ORIGINAL ARTICLE

Comparison of Ocular Surface Squamous Neoplasia Recurrence with and without Post-Surgical Mitomycin C 0.02%

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Abstract

Background: Ocular surface squamous neoplasia (OSSN) is the most common non-pigmented ocular surface tumour that presents with a high recurrence rate after surgical excision.

Objective: The study assesses the effectiveness of topical Mitomycin C (MMC) after surgery to minimise OSSN recurrence.

Methodology: This observational, prospective, comparative study was conducted at the LRBT Eye Hospital in Karachi from January to December 2023. Histological examination of 36 patients with OSSN showed no evidence of invasive disease. These patients were then placed in one of two groups using clinical decision-making and patient preference. The first group received surgery alone, and the second group received surgery and postoperative MMC (0.02%). Patients were followed up at 1, 3, and 6 months to look for recurrence as well as complications. Statistical analysis was done using SPSS v25 and used Pearson's Chi-Square test for recurrence difference.

Results: Recurrence rates at three months were 5% in the MMC group and 22% in the control group. At six months, the recurrence rate was 11% in the MMC group while the surgery-only group was 16%. Although it was not statistically significant (p=0.335), there was a trend towards lesser recurrence in the MMC group. Postoperatively, some patients had conjunctival hyperemia (25%) and conjunctival scarring (5.6%).

Conclusion: Hence, it is suggested that adjunctive MMC may reduce OSSN recurrence after surgical excision without significant adverse effects.

Keywords: *Ocular surface squamous neoplasia, mitomycin C, OSSN recurrence, adjuvant therapy, conjunctival neoplasia.*

INTRODUCTION

Ocular surface squamous neoplasia (OSSN) represents a spectrum of dysplastic changes of the conjunctiva and cornea, clinically associated with conjunctival intraepithelial neoplasia (CIN) and squamous cell carcinoma (SCC). It occurs as the most common non-pigmented tumour of the ocular surface. OSSN is classified as a rare disease with the exception of certain geographical areas, such as sub-Saharan Africa, which reports a frequency of 3.4/1000 annually in comparison to America and Europe, reporting an incidence rate of 0.18/100,000 annually. This increase in occurrence in developing nations signifies the many environmental and immunological elements contributing to the OSSN pathogenesis [1, 2]. Such risk factors for OSSN include extended exposure to UV rays, HIV, HPV, and other chronic inflammatory diseases like allergic conjunctivitis [3].

For OSSN management, the standard approach is surgical excision employing the no-touch technique intended to prevent seeding and recurrence of the tumour. It is mostly referred to as the gold standard for localised lesions because it also allows for histopathological verification of the diagnosis and evaluation of surgical margins [4]. Despite this, the recurrence rate after surgical excision is estimated between 5% and 69% based on how thorough the excision was and factors such as operative margins being positive or high-grade lesions, which suggest more advanced illness [5]. In an attempt to reduce recurrence and treat residual disease, there has been an increasing use of adjunctive therapies such as topical chemotherapy agents and immunomodulators. The shift toward OSSN adjunctive management is evident in the increased use of adjuvants observed between 2003 and 2012, changing towards a more multi-faceted approach [6].

Mitomycin C (MMC) is the most frequently used adjunctive therapy in OSSN. MMC functions by crosslinking DNA to inhibit DNA synthesis, causing cell cycle arrest and a subsequent apoptosis of those cells actively undergoing replication [7]. Therefore, during OSSN treatment, topical MMC is applied in a post-operative setting to eliminate any residual neoplastic cells and prevent the chance of re-replication. Literature shows that adjunct MMC decreases recurrence rates compared to surgery alone, but more so with positive margins or incomplete excision [8]. The challenge, however, with this drug is the potential topical adverse events that are conjunctival hyperemia, dry eye, punctal stenosis, and corneal toxicity, which may necessitate specific patient selection to apply this adjunct appropriately [9].

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Several retrospective and prospective studies have shown the efficiency of MMC as an adjunct therapy to surgical excision. Blasi *et al*. assessed recurrence rates of surgical excision compared to excision plus adjunctive treatment with topical MMC, and excision plus subconjunctival IFN-α-2b (IFN-α-2b). The rates of recurrence were: 72% in the surgery group, 31% in the MMC group, and 15% in the IFN-α-2b group. Thus, both MMC and IFN-α-2b are effective adjunctive therapies [10]. Hirst *et al*., in a randomised controlled trial, assessed the efficacy of MMC compared to placebo in patients with non-invasive OSSN. The study found that 92% of patients in the MMC group achieved complete clinical resolution within 6 to 8 weeks, whereas none in the placebo group did [11].

