Original Research Article

To study the effect of topical Mitomycin C as an adjunct in ocular surface squamous neoplasia

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Abstract

Background: Ocular surface squamous neoplasia (OSSN) in a broader terminology newly introduced in the field of ophthalmology that includes conjunctival malignancies which ranges from mild epithelial dysplasia to invasive squamous cell carcinoma. The routinely used topical chemotherapy for OSSN is mitomycin C (MMC), 5-fluorouracil, interferon-alpha, and cidofovir, and among these, MMC is usually preferred by most of the ophthalmologists because of its cost-effectiveness and lesser side effects. **Aim:** The aim of study was to evaluate the role of MMC as an adjuvant therapy in the management of OSSN. **Methodology:** Patients in the age group of 40 years and above with a diagnosis of OSSN were included as our study subjects. The diagnosis of OSSN was made based on the clinical presentation. A total of 20 patients with OSSN were taken as our study subjects. The tumor was surgically removed in toto along with 3–4 mm of uninvolved conjunctiva. Further, 0.4 mg/ml of MMC was applied over the excised site. Postoperatively, 0.04% MMC eye drops were given for 2 weeks with a dosage of 4 times/day. **Results:** Postoperatively, only single patient (4%) had recurrence which had developed after 6 months.. Other postoperative complications that had occurred were one patient had allergic conjunctivitis and the other patient had punctate erosion. Rest all patients were have no symptoms after the procedure and application of MMC. **Conclusion:** The topical use of MMC eye drop in the concentration of 0.04% has shown superior clinical results without any side effects and with a very few recurrence rate during the follow-up period of 1 year.

Keywords: Mitomycin C, opthalmology, ocular surface squamous neoplasia, recurrence rate

Introduction

Ocular surface squamous neoplasia (OSSN) is a spectrum of benign, pre-malignant and malignant unilateral less progressive epithelial lesions of the conjunctiva and cornea. Ocular surface squamous neoplasia term was first given by Lee and Hirst. The aggravating factors are ultraviolet light exposure, human papilloma virus (type 16) infection, AIDS, xeroderma pigmentosum, stem cell therapy, genetic predisposition, smoking and immunosuppression. According to theory of Lee and Hirst, it states that any alteration in the limbal stem cells may lead to abnormal epithelial maturation and metaplasia. It usually occurs in the inter palpebral fissure, typically at the limbus, even though it may be found elsewhere. It is usually seen in late adulthood life with ocular irritation or a mass. These lesions are also seen in young adults, with sign and symptom like xeroderma pigmentosa and HIV infection[1-3].The lesions appear clinically as gelatinous, leukoplakic, papilliform, nodular or disseminate, and may be flat or elevated[4,5]. A feeder vessel is occasionally presentThe diagnosis is most often made by clinical examination.To get definitive diagnosis incisional or excisional biopsy[6, 7] and fine-needle aspiration biopsy, have been to be done. The conventional therapy for OSSN is wide surgical excision and cryotherapy. However, there is high recurrent rates of up to 50%[8,9]. It has been seen in some cases multiple consequences such as destruction of normal limbal stem cells and conjunctiva causing corneal neovascularization and symblepharon formation. Adjunctive therapies such as beta radiation[10], immunotherapy[11, 12] and topical chemotherapy[13,14] have been used in an to decrease the recurrences and to prevent or minimize scarring from repeated surgeries.

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Topical mitomycin C MMC has been used for the treatment of OSSN since 1994 by several investigators[14-20]. They reported favourable results from using various concentrations and durations of MMC for the treatment of primary and recurrent OSSN. Due to very high recurrence rate, conservative medical treatment is gaining fast popularity It is mainly done by means of topical chemotherapy. The regularly used agents are mitomycin C (MMC),5fluorouracil, interferonalpha, and cidofovir. Among all these, MMC is usually chosen because of its cost effectiveness and few side effects[8]. Its action is by inhibiting the production of DNA, thereby inducing cell apoptosis and necrosis. It also act by suppressing the cellular RNA and protein synthesis[9,10]. The application of topical chemotherapy after surgical excision had revealed a momentous reduction in the recurrence rate of OSSN.

Aim

The aim of the study was to evaluate the role of MMC used as an adjuvant therapy in the management of OSSN.

Methodology

A prospective study was conducted on 20 subjects. The study was approved from the ethical committee and the consent of all was taken. The patients in the age group of 40 years and above were included in the study with a diagnosis of OSSN. A detailed history on demographic details, symptoms and its durations, exposure to risk factors were taken. The diagnosis of OSSN was done on the clinical examination and the cytological picture. Patients having lesions with scleral involvement, intraocular and orbital involvement, and any ocular diseases,systemic illness such as HIV or any other immunocompromised conditions; and pregnant women were excluded from the study. The subjects included in study were diagnosed cases of OSSN by slit-lamp bio microscope and OSSN with < 5 clock hour involvement/15 mm in diameter. Clinical examination of the subjects included visual acuity, refraction, anterior segment, evaluation for shape, size, extent mobility of the lesion, anterior chamber reaction,

involvement of cornea, sclera, fluorescein, and 1% rose bengal staining under slit-lamp biomicroscopy. The appropriate protocol for treatemnent of OSSN is surgical excision of the lesion with a 3 mm of healthy rim, using no irrigation and single touch technique. After removal of tumour, cryotheraphy was done to the cut end of conjunctiva under surface for 20 seconds and the cornea and limbus for 10 seconds using double freeze thaw technique. The ocular surface was left to heal or amniotic membrane grafting was done if the ocular surface defect was more than 25 × 25 mm. On confirming epithelial healing, topical Mitomycin C 0.04% four times a day to all postoperative patients in 3-4 cycles of alternate on and off weekly courses was advised. Preoperative topical Mitomycin C was used in cases of large mass or when surgery had to be postponed. Patients were called for follow up weekly after the start of treatment protocol and monthly after treatment ended. At the time of each visit, slit-lamp examination with rose bengal 1% and sodium fl uorescein 1% drops was performed along with routine examination for recurrence of tumor and corneal alterations like keratitis or erosions.

