Two Cases of Consecutive Toxic Anterior Segment Syndrome after Uneventful Trabeculectomy Surgeries in a Tertiary Center

Tatiana M. Gil-Martínez, María J. Herrera, Vanessa Vera

Centro Diagnóstico Oftalmológico de Oriente, Lechería, Venezuela; Unidad Oftalmológica de Caracas, Fundación AVAO, Caracas, Venezuela

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Abstract
Toxic anterior segment syndrome (TASS) is a severe, acute, sterile intraocular inflammation that occurs the same day or in the early stages after intraocular surgery. It has been most commonly reported after phacoemulsification. We report 2 cases that developed TASS after sequential uneventful trabeculectomy surgeries, in which a quaternary ammonium compound was used for the disinfection of surgical instruments. Good outcomes were achieved, possibly related to the fast treatment initiation.

Introduction
Toxic anterior segment syndrome (TASS) is a severe, acute, sterile intraocular inflammation that occurs the same day or in the early stages after intraocular surgery. It has been most commonly reported after phacoemulsification [1–4], keratoplasty, and less frequently, after posterior segment surgeries [5, 6].

The overall incidence of TASS was found to be 0.22% in a large case series published by Johnston [7]. Additionally, a significant number of reported cases have occurred as clusters of outbreaks [1, 8]. The origin of this reaction seems to be noninfectious substances introduced into the eye during surgery [1, 7–9], producing a breakdown of the blood–aqueous barrier [10].
Various exogenous chemicals have been identified as the cause of TASS [11, 12] such as residues left behind during cleaning and sterilization of surgical instruments, irrigating solutions with incorrect pH, osmolarity or ionic composition, preservatives, stabilizing agents, denatured ophthalmic viscoelastic devices, endotoxins, heavy metals, intraocular medications at toxic doses, and ointments [10].

According to the literature, common signs of TASS are presence of cells, flare, and fibrin formation (anterior chamber [AC] inflammatory response); as well as corneal edema without compromising the posterior segment. It is typically characterized by an acute presentation (12–48 h after surgery), without salient complaints of pain [1, 13, 14]. To our knowledge, this is the first paper reporting TASS after trabeculectomy surgery.

**Case Report/Case Presentation**

**Surgical Interventions Overview**

Both patients, underwent trabeculectomy with mitomycin C (MMC) in their right eyes, performed consecutively on the same day, by the same surgeon, and at the same operating room.

In each case, after topical anesthesia with lidocaine, the eye was prepared with 5% povidone iodine solution and the field covered with disposable surgical drape. A fornix base peritomy was performed, cautery was applied to bleeding vessels and a quadrangular scleral flap created. MMC at 0.4 mg/mL was applied with sponges for 3 min under tenon and washed with 40 cm$^3$ of balanced salt solution (BSS). A side port was created to inject carbachol, followed by viscoelastic Hydroxy PropylMethylCellulose (Appavisc$^\text{®}$). A blade was used to enter the AC from behind the hinge of the scleral flap and Kelly Punch to create the ostomy followed by an iridectomy. Sutures with 10-0 nylon were used to close the scleral flap (releasable sutures) and conjunctiva in a watertight fashion. The viscoelastic was removed from the AC with BSS and a subconjunctival injection of dexamethasone was given at the end of the case. Ocular patch with sterile topical antibiotic and steroid ointment (tobramycin + dexamethasone) was placed. The overall surgical time for each case did not exceed 30 min.

**Case One**

**Baseline**

The patient was a 45-year-old male, with history of bilateral retinal detachment due to tractional diabetic retinopathy. Status post-several retinal surgeries OS with no light perception (LP). History of transscleral cyclophotocoagulation with micro pulse OD followed by peripheral laser iridotomy due to pseudophakic pupillary block.

