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ROLE OF TOPICAL INSULIN EYE DROP AND ITS COMPARISON WITH PACK-CXL IN CASE OF NON HEALING CORNEAL ULCER

Ophthalmology

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ABSTRACT

Present study evaluates efficacy of topical insulin eye drops and PACK-CXL in treatment of non-healing corneal ulcer. For this total 20 patients of corneal ulcer were taken and categorise as two groups, Group-1 and Group-2. Patients of Group-1 were treated with topical insulin eye drop, while Group-2 with PACK-CXL. In result, mean area of ulcer before starting treatment in Group-1 was 25.45 ± 16.5 mm^2 and we observed complete corneal reepithelization in all patients, with mean duration of reepithelization seen in 35 days. In group-2 mean area of non-healing ulcer before starting treatment was 20.58±10.63 mm^2, after PACK-CXL, we observed complete corneal reepithelization in all patients with, mean duration of 25.4 days. Final visual acuity was improved from baseline in both groups. Both topical Insulin eye drop and PACK-CXL can promote and accelerate corneal reepithelization of non-healing corneal ulcers but topical insulin eye drop is cost-effective with no adverse effect.

KEYWORDS

Non-healing ulcer, insulin, PACK-CXL, reepithelization

INTRODUCTION

Cornea forms one sixth anterior part of the eye and it act as the principal refractive surface, accounting for about 70% of the total refractive power. Corneal epithelium is the outermost layer of the cornea, so it is highly prone to common ocular pathogenesis such as abrasions and corneal epithelial defect, keratitis, corneal ulcer. The corneal epithelial cells are continuously regenerated from limbal stem cells, the epithelium completely self-renewed over approximately 7-10 days. Consequently, an acute epithelial defect/corneal ulcer are a lesion that typically cures within seven to fourteen days. In contrast, a non-healing ulcer does not respond to typical treatment of eight weeks. Currently various modalities are being use in the treatment of non-healing corneal ulcer like amniotic membrane grafting (AMG), recombinant nerve growth factor (rNGF), epidermal growth factor (rEGF) and PACK-CXL.

Insulin-like growth factors (IGFs) are essential for corneal epithelial cell development, differentiation, and proliferation and act via insulin receptors and IGF receptors. Epithelial cells and keratocytes of the cornea express IGF-I, its receptors, and insulin receptors. Insulin, a potent anabolic hormone, is intimately related to IGFs, as established in tear film by Rocha et al. [1] for the first time. The safety of topical Insulin for human ocular usage has been demonstrated[2]. David Diaz-Valle et al.[3] found in their study that topical insulin eye drop can promote and accelerate corneal reepithelization of refractory PED. Thus, topical Insulin eye drop seems to be an efficacious treatment modality for nonhealing corneal ulcer

New techniques, PACK-CXL, which has antimicrobial qualities and reinforces corneal stroma by forming a new covalent bond between collagen fibrils, have been proposed to improve treatment outcomes with fewer adverse effects. Wallensak et al[4], introduced corneal CXL as a minimally invasive procedure to halt the progression of keratoconus. In the corneal CXL UVA radiation and riboflavin as photochromophor are use. The interaction between riboflavin and UVA causes a photo-oxidation reaction and produces reactive oxygen species; these react with corneal collagen fibril and proteoglycan, forming new covalent bond between them. This has been shown to increase the biochemical stiffness of cornea. Corneal CXL is proposed to be effective for treating infectious keratitis due to the antibacterial qualities of photoactivated chromophore (riboflavin) and UVA radiation. First, ultraviolet (UV) radiation has a powerful antibacterial effect because it directly destroys the DNA and RNA of microbes, hence preventing their replication[5,6].

Riboflavin has a microbicidal effect due to its interaction with microbial nucleic acids, direct damage to pathogen cell walls, oxidation of nucleic acid residues by reactive oxygen species produced by photo activation, and increased resistance of the stiffened cornea to enzymatic damage from microbes[7]. Compared to UV-A alone, the combined action of UV-A light plus riboflavin is 10 times more harmful to microbes. The ninth CXL congress establishing different designations between CXL for ectasia and CXL for viral keratitis , for latter they designate photoactivated chromophore for infectious keratitis (PACK-CXL).There have been various studies done in different part of the world to establish the efficacy in resistant nonhealing corneal ulcers. Thus PACK-CXL seems to be a good alternative treatment as an adjuvant in case of nonhealing corneal ulcer. Primary objective of the present study is to compare the efficacy of corneal cross-linking and topical insulin eye drop in the treatment of refractory non-healing corneal ulcers.