Tables

Table 1: Agewise Distribution

No	Age (yrs)	No	Percentage(%)
1	40-50	3	15
2	51-60	10	50
3	61-70	6	30
4	71-80	1	5

Table 2: Genderwise Distribution

Sr No	Gender	No Of Subjects	Percentage(%)
1	Male	12	60
2	Female	8	40

Table 3: Symptoms of OSSN

Sr no	Symptoms of OSSN	No No Of Subjects	Percentage(%)
1	Foreign body sensation	3	15
2	Foreign body sensation+mass per eye	6	30
3	Mass per eye	8	40
4	Injury+redness	2	10
5	Redness	1	5

Table 4: Duration of presentation of OSSN

Sr No	Duration of presentation of OSSN	No Of Subjects	Percentage(%)
1	<2 weeks	1	5
2	2 weeks-<2 months	4	20
3	2 months-<4 months	2	10
4	4 months-<6 months	6	30
5	>6 months	7	35

Table 5: Risk factors in OSSN

Sr.No	Risk factors in OSSN	No Of Subjects	Percentage(%)
1	Sunlight	5	25
2	Sunlight+smoking	4	20
3	Smoking	8	40
4	Petroleum products	3	15

Table 6: Marginal clearance post-surgery

Sr no	Margin showing dysplasia	No (%)
1	Free margin	7 (35%)
2	At least one margin	9(45)
3	With two margin	4(20%)

Results

The study was conducted on 20 patients with OSSN with age group from 40 years to 80 years. Four group were made of 40-50 years,51-60 years,61-70 years,71-80 years.Youngest patient in the study was of 45 years and oldest patient was of 73 years. There are 3 subjects in age group of 40-50 years with 15% of all subjects, while of 51-60 years are 10 (50%),61-70 years are 6(30%),and last 71-80 are 1(5%).Among 20 subjects 12 are male 60%,while 8 are female 40%.(Table1,2). The OSSN show symptoms like Foreign body sensation in 3 subjects(15%),

Foreign body sensation and mass affecting 6 subjects(30%),only mass was seen in 8 subject with maximum of 40%.While injury and redness was seen in 2 subjects (10%) and only redness was seen in 1 subject.(5%).(Table 3). The duration of OSSN was considered in the study,out of which more than six months was seen in more subjects ie 7 (35%), less number of subjects were seen in less than 2 weeks ie 1(%). 4 subjects were present in 2 weeks -4 weeks duration with 20%,whereas 2 and 6 subjects were seen in 2 month -4 months and 4month -6 months with 10% and 30 % respectively.(Table 4). The causative agent of OSSN are many out of which only four risk factors were included in the study smoking was seen more in 8 subjects (40%),while sunlight was seen in 5 (25%) subjects, Petroleum products in 3 (15%) subjects, and in 4 subjects (20%) sunlight and smoking was the risk factor for causing OSSN.(Table 5). The post surgical marginal clearance was also considered in the study at least one margin was seen in more subjects 9 (45%) and margin clearance with dysplasis of two margin was seen in less number of subjects.(Table 6).

Discussion

Ocular surface squamous neoplasia (OSSN) in a broader terminology newly introduced in the field of ophthalmology that includes conjunctival malignancies which ranges from mild epithelial dysplasia to invasive squamous cell carcinoma (SCC). The frequent chemotherapy agent used for OSSN are 5 flurouracil, MMC, or interferon. Considering the cost factor and least adverse events, we preferred MMC as an adjuvant therapy along with surgical excision for assessing its efficacy in the treatment of OSSN. The study was done 20 subjects out of there were more number of male subjects as compared to female subjects which was similar to study done by other authors[21,22]. The risk factors affecting OSSN are sunlight, smoking, petroleum products ,almost all sunlight and smoking was the main risk factor of OSSN in our study which was similar to other studies[6,23]. The symptoms seen in OSSN are foreign body sensation, mass per eye, tumor, redness, injury, foreign body sensation and mass ,Redness and injury were included in the study .Out of these maximum number of subjects included with symptoms were matching with the study compared with other reports published. The duration of OSSN was also included from less than 2 weeks to 6 months which was also similar to other studies comparing the number of subjects involved. Prabhasawat et al[20]. The Primary treatment for OSSN is surgical excision of lesion, as it is impossible to exclude invasive disease on clinical grounds or with impression cytology Inspite the effort to excise the tumor with a wide healthy rim, only three cases (35%) had marginal clearance which was similar to study done by Shashikala Puttaswamy et al[24]. As considering various topical agents Mitomycin C, an alkylating agent which acts by inhibiting DNA synthesis and produces cell death by apoptosis and necrosis was preferred as adjunct in ocular surface squamous neoplasia[15]. As this drug has a privileged action for rapidly dividing cells, acts as a important antitumor agent and since 1994.A several groups have reported that use of MMC in the treatment of both primary and recurrent OSSN is very beneficial.

Conclusion

OSSN is relatively common and a serious neoplastic disorder reported in the ophthalmology department. The standard method of treatment is wide excision, which commonly results in a high recurrence rate. The use of MMC eye drop in the concentration of 0.04% has shown good clinical results without any serious side effects and with a very less recurrence rate .More number of large sample multicentric studies with a longer follow up period is warranted to substantiate our findings.

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