Nonetheless, there is very little published information on the use of MMC in certain areas like South Asia, which have their own environmental and genetic treatment outcome modifiers. Moreover, what the optimal concentration and duration of MMC therapy is, is still being studied, with 0.02% MMC being one of the more popular regimes due to its efficacy and safety profile.

Considering the lack of regional literature, alongside the constantly changing treatment algorithms of OSSN, this study intends to assess the efficacy of adjuvant topical Mitomycin C (0.02%) for decreasing recurrence after surgical excision. This study aims to investigate whether there is a difference in the recurrence rates between patients who have had surgery and those who have had surgery with adjuvant MMC, in attempting to address the complications of possible tumour recurrence and substantiating the case for MMC use.

METHODOLOGY

A prospective, comparative, observational study of patients with primary OSSN was conducted from 1st January to 30th December 2024 at the LRBT tertiary eye care hospital, Korangi, Karachi.

The sample size was determined using the two-population proportion formula. In light of this, $P_1 = 72\%$ and $P_2 = 31\%$, where P_1 denotes the recurrence rate in the surgery-only group and P_2 the recurrence rate in the Mitomycin C group, based on a prior study by Blasi *et al*., which assessed recurrence rates between surgery alone and surgery with adjunctive topical MMC [10]. With a 5% level of significance ($\alpha = 0.05$) and a study power of 80% ($1-\beta = 0.80$) for a one-sided hypothesis, the final sample size was calculated to be 36 patients (18 in each group) using the WHO sample size calculator. This sample size was sufficient to detect a statistically significant difference in recurrence rates between the two treatment arms.

All the patients enrolled in the study signed a written informed consent. Our inclusion criteria included all histologically confirmed non-invasive OSSN occupying less than 5 clock hours. All the surgical excision was performed by a single ocular surgeon. People with recurrent disease, previously treated, those with underlying predisposing conditions like xeroderma pigmentosa, and lesions with scleral extension were excluded from this study. Patients were assigned to treatment groups based on clinical decision-making and patient preference.

All the patients were examined on a slit lamp by a single examiner. Patient's demographic data, location, size of the lesion, and laterality of the eye were recorded. The size of the lesion was measured in clock hours. All the patients underwent surgical excision under local anaesthesia. The lesion was excised superficially from the cornea and conjunctiva with at least a 2 mm safe margin from the conjunctiva. Double freeze cryotherapy was applied. All the specimens were sent for histopathology.

All the patients, including control and treatment groups, received chloramphenicol and dexamethasone 4 times a day for 2 weeks. In addition, patients enrolled in the treatment group received Mitomycin C 0.02% 4 times a day for 2 weeks. The patients were examined at months 1, 3, and 6. At each visit, the patients were examined on the slit lamp for possible complications of surgical excision, adverse effects of the drug or recurrence. Recurrence of the disease was defined as the presence of the clinical disease in the same eye after complete resolution of the lesion following primary treatment. The primary outcome measured was the recurrence rate, and the secondary outcomes were possible adverse effects of surgery.

The data analysis was conducted using SPSS version 25. Descriptive statistics were calculated for demographic variables, histopathological findings, and complication rates. A p-value less than 0.05 was deemed statistically significant. Pearson's chi-squared test was used to compare the recurrence rates between the two groups.

RESULTS

The study evaluated 36 patients who had a surgical excision performed for OSSN, with half of the patients having postoperative eye drops containing mitomycin C. The percentage of age distribution as shown in **Fig. (1)**, that 44.4% of the patients were in the range of 50-60 years, followed by 30.6% that were over 60 years, 19.4%

that were between 40-50 years and 5.6% that were in the 30–40-year age group.

