

Propranolol eye drops in patients with corneal neovascularization

Luca Filippi, MD^{a,*}, Cinzia de Libero, MD^b, Barbara Zamma Gallarati, MD^b, Pina Fortunato, MD^b, Elena Piozzi, MD^c

Abstract

Rationale: Studies performed in animal models of corneal neovascularization suggested the possible efficacy of a treatment with propranolol. Corneal neovascularization is one of the most feared complications of Stevens–Johnson syndrome that frequently involves ocular surface. We report the first 2 patients with severe ocular neo-vascularization treated with different degrees of success, with propranolol eye drops.

Patient concerns: Two patients with corneal neovascularization complicating the Stevens–Johnson syndrome, not responsive to steroids and cyclosporine, were treated with propranolol eye drops.

Diagnoses: Corneal neovascularization was detected by ophthalmoscopic evaluation.

Interventions: Topical treatment with propranolol eye drops at different concentrations.

Outcomes: Both patients reported dramatic subjective benefits (reduction of photophobia and discomfort) without adverse effects, and in the patient with a less advanced disease, an objective reduction of neovascularization and an improved visual acuity was observed.

Lessons: This experience suggests that propranolol might be an inexpensive, safe and effective treatment in counteracting the progression of corneal neovascularization.

Abbreviations: β -AR = β -adrenergic receptor, SJS = Stevens–Johnson syndrome, TEN = toxic epidermal necrolysis.

Keywords: beta-blockers, propranolol, Stevens–Johnson syndrome, toxic epidermal necrolysis

1. Introduction

Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are rare acute inflammatory vesiculobullous reactions of the skin and of the mucous membrane, often concomitant with the assumption of drugs or, less frequently, infectious agents. Its incidence is assessed approximately 1.2–12.3 new cases /million/year.^[1] The disease is characterized by massive apoptosis of keratinocytes and detachment of the skin and mucosal surfaces at the dermo-epidermal junction. The clinical relevance of this syndrome is strictly related with the extension of skin or mucosa involvement. When <30% of the body surface area is involved, this disease is defined as SJS. When the body involvement is

>30%, the syndrome is called TEN, the skin detachment is massive, and the prognosis is poor, with mortality rates up to 35%.^[2]

In survivors, the involvement of the ocular surface in the acute phase of the disease has been observed in 60% to 100% of adult patients.^[3] Acute eye involvement ranges from conjunctival hyperemia to significant ocular surface sloughing, including the tarsal conjunctiva and eyelid margins. A percentage ranging from 20% to 79% of survivor patients experiences chronic ocular disease with chronic inflammation, desiccation, stromal opacification, ocular surface keratinization, corneal/conjunctival neovascularization and scarring leading to blindness, one of the most feared and significant sequelae of SJS/TEN.^[4–6] Corneal neovascularization is a particularly disabling feature because the area of the new corneal vessels, the increase in vascular permeability with edema and bleeding, lipid deposition, and scarring contribute to induce a dramatic visual loss.^[7]

Conventional treatments for ocular SJS/TEN include immunomodulatory treatments such as steroids, intravenous immunoglobulin or cyclosporine,^[8,9] or angiogenesis inhibitors,^[10] and currently, although to date only small case series have been published, amniotic membrane transplantation appears to be a very promising therapeutic strategy.^[5,11] Although for patients with ocular SJS/TEN the therapeutic opportunities are increasing, the treatment of severe ocular neo-vascularization remains challenging.

Recently, nonselective β -adrenergic receptor (β -AR) antagonists have been demonstrated to reduce angiogenesis,^[12–20] suggesting a possible therapeutic effect also in corneal neovascularization. We report the first 2 patients with severe ocular neo-vascularization treated, with different degrees of success, with propranolol eye drops.

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^a Neonatal Intensive Care Unit, Medical Surgical Fetal-Neonatal Department,

^b Pediatric Ophthalmology Unit, "A. Meyer" University Children's Hospital,

Florence, ^c Pediatric Ophthalmology Unit, Niguarda Ca' Granda Metropolitan Hospital, Milan, Italy.

* Correspondence: Luca Filippi, Neonatal Intensive Care Unit, Medical Surgical Fetal-Neonatal Department, "A. Meyer" University Children's Hospital, Viale Pieraccini, 24 I-50139 Florence, Italy (e-mail: l.filippi@meyer.it).

