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Treatment of Corneal Vessels: Which Modality is Ideal for an Optimal Result?

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Authors' contributions

This work was carried out in collaboration among all authors. Author IA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors FE and IER managed the analyses of the study and the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Corneal neovascularization (NV) is characterized by the invasion of new blood vessels into the cornea from the limbus. It is caused by a disruption of the balance between angiogenic and antiangiogenic factors that preserves corneal transparency.

Corneal vessels management has benefited from advances in medical research especially when it comes to the treatment of angiogenesis. The aim of this study is to compare the efficacy of sub conjunctival injections of anti-VEGF with that of fine needle diathermy in the treatment of corneal vessels, and to compare these results with those obtained following the combination of the two therapeutic. A prospective study was conducted in the ophthalmology department of the university hospital center of Casablanca including 60 patients with corneal vessels that we decided to treat randomly by sub conjunctival injections of anti-angiogenic drugs or by fine needle cauterization a third group of patients was treated by the combination of the two treatments. Our study showed a superiority of the treatment by cauterization compared to the injections of antiangiogenic agents however a better response was observed in the patients having received the two treatments.

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1. INTRODUCTION

The avascularity of the cornea is one of its unique features. Absence of vessels helps to maintain the cornea in a transparent state and also confers a degree of immune privilege to the cornea [1].

The cornea is a tissue maintained avascular due to a balance between the anti-angiogenic factors expressed at its level and the repression of pro-angiogenic factors. This equilibrium can be disturbed during prolonged corneal aggression leading to a hyper-expression of pro-angiogenic factors that result in the formation of corneal vessels in the corneal stromaanda loss of normal transparency of the cornea [2].

Corneal neovascularization is the pathological ingrowth of vessels to cornea from the limbal vessels. Depending on their stroma situation, the type of vessels is threefold, those of the deep, medium stroma, and finally the superficial vessels between the epithelium and the Bowman membrane. Corneal neovascularization is typically secondary to one of two types of conditions, inflammation or hypoxia. There are different situations in which the corneal neovascularization can be encountered such as the cases of ocular burns with destruction of the limbal tissue or in case of infection, corneal trauma, contact lenses, rejection of corneal transplant, limbic tumors or inflammatory episodes in autoimmune diseases.

Until mid-2000s, there was no specific treatment, ophthalmologists used local corticosteroids off-label. Corneal vessels management has benefited then from advances in medical research especially when it comes to the treatment of angiogenesis, which has made it possible to switch from corticosteroids that provide numerous side effects to anti-angiogenic molecules and even lasers.

1.1 The Purpose of the Study

Evaluate and compare the efficacy of a subconjunctival injection of Bevacizumab and fine needle diathermy (FND) and their combination on reducing corneal neovascularization.

2. MATERIALS AND METHODS

We conducted a prospective comparative study in the ophthalmology department of the university hospital center of Casablanca in accordance with the Helsinki Declaration. The study lasted a year from December 2018 to December 2019.

Sixty patients were included in this study, all of whom had corneal vessels on a stromal scar following a treated corneal abscess that we decided to take in order to prepare them for a possible corneal transplant, vessels were stable and non-inflammatory. Patients with associated ocular conditions like glaucoma, uveitis or posterior segment pathology were excluded from the study.

For the treatment of these corneal vessels, patients were randomly divided into three groups of 20 patients: the first group (group A) received 5 subconjunctival injections of Bevacizumab (0.1 ml of a concentration of Bevacizumab at 25 mg / mL at one month interval), the second (group B) was treated by a fine needle diathermy, and for the third group (group C) we used a combination of the two treatments. All patients signed informed consent after receiving explanations about the study modalities.

Patients in the three groups received antibiotic (ciprofloxacin) and corticosteroid eye drops after the procedure.

The dilution of Bevacizumab was done in the operating room under sterile conditions from the marketed solution (Avastin®), all the vascularized quadrants were injected.Injections were made under topical anesthesia (oxybuprocaine hydrochloride 0.4%: cebesine®).

