	25	21

5. Discussion

When the study was first done in 2017, it was noticed that there was a sudden surge of patients during a particular time of the year, namely in the month of February- March. Although sporadic cases visit the outpatients department throughout the year, this particular seasonal predilection warranted that the study is extended for one more year to ensure that this phenomenon was not a mere coincidence. A similar seasonal predilection had also been reported by Basak et al[3] Repetition of the same event during the same months in the subsequent year led us to believe that the reason was socio religious. The Hindu festival of Shivaratri is held during this time, for which flowers of this plant become necessary. That might explain the sudden rise of incidence of *Calotropis* related toxicity during this period of time.

Corneal toxicity of the milkweed family is not restricted to crown flower alone. Other members of the *Asclepias* family like *Asclepias Currasavica, Asclepias Tuberosa, Asclepias fruticosa*, and *Calotropsis Procera* have been reported to cause similar clinical manifestations.[4–6] The aetiology appears to be related to the presence of cardiac glycosides in the latex of stem and leaves of these plants.[7] Isolated toxins from these plants include calotropin, ucharin and calactin.[8] These have the capacity to penetrate the intact corneal epithelium and cause a blockade of the ATPase energised sodium pump located in the corneal endothelium.[8,9] The integrity of the epithelium is affirmed by the absence of fluorescin staining across both the groups. The effect on the cornea then, is the development of isolated stromal edema which develops within a few hours of exposure. This delay – and onset – is remarkably similar to the appearance of digitalis keratopathy after topical administration of digoxin drops.[10,11]

The progression of clinical events reflects the pattern and mode of action of cardiac glycosides on the cornea. Na^+K^+ ATPase exists in two isoforms – α and β. Of these, cardiac glycosides have an enhanced affinity for binding at $\alpha 1$ subunit.[12] Although the distribution of sodium pump isoforms in the cardiac musculature and their relation to cardiac glycosides has been extensively studied, similar information about the corneal endothelium is inadequate. In the cardiac muscles, blockade of the ATPase pump not only causes an increased concentration of sodium inside the cells, but also simultaneously increases the Ca ion concentration due to its action on the sodium calcium exchanger (NCX). This increased Ca concentration is further responsible for cardiac arrhythmias often noticed with digitalis /cardiac glycoside toxicity.[12] A similar effect is however nonexistent in the cornea.[13,14] What was seen instead was an ATPase pump system blockade induced corneal stromal edema which was transient, self limiting and reverted without any residual inadequacy. The absence of pain and fluorescin uptake exculpated the corneal epithelium from any role in this disease process.

In our study all patients across both groups showed complete resolution of corneal edema by day five. This was consistent with other studies which reported the same between 72 and 96 hours.[5,6] The author's experience with another milkweed variant was that the edema resolved by 48 hours.[4] These differences in timing of resolution may probably be due to subtle variations in toxin profile of each species.[5] As all the patients in both groups reached the same clinical endpoint in the same period of time, a detailed statistical analysis became inessential.

The role of topical steroids was emphasised by Hatou et al[15] who suggested that topical dexamethasone increased the activity of Na^+K^+ ATPase pump in cultured corneal endothelial cells. This was because there was an in vitro increase of $\alpha 1$ subunit expression as well as $\alpha 1$ subunit enzyme activity. In reality however, no difference was noted in time of resolution of corneal edema between the two groups. Other studies – which had not used topical dexamethasone as a therapeutic instrument – also did not report a longer recovery time.[4,6] Keeping in mind the potential adverse effects of topical steroids, the authors felt that its use in this condition would be justified only when its

benefits definitively outweighed the risks.

On extensive search of the literature, the authors did not come across a similar study where different therapeutic approaches for botanical toxin induced corneal edema had been collated and compared. That perhaps made this study unique. On the flip side, it was felt that a structural evaluation of the corneal endothelium in the form of specular microscopy would possibly have provided additional information which could have led to further understanding of the disease process.

6. Conclusion

It was concluded that the basic cause of corneal edema following contact with plants of the milkweed family was blockade of the ATPase energised sodium pump located in the corneal endothelium. This blockade was transient, and resolved uneventfully with a predictable outcome. Medicines like topical steroids did not seem to expedite the resolution process, although in vivo experiments might have shown results that are contrary. More evidence about the benefits of application of topical steroid is necessary before its use can be accepted as a therapeutic benchmark in these clinical situations.

7. Source of Funding

None.

8. Conflict of Interest

None.

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