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Outcomes of Post-Operative Topical Bevacizumab in Primary Pterygium Surgery: A Case Series

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Abstract

Background: To determine the efficacy and tolerability of topical bevacizumab as an postoperative adjunct in reduction of recurrence following primary pterygium surgery with conjunctival graft at a two year follow up.

Methods: Prospective, non randomized case series. Twenty three consecutive patients with primary pterygium, without any ocular or systemic contraindication to bevacizumab were recruited for the study, with informed consent. All patients underwent primary pterygium excision with rotational conjunctival autograft. Postoperative regimen included plain antibiotic eye drops, preservative-free artificial tears from post operative day 1 and topical bevacizumab (1.25 mg/day), from day 4 postoperatively, q.i.d, for 30 days. Primary outcome measure: Recurrence of pterygium and side effects of treatment.

Results: Mean age: 43.12 ± 3.24 years; The mean follow-up was 34.25 ± 2.4 months. Eleven patients were available for the 3 year follow up. None of the patients had a recurrence till the end of follow up. Post operative sequelae of surgery included dellen (2), hyperemia (1) and foreign body sensation (4), all managed. No side effects of topical therapy were noted (dellen occurred before starting bevacizumab therapy).

Conclusion: Topical bevacizumab is a potentially useful, convenient and safe therapy as an adjuvant to pterygium surgery. Its safety and efficacy can be further verified with the help of a randomized trial.

Keywords: Pterygium; Bevacizumab; Recurrence; Topical

Introduction

Recurrence of pterygium [1] following primary pterygium excision with conjunctival autograft is a common sequel that can be frustrating, both to patients and the operating surgeon. Numerous methods have been described to reduce the recurrence rate, such as topical mitomycin C [2], 5-Fluorouracil [3] and irradiation. These wound modulators also carry complications such as scleral thinning, corneal damage and consequences of radiational exposure.

Vascular Endothelial Growth Factor (VEGF) levels are known to increase during the healing response post inflammation, with the peak reaching around day 7 [4-7]. Bevacizumab (Avastin, Genentech) has been shown to have numerous beneficial off label uses with respect to systemic and ocular disease, most notably in wet age related macular degeneration. It has been shown to be relatively safe, though untoward ocular and systemic side effects have been reported. Considering that primary pterygium, is a fibrovascular proliferation combined with subconjunctival elastotic degeneration [1] and that VEGF levels have been shown to be increased in pterygia and post inflammation [5], anti VEGFs have been used in treating primary and recurrent pterygia using different modes of administration [7-13]. Peak VEGF levels during the healing response have been found around day 7 post surgical or non surgical insult and subsequent inflammation, and this continues to day 30, when it gradually dies down [4,14]. Topical bevacizumab has been suggested for impending pterygium recurrence [10]. The aim in prescribing topical bevacizumab starting post operative day 4 and continuing for a month was to study in a preliminary manner. The outcomes of topical bevacizumab started in and around the peak VEGF secretion on pterygium recurrence and the side effects of topical bevacizumab therapy.

Materials and Methods

This was a prospective, non-randomized uni-centric, case series, carried out from 2007-2009, and included twenty three consecutive patients with primary pterygium. One eye of each patient was randomly selected for the study, in case of bilateral pterygia (Figure 1). All patients had either a unilateral or bilateral primary pterygium, with no other associated ocular or systemic disorder, and were scheduled to undergo pterygium excision with conjunctival autograft. The Ethics Committee consented for the study.

Except for the primary pterygium, none of the patients had any

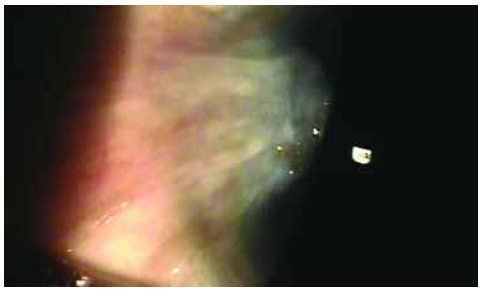

Figure 1: Shows a preoperative photograph of a patient scheduled for surgery.

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systemic or ocular disease. All underwent a slit lamp and fundus examination (both eyes) along with the best corrected visual acuity (BCVA-both eyes). Schirmer's test 1 and basic secretion test along with the tear film break up time (TBUT) test were carried out. Systemic investigations included blood pressure measurement, prothrombin time, clotting time, bleeding time (all to rule out any hemorrhagic tendency), fasting and post prandial blood sugar levels, hemoglobin levels, total and differential white blood cell count (to rule out systemic infections) and erythrocyte sedimentation rate determination by the Westergren Method. Urinalysis was also carried out (gross and microscopic). A physician reference was also included as part of the preoperative examination protocol.

