Subconjunctival Bevacizumab Injection in Treatment of recurrent Pterygium

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حقن مادة ال بيفا سيزوماب تحت المنظمة لعلاج عودة ظفرة العين بعد الاستئصال الجراح

ملخص : دراسة استكشافية تمت في مستشفى الحكيم العام في النجف الاشرف لدراسة تأثير وفاعلية حقن مادة البيفا سيزوماب تحت المنظمة لعلاج حالات 100 مريض يعانون عودة ظفرة العين بعد استئصالها جراحيا. تمت مراقبة المرضى لفترات لا تقل عن 6 أشهر بعد اخر حقنة، لم تسجل خلال فترة البحث أي أضرار أو اعراض جانبية لحقن العقار كما أثبتت الدراسة فاعليته للعقار في تحجيم وتخفيض لون الظفرة واحتفالها مع الحد من نمو حجمها وامتدادها على القرنية.
Abstract:

**Objective:** to determine the clinical effect of subconjunctival injection of bevacizumab regression or halting growth in patients with recurrent pterygium.

**Method and materials:** The study was an off-label; 2-dosing, interventional case series involving 20 patients with recurrent pterygium. They received subconjunctival bevacizumab (0.2ml/2.5mg). Vascularity and thickness of pterygium were graded. Size of pterygium (measured by surface area in cm²) was recorded from baseline to 6 months after injection. Treatment-related complications and adverse events were reported. Main outcome of measurements was the change in grading, size, vascularity, thickness, color intensity.

**Results:** 9 males (45%), 11 females (55%) of 20 patients were conducted in study with a mean age of 50.46 ± 18.30 (range 38-70). There was a significant reduction in grading with significant difference in the mean surface area of pterygium at different intervals (P=0.05) and the size of pterygium was reduced. The reduction of color intensity was significant (P=0.031). No significant topical or systemic adverse reactions were recorded.

**Conclusions:** Subconjunctival bevacizumab injection is useful in management of patients with recurrent pterygium without significant local or systemic adverse effects.

**Key Words:** subconjunctival Bevacizumab, recurrent pterygium
**Introduction**

Pterygium is a triangular sheet of fibro vascular tissue that invades the cornea (1, 2). It occurs in the interpalpebral fissure, more common on the nasal side of the eye and often bilateral (1- 3). Physicians have known pterygia for thousands of years (2, 4-6) but the pathogenesis of pterygia is not fully understood (7-10).

Various studies have implicated environmental factors, such as ultraviolet light, chronic irritation, and inflammation. Recent studies have also provided evidence implicating genetic components, antiapoptotic mechanisms, cytokines, growth factors, extracellular matrix remodeling, immunological mechanisms, and viral infections in the pathogenesis of the disease (7-11).

Vascular growth factors such as vascular endothelial growth factor (VEGF) have been detected in pterygium (12-15). There is marked elevation of VEGF in pterygia in comparison to normal conjunctival samples (12-15). Although the pathogenesis of pterygia is still poorly understood, their formation and progression are known to depend on neovascularization. It has been postulated that the development of pterygia depends on a changed angiogenic stimulator-to-inhibitor ratio. Jin and colleagues showed that pterygia contain drastically decreased levels of pigment epithelium-derived factor, angiogenic inhibitor, and elevated VEGF levels (15).

The treatment of pterygium is still controversial, with various treatments being advocated in the scientific literature (16). As pterygia is composed of proliferating fibrovascular tissue and its formation and progression require neovascularization (17-18), many molecules that positively regulate angiogenesis have been identified, suggesting that growth factors may be involved directly or indirectly in the pathogenesis of pterygia.

Bevacizumab (Avastin) is a full-length, humanized, monoclonal antibody against all types of VEGF. It binds to and neutralizes the biologic activity of all types of human VEGF, so it prevents interaction with its receptors on the surface of endothelial cells (17). Bevacizumab has been used to treat choroidal neovascularization due to age-related macular degeneration (ARMD), and more recently diabetic macular edema. Various clinical trials have shown that when administered intravitreally, it is well tolerated and associated with improvement in visual acuity, decreased central retinal thickness, and reduction in angiographic leakage (18-20). This study determined the clinical effect and safety of subconjunctival injection of bevacizumab for recurrent pterygium.

Once validated, this technique may obviate the need for surgery as well as provide an alternative form of therapy for recurrent pterygia that is simpler, faster, and easier to perform compared to existing methods of pterygium removal.

**Patients and Methods**

This off-label, 2-dosing, interventional case series was conducted in patients with recurrent pterygium from March 2010 to July 2011. 20 patients, 9 males (45%) and 11 females (55%) are involved with a mean age of (50.46 ±18.30 years), range (38-70) (table 1).

Each pterygium was measured and graded according to Tan and coworkers’ grading scheme proposed in 1997(21). Grading was based on the visibility of the underlying episcleral blood vessels. This has been previously described and validated as a marker of severity. The pterygia were classified into grades 1, 2 and 3 based on slit lamp evaluation.

