CORNEAL COLLAGEN CROSSLINKING IN THE MANAGEMENT OF ADVANCED NON-HEALING MICROBIAL KERATITIS.

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ABSTRACT
We used CXL as a treatment modality for non-healing corneal ulcer as it strengthens the cornea, reduces risk of corneal perforation which complicate microbial keratitis.

INTRODUCTION
Infectious keratitis is a major cause of visual impairment and blindness worldwide. It is a leading cause of blindness especially in the developing world.

Microbial keratitis, also known as infectious corneal ulcer, occurs because of the proliferation of bacteria, viruses, fungi or parasites within the corneal tissues and associated with inflammation and tissue destruction. Delayed initiation of appropriate therapy can result in poor visual outcomes in up to 50% of infectious keratitis. Ocular trauma and corneal ulceration results in 1.5 – 2 million new cases of corneal blindness.

AIM
To evaluate the role and safety of corneal collagen cross linking in the management of culture proven non healing microbial keratitis.

MATERIALS AND METHODS
- **STUDY DESIGN**: Hospital based Prospective experimental study.
- **STUDY LOCATION**: The study will be conducted in OPHTHALMOLOGY department of S.M.S Hospital & attached group of hospitals, Jaipur.
- **STUDY POPULATION**: patients attending OPHTALMOLOGY O.P.D & cornea clinic of SMS hospital.
- **STUDY DURATION**: The duration of the study will be from December 2016 for 12 months or till the sample size is achieved.

SAMPLE SIZE:
Sample size was calculated 13 subjects at alpha error 0.05 and power 90% assuming difference of means to be detected in mean preoperative pain improvement (p value <0.01). Mean improvement in pain according to Wong Baker FACES pain rating scale was 2.59. There was a significant effect on pain improvement (p value <0.01).

SAMPLE PROCEDURE:
Study was conducted on 30 patients who underwent corneal collagen cross – linking.

After explaining the study, surgical procedure, and possible complications, an informed consent was obtained.

ELIGIBILITY CRITERIA
- **INCLUSION CRITERIA**: Patients with culture proven bacterial and fungal keratitis which were treated with antibiotics /antifungals and those who did not respond to at least 2 weeks of topical medications.

EXCLUSION CRITERIA:
- Patient with perforated corneal ulcer
- Endophthalmitis
- Viral keratitis
- pregnancy

DISCUSSION
Infectious keratitis is a severe ocular infection and one of leading causes of monocular blindness worldwide. The incidence of microbial keratitis ranges from 6.3 to 710 cases per year and even more common in contact lens wearers. Various micro-organisms including bacteria, viruses, fungi and parasites may cause microbial keratitis. This infection and inflammation reaction may lead to ulceration, corneal melting and perforation if not treated adequately. The increasing resistance to antimicrobial agents has contributed to a dramatic increase in keratitis related complications with devastating consequences. Therefore, current research focuses on innovative treatment option beyond antimicrobial for the management of microbial keratitis, particularly for the treatment of resistant form.

TREATMENT AFTER PROCEDURE
- **For bacterial ulcer**: Empirically F. Cefazol in 5% & F. tobramycyz in 1.3% are administered 1hourly round the clock for first 48 hours, then decreased to 2 hourly during the day & 4 hourly during night. Once healing is ensured further decreased to 4 – 6 hourly.
- **Cycloplegics**
- **Antiglaucoma drugs acc to IOP**.
- **If the infiltration resolves topical antibiotic is stopped without tapering**.
- **For fungal ulcer**: Natamycin 5% - Drug of choice for filamentous fungi.
- **Amphotericin B 0.15% - Drug of choice for candida**.
- **Topical Antifungal** to be given for at least 2 weeks after resolution of infection in all cases. Topical Voriconazole 1% - Recalcitrant fungal keratitis.
- **Topical Antifungal** are to given hourly during the day & 2 hourly during night. Once the infiltrate start resolving frequency is reduced to 2 hourly until the completion of resolution.

FOLLOW –UP: Follow up examination was done at every third days after surgery.

All the examination was performed by a single observer to avoid bias, both pre and postoperatively. During follow up, the patients were assessed for:
- Visual acuity
- Pain
In severe and unresponsive cases, it may be necessary to perform emergency keratoplasty to eradicate the infections and to preserve the eye. In patients undergoing therapeutic keratoplasty for non-healing microbial keratitis, approximately a third of transplanted grafts becomes re-infected. So always need to find an alternative to therapeutic keratoplasty when medical management fails.

Tsunagita et al showed that the combination of riboflavin and UVA causes a deactivation of the RNA in tobacco mosaic virus [10].

Martins et al opined that a combination of UVA – riboflavin has antimicrobial properties in vitro against microorganism causing microbial keratitis [9].