Informed consent was obtained from the patient, after a detailed explanation about the procedure, the topical regimen and side effects, cost (cost of treatment was borne by the patient) and outcomes. Informed consent about clinical photography on the condition of anonymity was also taken.

A standardized surgical technique performed by a single surgeon (AAS) was used to excise the pterygium. After topical anaesthesia, an initial nick was made in the region of the head of the pterygium, between the head and underlying cornea, with a 15 no. blade attached to a Bard Parker knife handle, to define the plane of dissection.

Further dissection was carried out using a crescent knife (Alcon Laboratories Inc, Fort Worth Texas.), ensuring adequate depth to clear the pterygium tissue *in toto* and at the same time ensuring that excessively deep dissection was avoided. Dissection was carried further into the limbal and scleral region, and the pterygium tissue excised.

The area of the defect in conjunctiva, following pterygium excision was measured, and an appropriately sized graft was taken as a rotation flap from the superior conjunctiva, and secured in place using 10-0 nylon sutures. Sutures were rotated at the end of the procedure to bury the knots. Cautery was not used at any stage. A patch was placed on the eye for two hours, in case of any minor bleeding from the conjunctival vessels. Follow ups were scheduled on post operative day 1, day 7, day 30, day 90, day 180, at one year, at eighteen months and finally twenty four months post operatively. Careful documentation, including serial photographs was performed to check for recurrence and other side effects. Patients were asked to report immediately if they had any ocular or systemic complaints. The postoperative topical drug regimen consisted of Antibiotic eye drops (moxifloxacin) were prescribed q.i.d, tapered over four weeks. Topical preservative free artifical tear eye drops (carboxymethyl cellulose 1%) were prescribed four times a day for 4 weeks, then reduced to an s.o.s. basis and topical bevacizumab (1.25 mg/ml; a total of 4 ml-prepared under sterile conditions) eye drops, four drops a day for 30 days, from postoperative day 4. The stability of bevacizumab over time when stored in appropriate conditions has already been studied and is proven [15]. Bevacizumab was prepared and diluted with 0.9% normal saline under validated aseptic conditions and stored at 2-8°C as recommended by the manufacturer [16]. The copy of the manufacturer's recommendation [16] was provided to the patient for further clarification of storage details and as a part of the informed consent to explain the potential side effects of the drug.

Punctual occlusion for five minutes was practiced after each drop. Patients were explained appropriate spacing between drops (a five minute gap) when more than one different topical medication was to be instilled simultaneously. In case the patient had an intra-operative event such as dellen formation, bevacizumab was started after resolution of the same, as the effect of bevacizumab on dellen healing is not known.

Suture removal was done at the end of 30 days. Patients were explained and given detailed written information on the potential complications of bevacizumab therapy and asked to report immediately at the slightest doubt of any complication.

The outcome measures were the recurrence rate of pterygium post operatively, and the side effects of the topical bevacizumab therapy. Recurrence was defined as observing at least one of the following in the area of excision: Re-growth of any fibro-vascular pterygium-like tissue crossing the limbus onto the cornea, fibro-vascular recurrence attaining the same degree of corneal encroachment as the original lesion, or re-growth exceeding 1 mm onto the cornea.

Results

The mean age of the patients was 43.12 years ± 3.24 years (range-35-49 years). The main indication for pterygium excision was cosmetic (seventeen patients), followed by visual disturbance (two patients, secondary to induced astigmatism). The remaining four had both cosmesis and visual disturbance as a chief complaint. Nineteen patients were available for a minimum follow-up of two years, with 11 of these patients available for follow up at the end of three years (Figure 3). The remaining four patients were only available for a mean follow up of 15.50 ± 4.2 months and were excluded from the analysis. However, none of these four patients had had a recurrence till the end of their follow up period. The mean follow-up was 34.25 ± 2.4 months (Figure 2). The mean preoperative best corrected distance visual acuity was 0.08 ± 0.09 log MAR units. The mean postoperative best corrected distance visual acuity was 0.05 ± 0.04 log MAR units.

The mean pterygium size as measured intra-operatively using a microscope reticule (measured from the posterior border of the corneal limbus to the apex of the pterygium) was 2.75 mm ± 1.25 mm (range

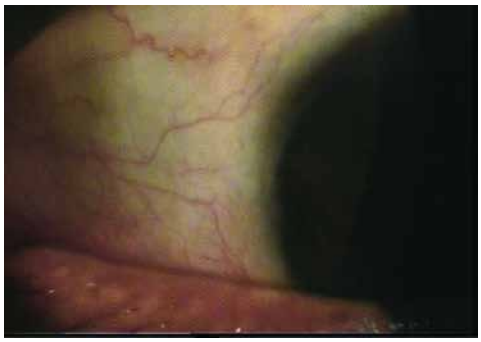

Figure 2: Shows the same patient at the 3 month follow up, i.e. two months after completion of bevacizumab therapy.

