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**Research Article,**

# To Evaluate Efficacy and Safety of MMC after Excision of Ocular Surface Squamous Neoplasia with Conjunctival Autograft

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## Abstract:

**Purpose:** This study was conducted to determine the treatment of histologically confirmed ocular surface squamous neoplasia by excision with conjunctival auto graft, and Mitomycin C.

**Methods:** A clinical study of 19 eyes of 19 patients in which excision with conjunctival autograft of ocular surface squamous neoplasia was done and treated with Mitomycin C 0.04% eye drop daily for two to three alternate seven day courses according to the protocol. All patients had weekly follow-up visits till the end of the treatment course, then biweekly visits for three months, and finally monthly visits thereafter.

**Results:** The mean ± SD follow-up period was 39.4±15.3 months (range 06-56 months). Four patients (21.05%) experienced recurrence after the initial treatment; three of them responded to re-treatment and were disease-free, thereafter, till the end of follow-up. Survival analysis with Kaplan-Meier was 94.74%, non-recurrence for 36 months (mean 37.83 months with S.D of 14.73) of follow-up. All patients reported mild to moderate redness and irritation which were controlled with lubricants and mild corticosteroid eye drops. No serious ocular or systemic side effects were seen.

**Conclusion:** Mitomycin C (0.04%) drops used daily for two to three alternate seven day courses were found to be safe and effective with lower recurrence rate for ocular surface squamous neoplasia (OSSN).

**Key words:** Mitomycin C, Ocular Surface Squamous Neoplasia, Epithelial dysplasia.

## Introduction:

Ocular epithelial dysplasia is relatively a common ocular surface change with wide range of clinical manifestations. These lesions represent approximately one third of all surgically excised acquired epithelial lesions of conjunctiva. It is sequentially progressive, increasing in severity, from minor superficial epithelial dysplasia (conjunctiva or corneal intraepithelial neoplasia (CCIN) to full thickness dysplasia [carcinoma in situ (CIS)] and invasive squamous cell carcinoma (SSC). Risk factors for developing CCIN and squamous cell carcinoma are human papilloma virus (HPV), HIV infection and ultraviolet exposure etc. These lesions are usually elevated, variably shaped, and sharply demarcated from the surrounding normal tissue. These can be gelatinous, velvety or leucoplastic in appearance; less often neoplastic process may diffusely involve the conjunctiva with indistinct borders. Most of these lesions have a relatively benign course and slow progressions, but malignant behavior of squamous cells have also been reported. Excision alone of these lesions, though fairly benign, may have difficulty to achieve tumor free surgical margin/zone; which might lead to recurrence, even after many years, almost in the range of 25-53%. Cryotherapy of the margin tissue around the excised tumor region, with or without, including sclera at the site of tumor base has also been used, which decreased the recurrence rate to nearly 11%. However, the

complication rate increased due to excessive freezing of limbal corneoscleral and conjunctival tissues, ciliary body, viz.; thermal inflammatory oedema, iritis, corneal and/or conjunctival scaring with/without fibrosis, hypotony, symblepharon, sector iris atrophy, deformities of fornices and lids etc. Mitomycin C (MMC) is a non-cell cycle specific alkylating agent with extraordinary ability to crosslink DNA with high efficiency thereby inhibiting DNA synthesis, mimics ionizing radiations. Recent publications have shown the efficacy and safety of topical MMC for conjunctival and corneal squamous cell carcinoma (SCC). Due to small sample sizes of the reported studies, and the variation in the medication concentration and duration, until now, there has been no approved guideline for treatment of OSSN with MMC. Another consideration is lack of information on the efficacy and safety of MMC in the Asian population affected by OSSN. In this study using more restricted protocol suggested by Wilson and associates, we studied the efficacy and safety of MMC in Asian patients in whom previous attempts of excisional biopsy for OSSN had left surgical margin involvement, in histopathological examination.

## Material and methods:

This study was interventional case series carried out as a single institution study on 19 eyes of 19 patients who come to the hospital.