Fine needle diathermy consists of introducing a fine needle of the monofilament (nylon 10.0) placed in contact with a diathermy set at low power in the vicinity of the neovasculature in order to occlude them by cauterization. Each vessel was treated individually except when there were several in the same quadrant, in this case the needle of monofilament 10.0 was placed tangentially at the limbus. When the vascularization exceeded two quadrants, the patient was summoned to complete the other quadrants not yet done so all patients received between one or two diathermy sessions.

This technique was performed under peribulbar anesthesia (Bupivacain+ Lidocain) in the operating room with monitoring of patients using an operating microscope set to low light.

For group C patients received one injection of Bevacizumab on the same day as the diathermy.

The patients were examined the day after the procedure, a week after then monthly. A detailed history of the cause, duration and prior treatment were noted.

Parameters studied were: Visual acuity, vascularized corneal surface and maximal regression of vessels judged on color photographic snapshots and tolerance to the different therapeutics used. All patients received regular follow-up with an average assessment after six months of treatment, p value less than 0.05 were accepted as statistically significant. The statistic analysis was performed by IBM SPSS statistics 20 Morroco.

3. RESULTS

Sixty eyes of sixty patients were included, they comprised 24 males and 36 females. The average age was 33 years old (range: 25-70).

The best corrected initial visual acuity of our patients ranged from 0.05 to 0.5 at the decimal scale**,** 39 patients (65%) had neovascularization of the two lower quadrants of the cornea, 26 of them (43.3%) had superficial corneal vessels (Table 1).

The mean corrected distance visual acuity (CDVA) before the treatment was 0.29 (±0.20) in group A, 0.35 (±0.10) in group B, and 0.32 (±0.15) in group C.

The clinical and epidemiological characteristics of the patients of the different groups before treatment are summarized in the Table 1.

For the group A who received subconjunctival injections of Bevacizumab, Patients received five injections and we noted a maximal regression of the vessels in 7 patients. 5 patients had as a complication a subconjunctival hemorrhage which disappeared over all after one week.

Regarding the second group treated by fine needle diathermy in such a way as to cauterize the vessels. This technique resulted in a regression of the vessels as early as 24 hours and their final disappearance was progressively spread over three weeks, 12 cases (60%) had a favorable response to the treatment*,* The most frequent complication seen was a transient whitening of the cornea especially around the needle entry in nine cases, which cleared within 24 hours and for the last group that received the combination of the two treatments, we noted 17 cases (85%) of correct response was observed in our study(Table 2, Fig 1). 3 patients presented with sub conjunctival hemorrhage. No other incidents were noted for the three groups and no case of poor tolerance to treatment was noted in our series.All cases resistant to different therapies were correlated with deep vessels.

We compared the results between the different groups and we noted a statistically significant difference between groups A and B and between A and C in favor of diathermy and combined treatment, also, the difference remained clearly significant between group B and C ($p<0.001$) with better results obtained under combined treatment ($p<0.01$).

Table 1. Clinical and epidemiological characteristics of the patients before treatment

Group	Sex (NB of patients)	Average age	Eye (nb)	Main etiology	Delay causal etiology-treatment (months)	CDVA	Corneal quadrant affected (nb eyes)	Corneal depth reached
A	F (15)	27	Right (12)	Contact lenses bacterial abscess	9	0.29	2 inf quadrants 10	Medium vessels13
B	M (11)	35	Right (15)	Fungal abscess	12	0.35	4 quadrants 8	Medium vessels16
C	F (12)	37	Left (11)	Bacterial Abscess	10	0.32	3 quadrants 6	Medium vessels15

Table 2. Result of the different therapies used

	Group A	Group B	Group C
Disappearance of the neovascularization	n=7 (35%)	n=12 (60%)	n=17 (88%)
Resistance to treatment	n = 3 (15%)	n =3 (15%)	n = 2 (10%)