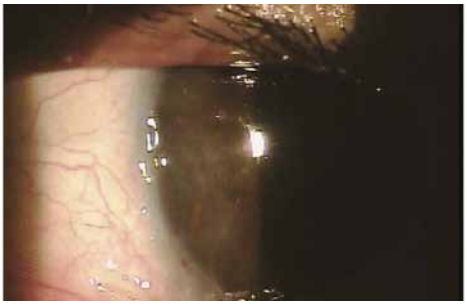

Figure 3: Shows the same patient at the three year follow up.

1.5 mm to 4.50 mm). None of the patients had a recurrence of the pterygium at the end of the respective follow up period.

One patient developed dellen postoperatively; he was started on intense lubricating therapy and the dellen resolved in ten days. He was started on bevacizumab therapy on the eleventh post operative day. One patient developed hyperemia and mild pain in the operated eye in the region of the autograft two months post operatively; he was put on flurbiprofen eye drops for four times a day for one week and symptoms resolved.

Four patients experienced a foreign body sensation from one week onwards post operatively, that persisted even after suture removal. Topical lubricant therapy was increased to four times a day up to two months post operatively, and the complaints reduced in all. There were no further complaints even when the topical lubrication was reduced to an OD dose.

None of the patients had any major ocular or systemic complication, such as scleral necrosis or systemic bleeding.

Discussion

Recurrence of pterygium is not an uncommon entity and is extremely frustrating for the surgeon as well as the patient. Numerous methods have been suggested for decreasing the recurrence rates, with varying degrees of success. These include, surgically, conjunctival and limbal autografts, and medically, the use of mitomycin C, beta irradiation and so on. However, surgical therapy is not foolproof as damage to the limbal stem cells while transplanting them can negate the efforts made to reduce recurrence, and medical therapy is not without side effects. Moreover, limbal stem cell transplant, combined with auto-grafts, does not always give noticeably better results in terms of preventing recurrence. Also, surgical treatment of pterygium with auto-grafts, with or without adjuvant anti-metabolite therapy, has been reported by various authors to have recurrence rates up to 39% [17-20].

Bevaciuzmab has been used in the scenario of an impending recurrence of pterygium [8]. Intralesional bevacizumab, without surgery, has also been reported to reduce pterygium size [9]. Multiple [7] sub conjunctival injections are cumbersome and potentially risky, as there is a chance, albeit minimal, of penetrating the sclera, a risk that is avoided by topical therapy. The subconjunctival route provides a depot from which systemic absorption and subsequent systemic complications are potentially possible. This is not to say that topical therapy does not result in systemic absorption of bevacizumab, but with punctal occlusion, the amount of drug absorbed systemically is significantly reduced. While earlier reports [7] demonstrated a good outcome with sub-conjunctival injections, a recently published study showed no difference between placebo and post surgical sub-conjunctival bevacizumab therapy, with recurrences occurring as early as nine months in spite of sub-conjunctival bevacizumab [17]. Our study, on the other hand, shows good outcomes in this relatively small case series on the usefulness of topical bevacizumab in primary pterygium surgery. We cannot comment on the early recurrences noted with subconjunctival therapy, as we have not used it thus far. The author believes, to the best of his knowledge, that this is the first study that incorporates into the topical regimen bevacizumab routinely post primary pterygium excision, starting day 4 postoperatively. Starting bevacizumab on day 4 also provides time for re-epithelialization, should there be epithelial irregularities induced secondary to pterygium excision, as the effect of bevacizumab on epithelial healing is, as yet, unknown.

Bevacizumab therapy has been shown to have off label uses in ocular disease processes. Some of its known complications are vitreal hemorrhage, stroke, bleeding tendencies and so on. Hence post topical instillation, patients were asked to practice punctal occlusion, to avoid systemic side effects, and all patients were explained in detail the symptoms of both the ocular and systemic complications to ensure they reported early, if need be.

There were no major side effects (the dellen noted resolved with intense lubrication and had occurred prior to bevacizumab therapy), either ocular or systemic, in any of the patients recruited for the study. The limitation of our study was of course the small sample size, thus suggesting the need for further studies with larger sample sizes, as would be required to influence practice patterns.

This preliminary study showed that topical bevacizumab therapy from post operative day 4 appeared to be a safe alternative as an adjunct to primary pterygium at least for the duration of the follow up period in all the recruited patients. Blunting the VEGF secretory peak probably neutralizes the fibrovascular response of recurrent pterygium. Bevacizumab therapy offers the potential of an effective adjuvant with no or minimal side effects. A larger clinical trial would be helpful in affirming this observation, and proving that this result is not due to chance.

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