Surgical excision of lesion with conjunctival autograft was carried out and the tissue sent for histopathology. Informed consent was taken of the patients and his/her family included in the study, with follow-up for almost 60 months. We have prospectively evaluated the efficacy and toxicity of topical MMC for OSSN. MMC 0.04% was prepared by dissolving the powder content of 2mg commercially available vial for injection (Mitomycin C) in artificial tear (Carboxyl methyl cellulose) and the bottle was shaken several times. Mitomycin C (0.04%) eye drop was given four times daily for one week and then alternate i.e. at third week. All patients were trained to shake the eye drop bottle several times before application, keeping the eye closed for at least 5 minutes after instillation and closing the punctum by applying pressure using forefinger for at least 1 minute. Artificial tear drops and corticosteroid (Loteprednol 0.5%) eye drops were administered if symptoms like redness and irritation occurred. The treatment cycle (MMC 0.04% eye drops 3-4 times daily for first week, second week gap, then again on third week, and so on) was repeated until the epithelial malignancy was judged to be completely and clinically regressed, using slit-lamp biomicroscopy, with detailed anterior segment drawing and slit-lamp photography. The clinical and histopathological data including age and gender of the patients, involved eye, tumor type and initial management, if taken, were recorded at Mohan Eye Care Hospital Pvt. Ltd. (any referrals were also noted at the time of first visit). Subsequently, detailed complete ocular examination with pre-auricular and submandibular lymph node palpation was performed and recorded. All pathological and histopathological examination was done and reviewed by only one pathologist. And based on the histopathological assessment, carcinoma in situ (CIN) or squamous cell carcinoma (SCC) was defined as the tumor that breached the basement membrane and exhibited stromal invasion. During treatment period, symptomatic side effects of the medication were inquired from the patients regularly at follow-up visits, based on the comprehensive list of MMC side effects profile presented in Martindale Textbook of Pharmacology (2004). Follow-ups were scheduled weekly till the end of treatment, then fortnightly for 3 months and monthly thereafter. All patients could have emergency visits, if needed. Evaluation of treatment for any side effects and the tumor status was done on every visit. During each examination tumor, globe and systemic status were re-assessed. The main outcome measured were tumor control (defined as the absence of clinical recurrence, detectable on slit-lamp examination) and any medication related toxicity (based on the patient symptomatology as per the listed potential complications, and physical examination).

## Result:

Nineteen patients with documented histopathological diagnosis of OSSN (CIN or SCC) came to our hospital, after requisite evaluation underwent surgical excision with conjunctival autograft and the excised tissue was sent for histopathological examination.

## Sex wise distribution:

Seventeen patients (89.47%) were male & two patients (10.53%) were female.

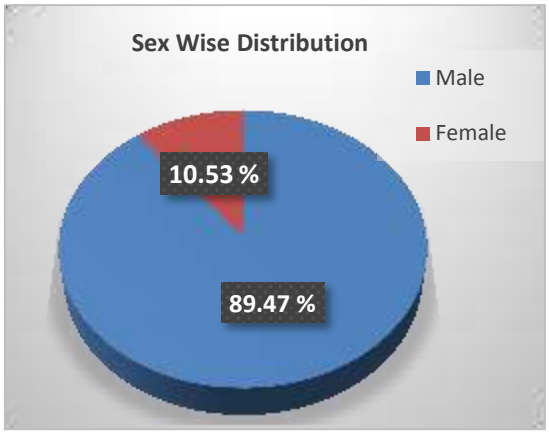


*Figure 1: Sex wise distribution*

## Age wise distribution:

Age of the patients ranged from 45 to 76 years (Mean 65.47yrs and SD 8.23).

## Eye involved:

Ten patients (52.63%) had right eye involvement, and nine (47.37%) had left eye involved.

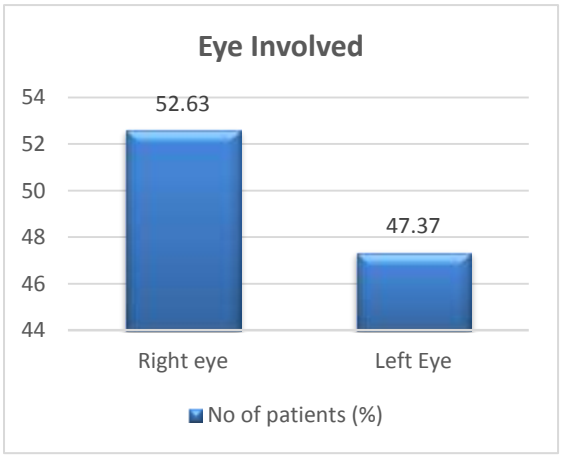


*Figure 2: Eye Involved*

## Pathological Diagnosis:

Histopathological diagnosis; 7 (36.85%) patients had CIN, 8 (42.10%) had SCC and 4 (21.05%) patients were having invasive squamous cell carcinoma.