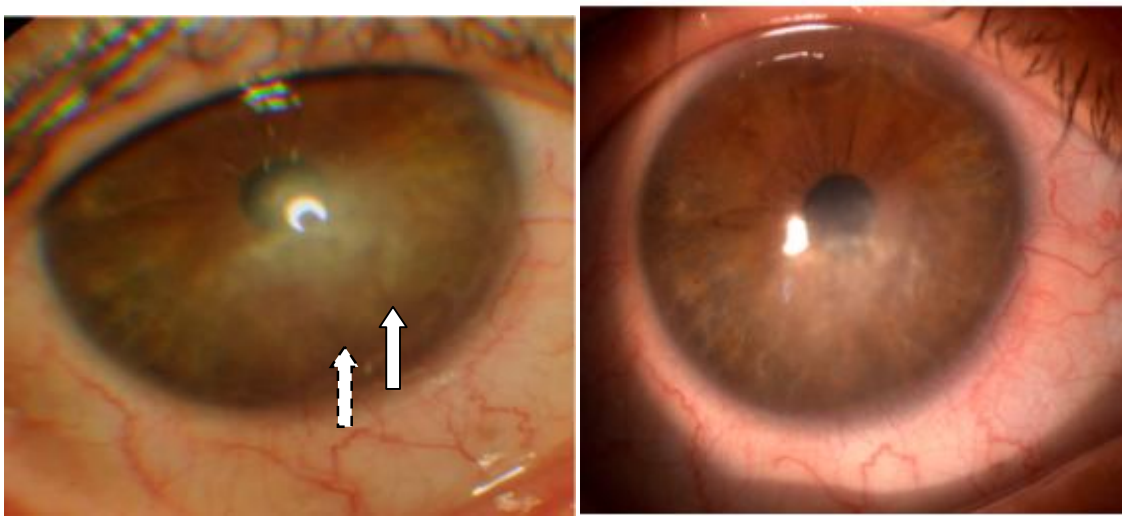

Fig. 1a. Corneal vessels before treatment b–Disappearance of vessels after combination of FND and anti-VEGF

4. DISCUSSION

Blood vessels are important for the host to mount a healing response against injury and infection. Corneal neovascularization occurs as a sequel to corneal insult resulting from infectious, allergic, toxic, anoxic, and immune causes where up on it serves to facilitate the healing process or acts as a warning sign of corneal distress [3].Once established, these vessels help to transport humoral and cellular elements of immunologic defense and raw material required for repair and regeneration. They also help to carry administered antibiotics and other drugs to the site of infection and at the same time eliminate toxic substances.

The disadvantage of the corneal neovascular response is that once the healing process is completed, the vessels often persist with circulating blood. This may interfere with corneal transparency by leakage of lipids or by recurrent inflammation.

There are many therapeutic modalities to reduce corneal neovascularization to improve visual performance (Table 3).The commonly used treatment is topical steroids but it has the risk of cataract and glaucoma with long-term use.

The pharmacological component is intended to treat vessels in their immature form. Anti-angiogenic molecules will be preferred to corticosteroids because of the lower risk of side effects. Bevacizumab being the most widely used molecule. Some authors reported the excellent effects of the anti-VEGF Bevacizumab antibody in inhibiting and regressing corneal vessels [4,5,6,7].

However Kim et al. have shown in a study that the use of Bevacizumab topically is not without side effects and it not only reduced neovascularization corneal but also driving loss of epithelial cells and progression of corneal thinning [8].

No regression of corneal vascularization was observed in 2 studies involving cases of recurrent pterygium and corneal transplant rejection, after penetrating keratoplasty [9,10].

In our study, the low response rate to sub conjunctival injections of Bevacizumab used at a dose of 2.5 mg could be explained by the age of the corneal vessels, because indeed several studies have shown that it is during the acute phase of the inflammatory process that the production of VEGF is at its maximum, and it is

during this phase that the use of anti-VEGF would be effective [11,12,13,14].

The need to repeat the injections would also limit the treatment with Bevacizumab.