MATERIALS AND METHODS

This prospective interventional comparative study was conducted over a time period of one year from December 2021 to December 2022 in the Regional Institute of Ophthalmology Prayagraj (a tertiary care referral centre), Motilal Nehru Medical College Prayagraj, after taking permission from institutional ethical committee . All patients were informed about all the investigations, treatment and procedure, informed written consent were taken. Patients with clinical sign and symptom of corneal ulcer who met the inclusion criteria were included in the study. Inclusion criteria was (1) Patients diagnosed with non-healing corneal ulcer, (2) Age 10-75 years, (3) Minimum corneal thickness ≥400 µm for Group-2 patients, and (4) All the patients who gave written consent.

Patients with history of corneal opacity and scarring, corneal degeneration and dystrophy, post PKP, lactating female were excluded from the study. A total 20 patients were enrolled in this study and were divided in two groups, Group -1, Group 2, each group had 10 patients. During the initial visit, detailed history of the patients was taken, and slit-lamp examination was done thoroughly. Ulcer was examined for its site, size, depth, infiltration and hypopyon (if present). Group -1 patients were treated with topical insulin eye drop at every 6 hours as an adjuvant treatment. The Insulin eye drop was prepared at a concentration of 1 IU/ml, using regular insulin solution .Insulin solution was diluted in a polyethylene glycol and polypropylene glycol base. Group- 2 patients were treated with PACK-CXL ,a minimum of 400 µm corneal thickness was consider safe for this procedure which was done by using AS-OCT.

According to Dresden modified protocol, riboflavin 0.1% solution was administered to the cornea at every 2 minute up to 30 minutes, followed by exposure of 370 nm UVA light (with a fluence of

3mW/cm^2) from the distance of 1 cm for 30 minutes. After PACK-CXL treatment, the eye was rinse with saline and fallowing which bandage contact lens was placed.

Contact lens was removed day after the procedure and patients were prescribed, topical antibiotics, oral NSAIDS and were followed weekly. The primary end point of the treatment was the complete corneal reepithelization with no stromal infiltrate and symptoms.

RESULTS

We enrolled 20 cases of refractory non-healing corneal ulcer in our study and divided them in two groups with 10 patients in each group. The antecedent diagnosis, duration of ulcer before starting treatment, number of antimicrobial drugs used previously and treatment duration showed a wide variation. The preop baseline characteristic and demography of the patients in each groups are summarised in table no 1A, 1B.

Table 1A: Demographic profile and clinical characteristic of Group -1 corneal ulcer Patients

Case	Age/sex	Laterality	H/O of Trauma	Duration of Symptom in Days	Previous treatment	Site of ulcer	Presence of hypopyon
1.	30/F	LE	absent	60	E/D Moxifloxacin QiD, Tobra mycin E/D qid	Central	-
2.	60/F	RE	absent	56	Moxifloxacin 1-1hour, natamycin E/D1-`1 hourly	Central	+
3.	35/M	RE	absent	66	Tobramycin E/D qid,ciprofloxacin E/d qid	Central	-
4.	30/F	LE	present	70	Fluconazole E/D qid,ciprofloxacin E/D qid	Para central	-
5.	40/M	RE	present	55	Natamycin E/d 1-1 hourly,Moxifloxacin E/D qid	peripheral	+
6.	46/F	RE	absent	75	Moxifloxacin E/D QID	central	-
7.	55/F	LE	present	67	Natamycin E/D 6 tims, fluconazole E/D 6 times a day	par central	-
8.	25/F	LE	present	54	Natamycin E/D 1-1 hourly	peripheral	-
9.	31/M	RE	absent	60	Moxifloxacin E/D qid	central	-
10.	41/M	LE	absent	65	Moxifloxacin qid	peripheral	-

TABLE 1B: Demographic profile and clinical characteristic of Group-2 Corneal ulcer Patients

Case	Age/sex	Laterality	H/O of Trauma	Duration of Symptom in Days	Previous treatment	Site of ulcer	Presence of hypopyon
1	42/F	RE	present	55	Natamycin E/D 6 tims, Moxifloxacin E/D 6 times a day	Central	-
2	48/F	RE	absent	70	Tobramycin E/D qid, Moxifloxacin E/d qid	Central	-
3	51/M	LE	absent	63	Moxifloxacin qid, Natamycin E/D qid	Para central	-
4	64/F	LE	absent	56	E/D Moxifloxaci QiD, Tobramycin E/D qid	peripheral	-
5	67/M	LE	absent	73	Natamycin E/d 1- 1 hourly, Moxifloxacin E/D qid	central	-
6	57/F	RE	absent	55	Moxifloxacin E/D qid	central	+
7	50/F	LE	present	60	Natamycin E/D 1-1 hourly, fluconazole E/D 1-1 hourly	peripheral	-
8	40/F	RE	absent	64	Moxifloxacine qid	central	+
9	47/M	RE	present	58	Natamycin E/D 6 tims, fluconazole E/D 6 times a day	central	-
10	40/M	LE	absent	70	Tobramycin E/D qid,ciprofloxacin E/d qid	peripheral	-