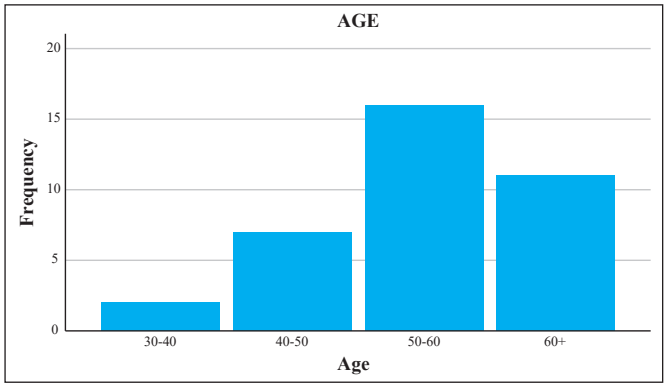

Fig. (1): Age distribution of patients.

The study had a greater number of males, as they made up 72.2% of the study group, whereas females comprised 27.8% of the total. Laterality was almost equally divided, with 52.8% of cases being from the right eye and 47.2% from the left eye, as shown in Table **1**.

Table 1: Demographic data and laterality.

Variables	Groups	Frequency	Percentage
Gender	Male	26	72.2
	Female	10	27.8
Eye involved	Left	17	47.2
	Right	19	52.8

Histopathological evaluation showed that 41.7% of cases are CIN 1, 44.4% CIN 2, and 13.9% CIN 3, as shown in Table **2**.

Table 2: Histopathology of diagnosed patient.

Histopathology	Frequency	Percentage
CIN 1	15	41.7
CIN 2	16	44.4
CIN 3	5	13.9

In the study cohort, there were two groups of patients, all of whom experienced surgery. The two groups were equally distributed; one group received treatment only through surgical methods, while the other group received postoperative treatment through the application of mitomycin C drops. Complications observed postoperatively were noticed in 36.1% of the total patients shown in Table **3**. The most reported complication that was noticed was conjunctival hyperemia (n=9), while the rest incurred conjunctival scarring (n=2) and symblepharon formation (n=2) as shown in **Fig. (2)**.

Table 3: Complications after surgery.

Complications	Frequency	Percentage
No	23	63.9
Yes	13	36.1

At the three-month follow-up, the patient who underwent surgery with post-op mitomycin had a 5% recurrence rate. This is quite lower than the 22% recorded in the surgery-only group. At six-month follow-up, the surgery with post-op mitomycin group had 11% of patients with recurrence, while the number was 16% for the surgery-only group, as shown in **Fig. (3)** Table **4**.

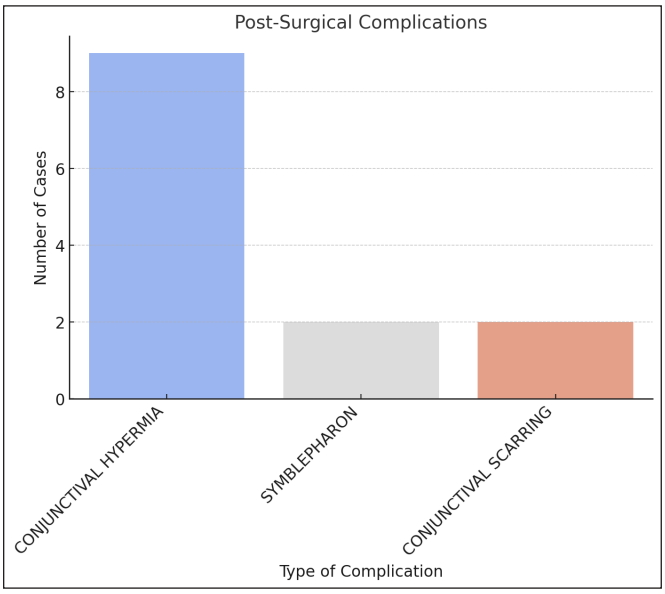

Fig. (2): Type of complication after surgery.

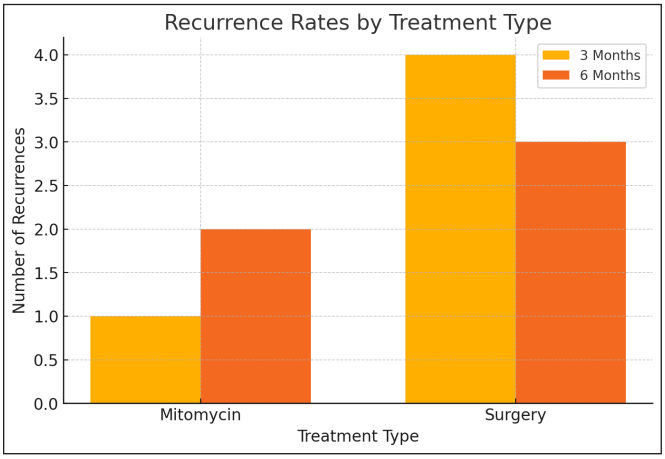

Fig. (3): Recurrence rate by treatment.