Preoperative baseline for OD was calculated; patient had secondary open angle glaucoma, best corrected visual acuity (BCVA) 20/400, and intraocular pressure (IOP) 32 mm Hg on maximal tolerated medical therapy with dorzolamide BID, timolol BID, and acetazolamide 125 mg TID. Trabeculectomy with MMC OD was performed as detailed above.

Postoperative Day One

Patient presented with decreased vision. Visual acuity (VA) was LP. On slit lamp examination, subconjunctival hemorrhage and severe conjunctival hyperemia were present along with a diffuse filtering bleb, moderate corneal edema, 3 + cells and 2 + flare in the AC with central fibrin mesh present, and 15% hypopyon shown in Figure 1, IOP was 8 mm Hg. Topical medication was increased to prednisone hourly (instead of QID); fortified antibiotics (vancomycin/ceftazidime) were started every 2 h and cycloplegia TID.
Postoperative Day Two
VA was LP. Slight improvement at slit lamp exam with mild corneal edema, 2 + cells and 1 + flare in the AC, fibrin mesh shrinkage, and 10% hypopyon, shown in Figure 2. IOP was 14 mm Hg.

Postoperative Week One
The VA had improved to hand motion. On examination, filtering bleb was present. Mild corneal edema, 2 + cells and 1 + flare in the AC with fibrin, and hypopyon still present but improving, shown in Figure 3. IOP was 12 mm Hg. Topical therapy was modified to discontinue
antibiotics, reduce prednisone to every 2 h and start nepafenac every 8 h TID and a tapering regimen of oral steroids starting at 50 mg at day.

Postoperative Month One
VA was 20/400 (back to baseline) with a diffuse filtering bleb present, and trace cells in AC with no hypopyon shown in Figure 4. IOP was 9 mm Hg. Cyclopentolate and oral steroid were discontinued. Treatment with topical nepafenac and prednisolone TID was maintained.

Case Two
Baseline
The second patient was a 63-year-old female with a diagnosis of primary open angle glaucoma OU. Right eye had a BCVA of 20/30 and IOP was 22 mm Hg on maximal tolerated medical therapy with latanoprost/dorzolamide QD and timolol/brimonidine BID. Lack of compliance, due in part to difficulty with access to topical medical therapy resulted in worsening of visual field showing evidence of progression shown in Figure 5. Therefore, trabeculectomy with MMC OD was performed.

Postoperative Day One
The patient presented with red eye and reduced vision. On examination, VA was hand motion with no improvement with PH. Biomicroscopy exam showed significant conjunctival hyperemia 360° with a diffuse filtering bleb, moderate corneal edema, 3 + cells and flare in the AC, and 5% hypopyon shown in Figure 6a, b. The IOP was 16 mm Hg. There was a high suspicion of TASS, but infectious endophthalmitis could not be ruled out. Topical treatment was increased to prednisone hourly (instead of QID), topical fortified antibiotics (vancomycin/ceftazidime) every 2 h and a cycloplegic (TID) to keep the pupil dilated.

Postoperative Day Two
The VA improved to 20/400. On slit lamp examination, the filtering bleb was present, with mild corneal edema, 3 + cells and 2 + flare in the AC and worsening of hypopyon to 10% shown in Figure 7. IOP was 16 mm Hg. No changes were made to the treatment regimen above.

Postoperative Week One
There was further improvement in VA to 20/200. Filtering bleb was present with mild vascularity, The AC showed 2 + cells without any hypopyon present shown Figure 8a–c. The
IOP was 8 mm Hg. The fortified antibiotics were discontinued, topical prednisolone reduced to every 2 h and topical nepafenac TID was started.

Postoperative Month One
The patient had BCVA of 20/40, a diffuse filtering bleb was present and the cornea was clear. The AC was quiet. IOP was 17 mm Hg on nepafenac and prednisolone TID.