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1.1. Cases Report

Patient 1. A young girl, 10 years old, was admitted to a hospital near Florence (Italy) on July, 2006. The patient, allergic to macrolides and penicillin, received cephalosporin for upper respiratory tract infection. After 5 days of treatment, the girl developed fever, abdominal pain, cutaneous erythema, and some blisters in the face and in the limbs. The initial diagnosis was SJS and a treatment with fluids replacement, methylprednisolone and teicoplanin was begun. In a few days clinical conditions worsened: intense erythema progressed rapidly to diffuse epidermolysis, dysuria, stranguria, and urinary retention appeared. Moreover, oral mucosa appeared strongly hyperemic with diffuse ulcerations. Therefore, the girl was transferred to our hospital where she was treated with systemic corticosteroids and intravenous immunoglobulin, associated to balneotherapy and surgical escharotomies. The first ophthalmic assessment detected severe conjunctival inflammation, chemosis, bullous lesions that prevented the exploration of conjunctival fornix, without corneal damage. A topical treatment with a combination of topical corticosteroids and antibiotics was started. An early symblepharon developed in a few days that was lysed by a curettage with a glass rod. The patient was discharged on September 2006 with topical steroid ointment and artificial tears. The cornea was still undamaged, the conjunctiva still intensely hyperemic. After a month, the young patient was operated for a rapidly developing nasal and temporal ankyloblepharon and recurrent symblepharon. In the following months, a progressive corneal involvement was observed, with intense photophobia and corneal ulcers, without signs of infection. Central corneal leukoma developed in right eye on February 2007. Discomfort for the patient increased in following years for the increasing photophobia, burning sensation, tearing, and foreign body sensation insensitive to treatment with artificial tears and topical steroids. On June 2015 bilateral keratopathy worsened and corneal neovascularization developed. Due to the poor efficacy of a new treatment with steroids, Cyclosporine 1% eye drops in

artificial tears were begun 3 times a day for a month, but unsuccessfully. The patients continued to alternate treatment with artificial tears and steroid until February 2017 (Fig. 1A), when we decided to try a treatment with 1 drop of propranolol 1% in both eyes, 3 times a day. Eye-drops were prepared by diluting propranolol hydrochloride powder (A.C.E.F., Fiorenzuola d'Arda, Piacenza, Italy) in sterile water for injections, at a concentration of 1%. The solution was prepared sterilely in compliance with the microbiological standards established by European Pharmacopoeia. Snellen visual acuity was 4/10 at both sides. After 3 weeks of treatment, photophobia dramatically reduced. On May 2017, despite treatment was well tolerated and no adverse effects were reported by the patient, propranolol concentration was reduced to 0.5%, increasing the number of administrations to 5 times a day, because plasma propranolol levels, measured on dried blood spots, were very high (maximum propranolol plasma concentration 3770 ng/mL). Reducing the eye drops concentration, plasma propranolol level significantly decreased and maximum plasma concentration dropped to 395 ng/mL. On June 2017, photophobia was well tolerable, corneal neovessels appeared significantly less congested, the eyelid hyperemia was reduced, and Snellen visual acuity improved to 6/10 on both sides (Fig. 1B). A further reduction of propranolol concentration to 0.3%, 4 administrations a day, was decided for the persistence of high plasma propranolol concentration, on November 2017, but a rebound of photophobia and corneal hyperemia suggested us to resume the previous dosage of 0.5%, 4 administrations/day. Currently, the patient is treated with 1 drop of propranolol 0.5%, 4 times a day, in both eyes, photophobia is well tolerated, corneal neovessels appears significantly less congested, the eyelid hyperemia is reduced, and visual acuity is improved to 6/10 on the right and 7/10 on the left eye.