Iseti et al demonstrated immediate regression of the corneal melting process and a significant decrease in infiltrate size after photo activated riboflavin in corneal collagen cross linking in 5 patients with therapy resistant bacterial or fungal ulcerative keratitis [11].

Similar in our study improvement in pain according to Wong Baker FACES pain rating scale is 2.59. There was a very significant effect on pain improvement with p value <0.01. Improvement in pain by Won Baker FACES pain scale from (6.40±1.99 to 3.27±3.81).

Hirak et al demonstrate that UVA radiation (365nm) in the presence of a photosensitizer such as riboflavin and pterin derivatives induces DNA damage. After UVA absorption, the riboflavin molecules cross over to a triple state and transfer energy to generate single oxygen. Singlet oxygen and superoxide anions then react with available groups nearby [6].

Geo et al studied the effect of CXL on prevention of melting in rabbit corneas after alkali burn and found that it could prevent and delay corneal melting. They showed that CXL reduced the destruction of corneal collagen fibres and infiltration of inflammatory cells in cornea [7].

Ebers et al performed CXL for treating corneal decompensation and non-healing corneal ulcer including sterile keratitis. They reported that CXL could be effective in some cases of sterile keratitis. One of the probable hypotheses explaining such an effect is that free oxygen radicals produced during CXL may directly inactivate proteolytic enzymes or damage leucocytes thus reducing the production such enzymes.

Sperfl et al markedly increased corneal collagen resistance against enzymatic digestion by trypsin and pepsin [12].

Wollensak et al, the authors found that CXL led to an increase in mechanical rigidity of the cornea, which was more prominent in human corneas as compared to porcine corneas [8].

Makdoumi et al used photoactivated CXL as primary therapy in patients (7 eyes, 6 patients) with bacterial keratitis and reported symptomatic relief and arrest progression of melting in all cases.

In our study improvement in pain according to Wong Baker FACES pain rating scale is 2.59. There was a very significant effect on pain improvement with p value <0.01. Improvement in pain by Won Baker FACES pain scale from (6.40±1.99 to 3.27±3.81).

Panda et al treated patients with antimicrobial – refractory, keratitis-associated corneal melting with PACK CXL. The melting was halted and emergency keratoplasty was avoided in all 7 cases [9, 10].

In our study 30 patients of non-healing keratitis after treatment with CXL 60 % healed without any complication 40% has need to therapeutic keratoplasty.

Kozobolis et al presented excellent clinical outcome after photoactivated CXL in 2 patients with combined bullous keratopathy and ulcerative keratitis [10].

Skaat et al reported good results of photoactivated – CXL in the management of refractory infectious keratitis in 6 patients, whereas PACL-CXL also has been applied successfully in the treatment of fungal keratitis and post LASIK keratitis associated with corneal melt. Said et al demonstrated the beneficial effects of PACK -CXL in cases of infectious keratitis with corneal melting. In the management of infectious keratitis with corneal melting, PACK -CXL could serve as valuable adjuvant therapy. This treatment may minimise or avoid severe complications such as corneal perforation, recurrence of the infection or both. Similarly, in our study 60 % of cases healed without any complication and only 40% cases needed further management.

RESULTS
The study showed the mean age was 55.43±16.50 out of which 60% were males 40% were females. Out of a group 30 patients, 60 % are healed after the treatment and 40% was non healing, in which superficial keratitis has a better prognosis compared with deep stromal and full thickness. Mean improvement in pain according to Wong Baker FACES pain rating scale is 2.59. There was a very significant effect on pain improvement with p value <0.01(Table 1).

| Table 1- Showing pain comparison pre-operatively and post-operatively |
|-------------------------|-------------------------|-------------------------|-------------------------|
| Mean | Sd | Mean | Sd | Mean | Sd |
| Pain | 6.40 | 1.99 | 3.27 | 3.81 | 0.0001 (S) |

Mean improvement in vision in log MAR after procedure is 0.16. There was a significant effect on vision with p value is <0.05. Out of a group of 30 patients, 60 % shows epithelial healing after procedure, with mean time for epithelial healing was 24.72±8.4. 60 % patients resolved infiltrate after treatment with mean time for resolution of infiltrate was 5.27±1.48.

Graph 1- Comparison of healing according to depth of infiltration
Graph 1: 60 % ulcers healed after the treatment and 40% were non healing, in which superficial keratitis had a better prognosis compared with deep stromal and full thickness.

CONCLUSIONS
The study showed that CXL appears to be an effective procedure in treating non-healing microbial keratitis with superficial stromal involvement. CXL can be an effective adjunctive treatment and add to the armamentarium of treatment modalities in the management of resistant microbial keratitis. This intervention may decrease the need to perform emergency penetrating keratoplasty. However, more research on a large number of eyes and more randomized clinical trials comparing the safety of CXL applications to routine antibiotics are recommended.

REFERENCES