None of the patients had any palpable lymph nodes in the head and/or neck region throughout the study.

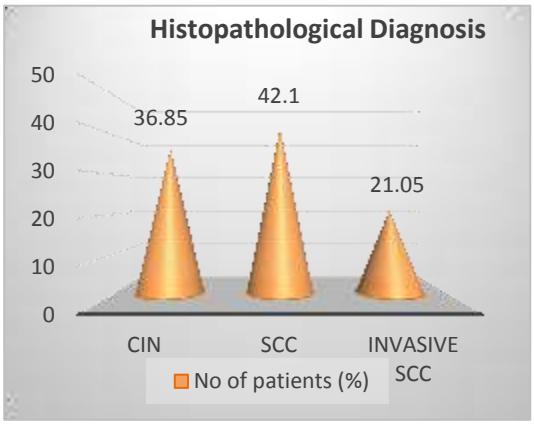


*Figure 3: Histopathological Diagnosis*

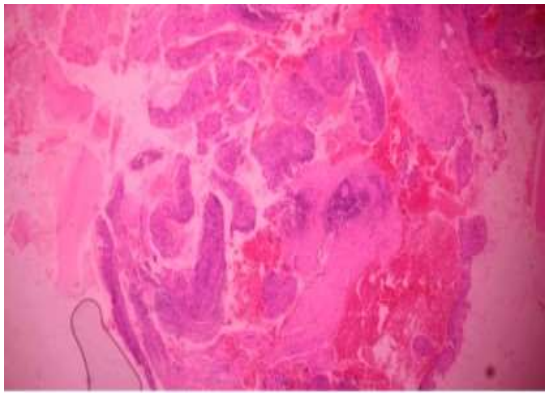

*Figure 4: Strip of epithelium with severe dysplasia*

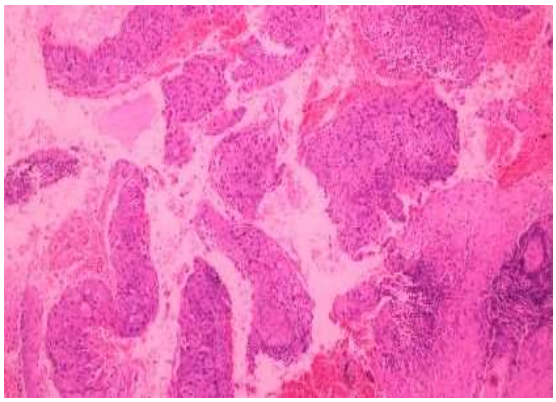

*Figure 5: Sub-epithelium showing mononuclear Cells and clusters of dysplastic cell*

## Treatment:

The management of CIN or SCC of the conjunctiva varies with the extent or recurrence of the lesion. Primarily all (19) patients of OSSN underwent wide excision with conjunctival auto-graft, followed by topical chemotherapy with 0.04% MMC. Conjunctival auto graft (CAG) taken from the healthy eye.

**Table: 1**

| No. of patients | No. of treatment cycle | Duration of treatment with MMC |
|---|---|---|
| **15** | 02 | 2 week |
| **04** | 03 | 3 week |
| **04** | Recurrence in 1st group | 3 patients responded well to re-treatment |