Patient 2. A young boy, 2 years old, was admitted to Niguarda Hospital of Milan (Italy) on May, 2007 for SJS/TEN following the administration of an antiepileptic drug. The first ophthalmic evaluation detected severe chemosis and conjunctival inflamma-

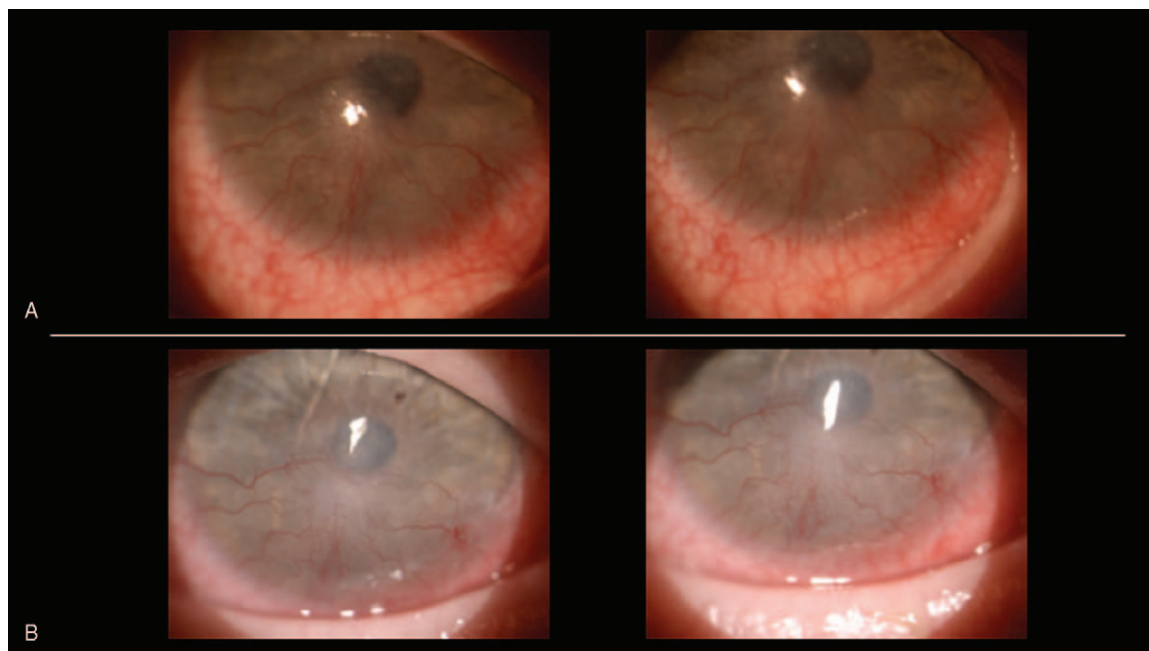


Figure 1. Corneal neovascularization in patient 1 immediately before (A) and after 4 months (B) of propranolol eye drops.

tion, without corneal alteration. In the first weeks, an annular ring was placed in order to prevent the development of symblepharon. Nevertheless, within a few weeks a progressive corneal involvement developed with progressive visual function reduction. Despite the use of topical steroids and artificial tears, a bilateral severe calcific band keratopathy and corneal neovascularization developed. The visual function rapidly deteriorated and an important photophobia developed so severe to prevent the opening of eyelids. This clinical condition lasted for many years compromising an acceptable quality of life, with poor response to treatment with steroids, and Cyclosporine 0.5% eye drops (Fig. 2). On March 2017, a treatment with 1% propranolol eye drops was begun, with 2 administrations a day. In a few days, a dramatic reduction of photophobia was referred from the patient, who was finally able to open the eyes. The objective evaluation was unchanged, because corneal leukoma and calcifications remained well evident. Currently the young patient reports a mild improvement of visual acuity, probably related with the reduced photophobia.

Appropriate institutional review board approved the report. Written informed consent was obtained from the patient 1 and from the parents of patient 2 for publication of this Case report.

2. Discussion

Oral propranolol, a nonselective β_1/β_2 -adrenoreceptor blocker, has recently been reported to be effective and safe in reducing the growth of infantile hemangiomas,^[12] thanks to its ability to inhibit angiogenesis,^[13] through a HIF-1 α -mediated inhibition of VEGF-A.^[14] This demonstration paved the way for the hypothesis that propranolol could counteract the progression of retinopathy of prematurity,^[15] or choroidal neovascularization, as was confirmed by animal studies^[16-18] and clinical trials.^[19,20]