Table 4: Recurrence rates by treatment type.

Treatment type	Recurrence at 3 months n(%)	Recurrence at 6 months n(%)
MMC (n=18)	1 (5.6)	2 (11.1)
Surgery (n=18)	4 (22.2)	3 (16.7)

No significant difference was observed in the two study arms' recurrence rates as suggested by the Pearson Chi-Square (χ^2=0.93, p=0.335). Table **2** shows that the Pearson Chi-Square test found no statistically

significant difference in recurrence rates between the two groups (p = 0.335). However, the mitomycin group had a trend toward lower recurrence, indicating an apparent benefit from adjunctive mitomycin therapy for postoperative recurrence rates.

DISCUSSION

Ocular Surface Squamous Neoplasia (OSSN) represents a spectrum of neoplasms of the eye's surface epithelium with varying grades from mild dysplasia to invasive squamous cell carcinoma, frequently associated with exposure to UV rays and infection with HPV [12]. Mitomycin C (MMC), a crosslinking agent of DNA, is known to many people for being an adjunct to surgical management of OSSN, significantly alleviating recurrence and improving outcomes [13].

This prospective, comparative study aimed to assess the role of adjunctive postoperative Mitomycin C (MMC) on recurrence rates in patients with primary ocular surface squamous neoplasia (OSSN) treated by surgical excision. While there was no statistically detectable difference in recurrence rates between groups in the statistical analysis, the data gave a clear trend towards lower recurrence rates in the MMC group. At 3 months, recurrence rates in the MMC group were 5% *versus* 22% for the surgery-only group, and at 6 months, 11% *versus* 16%, respectively. Although this trend is not statistically significant, it does imply that MMC may have a positive effect on tumour recurrence.

The decrease in recurrence noted in our MMC-treated cohort has been described in the literature as well. According to Patel *et al*., adjunct therapies have significant implications for OSSN, and adjunct agents can ameliorate surgical results if there is a high probability of residual neoplastic elements [14]. Similarly, Birkholz *et al*. provided an extensive review of the existing evidence showing that MMC reduces recurrence rates from 66.7 to 5.9% when applied as an adjunct to surgical excision [15]. Moreover, a systematic review by Sayed-Ahmed *et al*. substantiates these findings by showing that the use of adjuvant MMC resulted in a significantly lower recurrence rate when compared to surgery alone, especially in patients with positive surgical margins [16].

Nonetheless, the differences in studies achieving statistical significance may be due not only to the above-mentioned confounding but also a result of differences in study designs, sample sizes and/or follow-up times. The small sample size and relatively short follow-up period in our study may have been associated with a lack of power to detect a group difference.

Histopathological findings in our sample revealed a distribution of 41.7% conjunctival intraepithelial neoplasia (CIN) 1, 44.4% CIN 2, and 13.9% CIN 3. The findings corroborate previous studies but highlight the spectrum of OSSN– from mild dysplasia to higher grade lesions, which emphasises the urgent and effective need for treatment strategies [17]. The spectrum of disease severity is coherent with the study findings of Sayed-Ahmed *et al.*, where higher-grade OSSN lesions were shown to have boosted recurrence rates and hence benefit from adjuvant chemotherapeutic agents like MMC or 5-fluorouracil (5-FU) [16]. By limiting inclusion to non-invasive lesions of less than 5 clock hours in size, we were able to specifically address a target patient population in which surgical excision with adjuvant MMC was both safe and probably more efficient in lower recurrence.

The demographic findings for our cohort further confirm established risk factor profiles for OSSN. 72.2% of the patients were male, and most of them were between 50 and 60 years old. Any factors, namely prolonged ultraviolet exposure (UVR) as well as age, gender and any suggested genetic predispositions, serve as prerequisite components leading to OSSN, in which our data corroborate the aforementioned epidemiological findings [18]. These risk factors, together with environmental factors, call for appropriate post-operative treatment strategies to prevent recurrence.