Grade 1 (“atrophic”) had clearly visible episcleral vessels under the body of the pterygium. Grade 2 (“intermediate”) had partially visible episcleral vessels under the body of the pterygium.
Grade 3 ("fleshy") had totally obscured episcleral vessels underlying the body of the pterygium. On baseline examination, at least Grade 2 patients with pterygium were included in the study.

Table 1(Demography of the patients)

<table>
<thead>
<tr>
<th>Age(years)</th>
<th>Mean</th>
<th>Range</th>
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<tbody>
<tr>
<td></td>
<td>50.46</td>
<td>38-70</td>
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</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9</td>
<td>11</td>
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</table>

<table>
<thead>
<tr>
<th>Grade of pterygium</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11</td>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IOP (mm Hg)</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12.46±2.42</td>
<td>12-19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systolic Blood pressure(mm Hg)</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>122±7.7</td>
<td>100-140</td>
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</table>

<table>
<thead>
<tr>
<th>Diastolic blood pressure(mm Hg)</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>79.33±5.94</td>
<td>60-100</td>
</tr>
</tbody>
</table>

Exclusion criteria: included previous ocular surgeries except pterygium removal, conditions in which Bevacizumab is contraindicated including (allergy to bevacizumab, hypertension, proteinuria, bleeding tendencies, previous myocardial infarction or stroke, pregnant and lactating women), evidence of other ocular diseases except refractive errors, history of ocular trauma, pterygium invading more than 3 mm of the cornea and inability to follow up patient for the duration of the study. Full detailed history and full informed written consent was obtained from all patients included in the study.

A complete eye evaluation was performed for each patient. This included visual- acuity measurement, applanation tonometry, slit lamp examination, and anterior segment photography. The dimensions of the pterygium were determined by measuring its length in centimeters from base (using the caruncle as landmark) to apex, and width in centimeters at the base and apical areas. All injections were performed in operating room. Topical anesthesia using 0.5% proparacaine hydrochloride eye drops (Alcaine, Alcon), subconjunctival injection of 0.2ml (5mg) of Bevacizumab (100mg/4ml Roche) following the injection of 0.2 ml lidocain 2% in subconjunctival area of pterygium body using a 1-ml syringe with 29-gauge needle, the patient was asked to direct the eye in extreme horizontal
gaze to have adequate exposure of the pterygium and injection repeated on week2, the patient contacted with predetermined follow-up schedule. Patients were followed up after a week, one month, Three months and 6months from the last injection. In each visit, complete ophthalmologic evaluation was performed; any complications and adverse events were noted. Anterior segment photography using Topcon fundus camera with lens adapter for anterior segment imaging was done.

Post injection complications such as subconjunctival hemorrhage, persistent epithelial defect, infection and uveitis were noted. Any adverse events were noted, these may include systemic effects such as hypertension or any thromboembolic incidents, or any allergic reactions to the medications and products used in the study.

The drug was considered having a biological effect when any regression in the size or decrease in vascularity and thickness of pterygium grading occurred.

**Statistical analysis:**

Both descriptive and analytic approaches were used in the data analysis. Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS version 10). chi-square was used to determine the association between grades and time intervals. A $p$ value less than or equal to 0.05 was considered statistically significant.

**Results:**

This study showed that is no statistically significant difference between males and females in the mean pterygium size ($P >0.05$) during the follow up period. On comparing the pterygium gradings at different time intervals: statistically significant difference was noted ($p < 0.01$).

This study showed that the average of pterygium size reduction and the reduction of color intensity after 6 months follow up period were statistically significant ($P =0.01$), ($P =0.031$) subsequently. At baseline, there were 11(55%) patients with grade 2 pterygium and 9 (45%) patients with grade 3. On 6 months follow up 9 patients (45%) fall in the grade 1, 9 (45%) patients in grade 2 and only 2 patients remained in grade 3 (10%).
Table 2: Distribution of patients according to grading of pterygium related to time interval

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Grading</th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade I</td>
<td>Grade II</td>
<td>Grade III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0</td>
<td>11</td>
<td>9</td>
<td>20</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>.0%</td>
<td>55.0%</td>
<td>45.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>4</td>
<td>11</td>
<td>5</td>
<td>20</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>20.0%</td>
<td>55.0%</td>
<td>25.0%</td>
<td></td>
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<tr>
<td>3 months</td>
<td>8</td>
<td>9</td>
<td>3</td>
<td>20</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>40.0%</td>
<td>45.0%</td>
<td>15.0%</td>
<td></td>
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</tr>
<tr>
<td>6 months</td>
<td>9</td>
<td>9</td>
<td>2</td>
<td>20</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>45.0%</td>
<td>45.0%</td>
<td>10.0%</td>
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</table>

P<0.01

There is a statistically significant relationship between grade and time, P<0.01
Regarding the visual acuity changes, comparison of the Snellen’s visual acuity at different time intervals showed no statistically significant difference ($p > 0.05$). Systolic and diastolic blood pressure at different time intervals showed no significant difference ($p > 0.05$), table (3).