Our study therefore seems to show the efficacy of FND we noted diseappearance of neovascularizationin 60% of our patients.

Before the fine needle diathermy other procedures were used:conjunctival recession, cryotherapy, yellow laser, photodynamic therapy and the Argon laser photocoagulation among others and several studies have demonstrated the superiority of FND in terms of result but also in terms of safety of use and cost cheaper compared to other techniques because it does not require sophisticated equipment [15,16,17].

This technique can occlude in a single session all the vessels, whether efferent or afferent and at any depth. The development of a collateral circulation after this technique has been described thus making it necessary to repeat it [18].

A few side effects have been described in the literature, among others, precipitates or intra-stromal haemorrhage and temporary corneal haze.

No major complication like needle perforation was observed in this series. Only a white ring around the needle entry at the cornea, sub-conjunctival and intra-stromal haemorrhages were seen which completely resolved on follow-up. FND can also be repeated without any change in conjunctival or scleral architecture. In our study, we noted disppearance of corneal neovascularizationi n 60% of our patients. Thatte S et al. reported 100% of complete regression of vessels [19].

Another study demonstrated a success rate of this procedure in 82.3% of patients thus joining the results of our series [20].

Pillai et al. obtained due to FND an occlusion of all corneal neovessels in 8 out of 14 patients [21].

For group C, we noted regression of neovascularization in 88% of patients, combined use of subconjonctival Bevacizumab with fine needle diathermy seems to increase efficiency in treatement of corneal neovascularization.

In our series, the combination of the two procedures showed better efficacy on the corneal vessels compared to a monotherapy with FND or Bevacizumab, this could be explained by a potentiating effect of anti-VEGF on FND which would also limit post inflammation diathermy and therefore the risk of recurrence of neovascularization or the development of collateral circulation.

Table 3. Current approaches for the management of corneal neovascularization; advantages, limitations, and complications [23]

Treatment	Advantages	Limitations	complications
Corticosteroids	Reduction In inflammation and corneal neovascularization	Limited effects on pre-existing mature corneal vessels	Glaucoma, cataract
Laser	Simple and tolerable procedure, obliteration of corneal efferent vessels	Frequent reopening of the vessels, ineffective in extensive corneal neovascularization	Damage of corneal endothelium or crystalline lens
Fine needle diathermy	Simple, inexpensive It can occludevessels at anydepth. It has an equalefficacy for efferent and afferentvessels	Reopening of the vessels necessitating retreatement	Precipitates or intra-stromal haemorrhage and temporary corneal haze Whitening a round the needle entry at the cornea
Anti-VEGF agents	Effective on active young vessels	Expensive, Limited anti-angiogenic effects on stable, mature and deep vessels, Short half-lives	Persistant epithelial defetcs and stromal thinning with topical bevacizumab

Other studies have suggested that the combination of FND and Bevacizumab eye drops is an effective and safe option for treating new corneal vessels and that subconjunctival injections of Bevacizumab in addition to eye drops would have a better effect on the vessels [22].

5. CONCLUSION

The treatment of corneal neovascular diseases has long been controversial and the advent of new anti-angiogenic molecules has revolutionized their management. However, their efficacy remains limited to the acute phase with hyper-expression of VEGF.

Fine needle diathermy is a simple physical method for the management of stable corneal vessels .This technique can be used alone or in combination with other therapeutics mentioned above. Our experience has supported this observation, it is a better alternative than anti VEGF injections for the treatment of corneal vessels at any depth and even when they are old.

Also, we were able to demonstrate through our study that the addition of an anti-VEGF could potentiate the effect of FND on one hand and on the other hand the combination of the two procedures could reduce the number of subconjunctival injections for an optimal result.

The medium- to long-term evolution will be carried out in a subsequent study on a wider sampling so that the tolerance and the duration of this technique can be studied.

CONSENT

All patients signed informed consent after receiving explanations about the study modalities

ETHICAL APPROVAL

Ethical approval has been taken from ethics committee to carry out the study

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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