MMC, an alkylating agent derived from Streptomyces caespitosus, works by impairing a cell's DNA and blocking the synthesis of DNA and proteins in fast-growing cells [19]. Demirci *et al*. have shown that MMC is beneficial in ophthalmic oncology not only because it decreases recurrence, but also because it enhances the surgical results due to the reduction of post-operative inflammation and fibrosis [20]. Also, mitomycin C 0.02% was used continuously for 2 weeks rather than in a conventional cyclical manner. Similarly, Hirst *et al*. reported the use of MMC continuously for 3 weeks with no significant ocular complications [11]. Also, Ballalai *et al*. used MMC for 28 weeks with no break in between and reported corneal erosion in 17.4% [21]. Further studies are needed to establish the most effective regimen of MMC in OSSN treatment and to evaluate the integration of less toxic alternatives like Interferon alpha and 5-Fluorouracil, to establish an optimal management approach for OSSN.

LIMITATION AND FUTURE DIRECTIONS

Although the results of our study are encouraging, several limitations should be noted. The smaller sample size limits the generalizability of our findings. Having

a larger sample size would help increase statistical power and enable a more definitive assessment of the efficacy of MMC in reducing OSSN recurrence. In addition, the follow-up duration of 6 months may be too short to identify late recurrences. A longer follow-up duration may shed more light on the longer-term effects and possible late toxicity of MMC therapy. Also, clock hours were used as a standardised method for size estimation; this may not reflect precise lesion dimensions in millimetres. Future studies may benefit from using exact millimetre-based measurements to allow for better comparison. Another limitation is the single-centre nature of the study, which could lead to selection bias. It is recommended that multicenter studies be done in a randomised controlled style in order to confirm the findings and set treatment norms. Finally, adverse effects were reported but not graded for severity or duration, thus limiting the safety of MMC in this study.

Future research should focus on conducting larger, multicenter randomised controlled trials to confirm the clinical benefit of adjunctive MMC and determine its statistical significance in reducing OSSN recurrence. These studies should include longer follow-up periods of at least 12 to 24 months to evaluate long-term recurrences and late complications. Additionally, studies comparing different concentrations and dosing regimens of MMC could help establish an optimal treatment protocol that balances efficacy with safety. Comparative studies with other adjunctive agents, such as interferon alpha or 5-fluorouracil, would be valuable in determining the most effective and tolerable therapy. Development of risk stratification tools and predictive models based on histological and clinical features could help tailor therapy to individual patients. Lastly, further investigation into regional environmental risk factors, molecular biomarkers, and treatment adherence in South Asian populations is needed to improve OSSN management in diverse healthcare settings.

CONCLUSION

This study yields helpful information regarding the additional adjunctive use of mitomycin C in combating OSSN recurrence rates after surgical excision. Although these findings did not reach statistical significance, the observed trend towards reduced recurrence in the MMC-treated group indicates a hugely favourable clinical benefit. Mitomycin C remains one of the effective adjunctive agents, when used properly, that can enhance the outcomes of surgical interventions without compromising patient safety. Given its potential, further research with larger sample sizes, longer follow-up periods, and multicenter investigations is needed to establish definitive guidelines for MMC in the management of OSSN. Moreover, further investigations of MMC with additional adjuvant treatment options, like 5-fluorouracil or interferon alpha-2b, are necessary to create an even more effective treatment regimen for patients with OSSN.

ETHICAL APPROVAL

Ethical approval was obtained from the Ethical Review Board (ERB) of Layton Rahmatulla Benevolent Trust, Karachi (REF letter No. LRBT/TTEH/ERC/4501/12). All procedures performed in studies involving human participants were performed following the ethical standards of the institutional and/ or national research committee and with the Helsinki Declaration.

CONSENT FOR PUBLICATION

Informed consent was taken from all participants.

AVAILABILITY OF DATA

Upon fair request, the appropriate author will provide the data set.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Declared none.

AUTHORS' CONTRIBUTION

Dr. Hamama Barry: study concept, designing, manuscript drafting, critical review and revision of initial draft.

Dr. Zeeshan Kamil: Study concept, critical review

Dr. Maham Sultan: Result analysis

Dr. Saeed Iqbal: Revision of initial draft

Dr. Arfa Shaikh: Study concepts, manuscript drafting

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