Table (3): distribution of patients regarding the levels of blood pressure (means) at different time intervals

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Systolic blood pressure (mmHg)</th>
<th>Diastolic blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean P</td>
<td>Mean P</td>
</tr>
<tr>
<td>Baseline</td>
<td>122.±7.74</td>
<td>79.33±5.94</td>
</tr>
<tr>
<td>One month</td>
<td>120.67±10.32 &gt;0.05</td>
<td>76.66±8.16 &gt;0.05</td>
</tr>
<tr>
<td>3 months</td>
<td>121.33±10.6 0.64</td>
<td>81.33±8.34</td>
</tr>
<tr>
<td>6 months</td>
<td>119.3±10.99</td>
<td>78.67±8.34</td>
</tr>
</tbody>
</table>

Apart from subconjunctival hemorrhage which occurred in 4 patients (20%) and resolved within 2 weeks, no ocular surface toxicity, persistent epithelial defects, corneal abrasion, infections, or uveitis were reported during the study.

Discussion:
Surgery has been considered as a main treatment for primary pterygium; (5, 6) however, complications such as recurrence and even worsening of pterygium following the surgery may occur(7). The recurrence rate was estimated to be between 15% to 75% in simple excision and about 6% in the free flap operations. Some substances such as mitomycin C and 5-FU are recommended to decrease the chance of recurrence; however, their usage is associated with other undesirable complications such as infection and scleral necrosis (6-8). On the other hand, many patients ask for conservative treatment at least to suppress further progression of corneal neovascularization and abolish the symptoms, especially the congestion. Medical therapies have failed to give acceptable benefits in this relation (4-5). It is noteworthy to indicate that the pathophysiology of recurrent pterygium is different from that of primary pterygium, containing more fibrous tissues and abnormal neovascularization rather than elastic degeneration(4-6). VEGF level has been shown to be increased in pterygium and is suggested to be either directly or indirectly involved in its pathogenesis(12-15,17). Immunohistochemistry studies have shown that VEGF levels are more expressed in pterygium than in normal conjunctiva (12,15,22). Decreased anti-angiogenic factors, together with increased stimulators, have been hypothesized in the formation and progression of pterygia (15). The findings of abundant expression of VEGF in pterygium may lead to the anti-VEGF therapy development in order to induce the regression of blood vessels and size of pterygium. Pterygium is a chronic, degenerative disorder described histologically as elastic degeneration of conjunctival tissue. It has a stromal overgrowth of fibroblasts and blood vessels accompanied by an inflammatory
cell infiltrate and abnormal extracellular matrix accumulation composed of elastin and collagen (7).

In a study done by Asergadoo (23), he concluded that if pterygium is going to recur, it usually grows back or shows signs of recurrence during the first three months. Recurrence is sometimes seen as late as nine months. In a recent study to define the time interval necessary to follow patients after pterygium removal to identify a recurrence, a one-year follow-up time was likely acceptable (24). The minimum follow-up in this study was 6 months.

In a study on a rat model of corneal alkali burns, Manzano et al. have shown a 40% reduction of corneal neovascularization by topical application of bevacizumab (25). Over expression of VEGF in pterygium tissue (26, 27) and ocular inflammation (28) together with the abundance of new vessels supported the role of angiogenesis in the formation of pterygia. (26, 27, 29, 31) Vascular endothelial growth factor gene 460 polymorphism was associated with pterygium formation in Chinese female patients (32).

Bahar et al (31) reported the use of subconjunctival bevacizumab on corneal vessel density in recurrent pterygia. Subconjunctival bevacizumab was well tolerated but did not cause regression of corneal vessels in recurrent pterygia. No side-effects of subconjunctival bevacizumab injections have been reported so far (33, 36).

No local irritation, allergic reaction, or surface epitheliopathy was observed. This is in contrast with a 60% rate of spontaneous loss of epithelial integrity as recently reported by Kim et al (37) where the investigators used topical bevacizumab at a slightly higher concentration (1.25%) twice daily for a much longer period (3 months), and adverse effects generally appeared during the second month of treatment (37).

This suggests that the duration of treatment may well determine the safety of topical bevacizumab.

A study done by Dastjerdi shows a highly variable effect across the cohort treated with topical bevacizumab in the treatment of corneal neovascular vessels (NV). Generally, this study shows that topical bevacizumab 1% is effective in the treatment of clinically stable corneal NV as evidenced by a nearly 50% reduction in 2 corneal NV size (38).

Felipe et al in his study showed that subconjunctival injection of 1.25 mg bevacizumab given every 2 weeks for 10 weeks did not result in significant change in the size of the pterygium. No serious ocular and systemic adverse events were noted (39) but in this study, subconjunctival injection of 0.2ml (5mg) Bevacizumab significantly reduced the size of pterygium.

**Conclusion:**

This study showed that subconjunctival injection of bevacizumab is useful in treatment of patients with recurrent pterygium without local or systemic adverse effects. So simplicity of the procedure, cosmetic satisfaction and the lack of major complications after treatment lead us to recommend this regimen as the first choice for the treatment of recurrent pterygium.

**References:**