We treated Group-1 refractory corneal ulcer patients with topical insulin eye drops 6 hourly (with the mean age of 39.3 years). For patients in Group-1, the mean time between symptoms and start of topical insulin eye drops was 62.8 ± 14 days and the baseline mean area of non-healing ulcer was 25.45±12.01 mm^2. After starting insulin eye drops on subsequent follow up, we observed a statistically significant reduction ($p<0.05$) in the area of ulcer and complete reepithelization of ulcers were observed in all patients. The time taken for complete reepithelization ranged from 25-38 days with mean time being 35 days. We also observed a significant reduction in symptoms of patients along with improvement in final visual acuity from the baseline in all patients. Topical Insulin was thus found to be affordable, better tolerated with no adverse events were reported during treatment (Figure 1).

Group -2 patients were treated with PACK-CXL. In this group the mean symptom duration before PACK-CXL treatment was 62.4 ± 13 days and the mean area of non-healing ulcer before starting treatment was 20.58±10.63 mm^2. After PACK-CXL treatment a statistically significant ($p<0.05$) reduction were found in the areas of ulcer on subsequent follow-up period, there were observed complete corneal reepithelization in all 10 patients with the mean duration of 25.4 days (15-34 days). The final visual acuity was improved from the baseline in all patients. Thus, PACK-CXL is a promising treatment modality for the non-healing corneal ulcer with fewer complications (Figure 2).

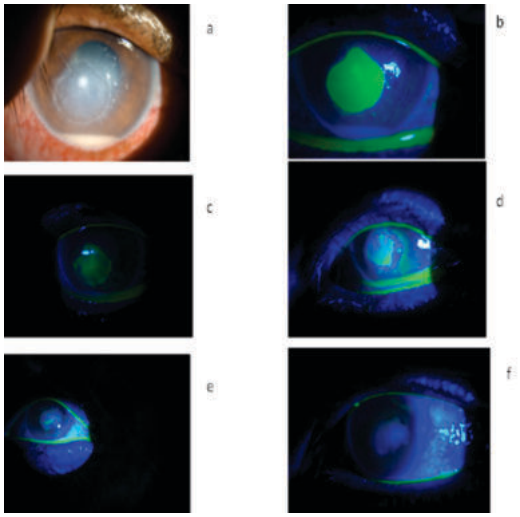

Figure 1: Slit-lamp follow-up images. A 60 years old female

developed non-healing corneal ulcer with hypopyon was treated with topical insulin eye drop. Slit-lamp photograph before starting treatment a and b. Slit-lamp images after 7 days of treatment ©, 14 days (d), 21 days (e), and 30 days (f) of topical insulin eye drop treatment are shown. After 30 days of treatment, the patient presented with complete corneal reepithelization (f).

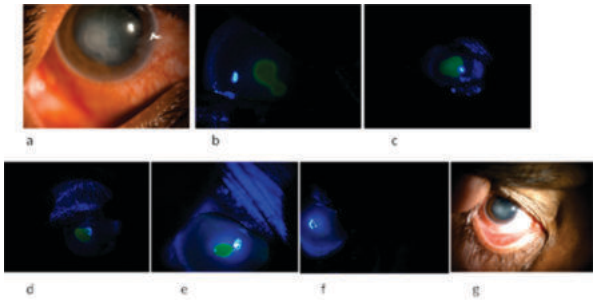

Figure: 2 Slit-lamp follow-up images. A 48 years old female developed non-healing corneal ulcer was treated with PACK-CXL. (a, b) Slit-Lamp images before starting treatment. Slit-lamp images after 1 day ©, 7 days (d), 14 days (e), and 21 days (f, g) of PACK- CXL are shown. After 21 days of PACK-CXL, the patient presented with complete corneal reepithelization (f and g)

DISCUSSION

We enrolled 10 patients in each group who developed non-healing corneal ulcer. In the current study the age of the patients ranged from the 30-60 years in Group-1 and 40-67 years in Group-2. But statistically, a non-significant difference was observed in age-wise distribution among groups (p=0.0966). David Diaz-Valle et al.[3] reported in their study that mean age of the patients was 72.2 years. Rosario Gulias et al.[8] found that the mean age of the patients were 48.24 years. In both the groups, gender wise distribution showed more females (60%) as compared to males (40%). This study finding corresponds to previous study of David Diaz-Valle et al.[3].