The follow-up period ranged from 06 to 56 months with the mean of 39.4 months and standard deviation (SD) of 15.3. Fifteen patients (78.95%) had no recurrences during the entire follow-up period; the disease free period, after initial treatment, ranged from 4 to 56 months (mean 39.8 months and S.D of 15.1). Only four patients (21.05%) experienced clinical recurrences; three were managed by just two additional 0.04% MMC courses till the end of follow-up period. In the three recurrent cases, which responded fully to re-treatment, eventually disease free follow-up period ranged from 18 to 36 months (mean 28 months and SD of 9.3). The fourth patient had recurrence of lesion after fourth month of initial treatment; however, there were signs of clinical response after fresh courses of 0.04% MMC; we considered that this case had recurrence due to treatment non-compliance. No recurrenceoccurred in the invasive SCC group. Survival analysis with Kaplan and Paul Meier method was performed for both initial response and the final outcome. Taking into account four recurrences, for 56 months, the non-recurrence rate was 78.95%. However, including 3 out of 4 cases of recurrence that responded to re-treatment, the final outcome in survival analysis was 94.74% of non-recurrence for 36 months follow-up (mean 37.83 months and S.D 14.73). All patients reported some degree of mild to moderate redness of eyes and irritation, which was controlled by artificial tear and NSAID/mild corticosteroid drops. None of the patients developed any other ocular complications reported with MMC (such as scleral melting, etc.) or any systemic complications attributable to MMC.

## Discussion:

The management of conjunctival and corneal SCC-CIN continues to evolve. Some alternative therapies to the standard surgical management include topical interferon, first described in one case by Maskin in 1994 followed by some other authors, with good results and few side effects. New modes of treatment such as photodynamic therapy (PDT) are under investigation. The classic method of excisional biopsy as defined by Shield et al. is not applicable for many patients having extensive lesions. Resecting 4mm of safety margin from the unaffected conjunctiva may cause severe ocular surface problems or may not be possible at all. Extensive partial thickness scleral bed removal may cause anterior staphyloma. Cryotherapy has its own complications and pure alcohol is highly toxic with high recurrence rates (up to nearly 53%), is also a matter of concern. Our study shows that complication and recurrence rates are greatly reduced due to excision of OSSN with conjunctival autograft. One major problem in investigations for new treatment modalities for SCC-CIN is the relatively low incidence and progression of the tumor which makes the design of double-blind randomized clinical trials (RCT) difficult. To evaluate the efficacy and safety of each mode of treatment, it seems, necessary to combine the result of several interventional case series from different ethnic groups. Another important consideration in assessing the effectiveness of treatment modalities is the risk of neoplastic recurrence many years later, which mandates long-term follow-up periods. Trend of OSSN to recur in the first few years may slightly decrease this concern. Topical MMC is a well-known drug that has been used for treatment of SSC-CIN in many studies with different results. The various results can be attributed to different drug concentration and/or treatment durations.Wilson et al. suggested the protocol of topical 0.04% MMC for seven days every alternate week. Our results show the safety and efficacy of that protocol in patients with excised SCC-CIN with conjunctival autograft. The mentioned protocol had been previously used by Shield et al. on ten patients with extensive conjunctival and corneal SCC with no recurrence at 6 to 50 month follow-up. Although four of our patients had recurrence with the initial protocol, three responded well to re-treatment with of

MMC. One of these four patients had recurrence due to treatment non-compliance and last to follow-up. Our decision on cessation of MMC courses was based on the clinical response. In cases without any apparent lesion on the slit lamp examination two alternate seven day courses were considered sufficient. Probably, if some others objective methods such as impression cytology (to assess the histopathological response) could have been utilized, our three recurrences would not have taken place. Inspite of demographic and procedural differences between our patients and the patients treated by Wilson et al. and Shield et al. protocol, our result are more encouraging. Further follow-up of these patients is warranted for more accurate assessments of the recurrence rate and long-term safety of MMC. Parenteral route of administration of MMC has a long list of systemic side effects; bone marrow suppression, profound leucopenia & thrombocytopenia, gastrointestinal toxicity, dermatitis, alopecia, fever, malaise, and cardio toxicity etc. Topical MMC, in such small doses that were used in our study is unlikely to cause any systemic side effects; furthermore we minimized the systemic absorption of MMC by punctual occlusion with forefinger pressure. None of our patients reported any complications attributable to systemic absorption of the drug.

## Conclusion:

OSSN is relatively common and a serious disease of concern. The standard methodology of treatment is wide excision with elaborate cryotherapy. However, serious complication and higher recurrence rates are the major concerns. MMC eye drop 0.04% has shown good clinical results without any serious side effects, when used as alternate seven day (weekly) course. We suggest wide surgical excision with conjunctival autograft and 2-3 courses of MMC 0.04% eye drop instead of two in all patients having OSSN; in absence of any objective method for per-operative histopathological assessments. Our protocol may result in greatly reduced complication and recurrence rates.

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