Recently, the anti-angiogenic effect of nonselective β -AR antagonists has been evaluated in animal models of corneal neovascularization, with conflicting results. A first study observed that propranolol eye drops 0.1 and 0.05%, administered twice a day for 7 days, was not able to reduce alkali-induced corneal neovascularization in rats.^[21] On the contrary, topical timolol 0.5% twice per day significantly reduced the area of neovascularization induced by silk sutures in rabbits,^[22] and similar results were obtained with 1% propranolol eye drops, 3 times a day for 2 weeks, starting immediately after suture removal.^[23] A more recent study, performed in mice subjected to corneal sutures, showed that 6 subconjunctival injection of 0.5%

timolol significantly reduced the corneal neovascularization, the inflammatory infiltration, and the expression of VEGF, TNF α and IL-6.^[24] Overall, nonselective β -AR blockers appears effective in counteracting corneal neovascularization, even though the discrepancy of the results can be related with the different doses and the different experimental models.

Based on this background, we decided to test the efficacy of propranolol eye drops in 2 young patients with a chronic corneal neovascularization (extremely more advanced in the second patient), unresponsive to canonical medical treatments. Although both patients reported dramatic subjective benefits (reduction of photophobia and discomfort), only in the first patient an objective reduction of neovascularization and a clear improved visual acuity was demonstrated. Despite our experience is extremely limited, it is very likely that the different efficacy was related to the different stages of ocular impairment in the 2 patients, suggesting a more effective action if treatment is started more precociously.

To our knowledge, this is the first clinical report where topical β -antagonists have been successfully employed in humans to evaluate the possibility to modulate corneal angiogenesis, and, obviously, many uncertainties still remain. First of all, the concentration of propranolol eye drops was arbitrarily chosen, inspired by animal studies. Despite the absence of adverse events, in the first patient the initial 1% concentration was reduced because plasma level of propranolol was surprisingly high. We cannot exclude that the extreme vascularization of cornea favors a rapid passage of the drug in the blood and a very high plasma peak. For this reason, in this patient we decided to reduce the concentration, increasing the number of administrations, and plasma maximum level decreased significantly. Secondly, if future experiences will confirm our results, the choice of the most appropriate timing of this treatment will be determinant. Our impression is that treatment with topical nonselective β -blockers should be administered as soon as the neovascularization begins to develop. Third, the most appropriate delivery system able to ensure a prolonged and/or continuous exposition of corneal surface to propranolol should be carefully evaluated.

3. Conclusion

Although the number of patients treated is absolutely too small to draw firm conclusions, our data suggest that propranolol might be a simple, inexpensive, well tolerated and effective treatment in counteracting the progression of corneal neovascularization. Further animal experiments and clinical trials are urgently needed to confirm our results and, eventually, to clarify the best schedule.

Author contributions

Conceptualization: Luca Filippi.

Data curation: Luca Filippi, Cinzia De Libero, Barbara Zamma Gallarati, Pina Fortunato, Elena Piozzi.

Investigation: Luca Filippi, Cinzia De Libero, Barbara Zamma Gallarati, Pina Fortunato, Elena Piozzi.

Methodology: Luca Filippi.

Supervision: Luca Filippi.

Validation: Luca Filippi, Cinzia De Libero, Pina Fortunato, Elena Piozzi.

Writing – original draft: Luca Filippi.

Writing – review & editing: Luca Filippi, Cinzia De Libero, Barbara Zamma Gallarati, Pina Fortunato, Elena Piozzi.

Luca Filippi orcid: 0000-0001-5310-9147.

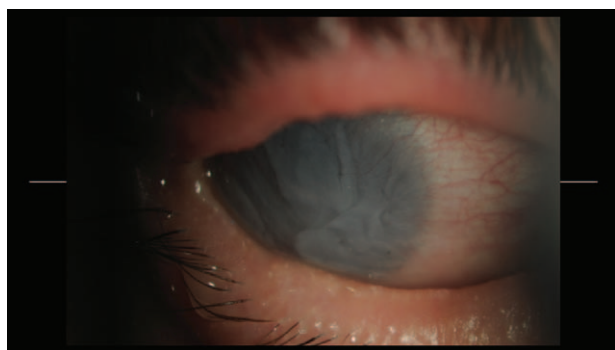


Figure 2. Severe calcific band keratopathy, corneal leukoma, and corneal neovascularization in patient 2 immediately before propranolol eye drops.

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