The mean duration of corneal ulcer before starting treatment was 62.80±6.68 days and 62.40±6.37 days in Group-1 and GROUP-2 respectively. Out of 20 patients, two patients in each group had hypopyon at the time of presentation. Whereas, Idrus et al.[9] reported hypopyon in 50% of cases and Erdem et al.[10] reported hypopyon in 23.07% of cases. According to etiology in both the groups majority of the patients had bacterial corneal ulcer followed by traumatic fungal corneal ulcer and in Group-2, two patients had neurotrophic corneal ulcer. Similarly Makdoumi et al.[11] used PACK- CXL in the treatment of bacterial keratitis. Panda et al.[12]. David Diaz-Valle et al.[3] treated patients with infectious keratitis (33%) with insulin eye drop.

In our study, according to the ulcer site, majority of patients were observed with central corneal ulcer in both the groups. This study finding corresponds to the studies of Naeima Elzelitni et al.[13]. Panda et al.[12]. The mean area of corneal ulcer before starting treatment was observed higher (25.45±12.01) mm^2 in Group-1 as compared to (20.58±10.63) mm^2 in Group-2, but statistically no significant difference (p-0.349) was observed in the mean area at baseline among the groups. 60% patients had depth of ulcer , ≥ 50% of corneal stroma while all patients of Group-2 had corneal ulcer depth ≤25% of corneal stroma, this difference is because ,we enrolled patients only with ulcer thickness ≥ 400 µm in Group-2.

Present study provides a range of time duration for reepithelization of corneal ulcers. The mean period for corneal reepithelization in the insulin-treated group was 35 days (25-38 days), while in the PACK-CXL group it was 25.4 days (15-34 days). Four patients in the Insulin-treated group demonstrated complete epithelization of corneal ulcer in 25-30 days, three in 31-35 days, and three in 36-40 days. In Group-2, three patients had complete epithelization of corneal ulcer between 14 to 20 days, six between 25 to 30 days, and one between 31 to 35 days. Overall, a non-significant difference was observed in duration of complete epithelization of the enrolled patients (p-0.103). David Dia et al.[3] observed mean area of PED before treatment was 17.6 ± 16.5 mm^2 and mean time of complete corneal reepithelization was 34.8±29.9 days. While Wang AL et al.[14] showed that addition of topical insulin in 6 patients of refractory neurotrophic corneal ulcer resulted in rapid and complete corneal re-epithelialization ranging from 7 to 25 days following initiation of treatment, this difference may be due to small sample size. After starting treatment, all the 20 eyes of non-healing corneal ulcer of both the Group-1 and Group-2 showed improvement in symptoms and reduction in the ulcer size and were completely re-epithelized.

Our data showed that final visual acuity was improved in both groups. In Group-1 majority of the patient´s baseline visual acuity (on Snellen chart) was found 6/60, while in Group-2 it was 6/24. The baseline visual acuity of Group-1 was worse than Group-2, the probable reason for this might be the depth of ulcers of Group-2 patients which were less than the ≤25% of corneal stroma. While the improvement in final visual acuity was similar in both the group, similar result was found in the study of David Dia et al.[3]

So we observed that topical insulin eye drops and PACK-CXL have ability to halt progression of ulceration and melting of corneal ulcer, may eliminate the need for emergency penetrating keratoplasty. In the presence of active corneal infection and anterior chamber inflammation, penetrating keratoplasty has greater rejection rates and more sequelae, including stromal synechiae, cataracts, glaucoma, and graft infection in that type scenario topical insulin eye drop and PACK-CXL can be a better treatment modality.

CONCLUSIONS

Topical insulin and PACK-CXL may be a simple and effective treatment for refractory non-healing corneal ulcer. Topical Insulin eye drop had no known adverse effete, economically affordable and easy to administered office based treatment, while PACL-CXL is a minimally invasive procedure, requires hospital stay and reported with complication such as post-operative pain, photophobia, dry eyes, keratitis , persistent epithelial defect and stromal melt, endothelial damage and corneal edema. Due to risk of these complication PACK-CL cannot be performed in patients with stromal thickness <400 um. This intervention may decrease the need to perform emergency penetrating keratoplasty.

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