Discussion

The American Society for Cataract and Refractive Surgery (ASCRS) suggests that improper cleaning of surgical material is the most common cause of TASS, as well as the use of enzymatic detergents and ultrasound baths. They are known to be the most frequent factors associated with this entity, for which they recommend avoiding their use in cleaning ophthalmic instruments [15].
In our center in Venezuela, we have been experiencing significant difficulties in the acquisition of ethylene oxide ampoules. Given this challenge, we have been using Lauryl Dimethyl Benzyl Ammonium Bromide (Gerdex® Laboratorios Rodeneza Europa, S.L. Madrid, España), a quaternary ammonium compound for the disinfection of surgical instruments with autoclaving for the past years in spite of the fact that this is not in line with the manufacturer’s recommendations. In our instrument cleaning protocol, after each surgery, the instruments are immersed in Gerdex® for 45 min, then rinsed in a double fanny pack with Lactate Ringer’s solution. The cannulas are irrigated under pressure 2 times with the same solution. After these steps, the instruments were used for the next surgical case (case one and two).

Quaternary ammonium compounds such as Gerdex®, are classified as intermediate and low-level disinfectants, recommended only for chemical disinfection of noncritical items (those that only come into contact with the skin) such as surfaces and equipment; their use for the sterilization of surgical instruments (those that penetrate sterile tissues and cavities) is not approved [16].

It is known that enzymatic detergents and other active ingredients can only be deactivated at temperatures above 140°C, and the autoclave only reaches a maximum of 120°C [17]. The only safe way to remove detergent residues is to use sterile water jet under pressure.

In our 2 cases, Lauryl Dimethyl Benzyl Ammonium Bromide (Gerdex®), a quaternary ammonium compound was used for the disinfection of surgical instruments (despite not
being recommended by the manufacturer for this use), and even when this substance was washed as detailed above, there may have been some residue inside or on the surface of the material used. After these experiences, the instruments cleaning protocols have been changed, to only use ethylene oxide ampoules as they become available.

Despite this being the most probable cause in both cases, we must keep in mind that TASS and endothelial toxicity are potential unwanted effects of the introduction substances or drugs into the AC, not only because of its own chemical composition but also because of preservatives and/or the pH of the formulation.

Events like iridocyclitis, macular edema, serous retinal detachment have been described after use of inappropriate concentrations of antibiotics in the AC [18–20]. It has also been reported that diluting vancomycin in sterile water instead of BSS can generate changes in osmolarity responsible for severe corneal edema and glaucoma [18].

Ophthalmic ointments applied at the end of surgery has been shown to cause TASS, according to a study published by Werner et al. [21], who reported 8 cases of TASS after phacoemulsification and described the presence of oily material in the form of a film in the corneal endothelium and an oily bubble in the AC, which was later confirmed with pathological studies when explanting the intraocular lens.

In our 2 cases, no antibiotics were injected into the AC, but a steroid ointment (tobramycin + dexamethasone) was applied at the end of the case. No evidence of oily particles floating or adhering to structures of the AC was observed during the postoperative period.

Yazgan et al. [22] investigated the profile of patients with TASS compared to controls and found that type 2 diabetes, systemic hypertension, hyperlipidemia, chronic ischemic cardiovascular disease, and kidney failure were significantly more common in patients with TASS. Case one has type 2 diabetes and history of TASS after vitreoretinal surgery (fellow eye) which was performed at another center and by another surgeon, supporting the hypothesis that the patient’s profile could play a role.

In 1983, Chen reported the first attempt to use mitomycin as an adjunct chemotherapy in glaucoma surgery for its antifibrotic effect [23]. Many studies support its benefits and surgeons use it routinely [24, 25] as its toxic effect over the endothelial cells, lens, and optic nerve seems to be low [26–28]. In our cases, MMC was used at dilutions that has been published to not produce ocular toxic effects and considered to be safe [26, 29, 30].

TASS has been associated with the use of viscoelastics [31, 32]. The viscoelastic used in the 2 patients presented in this article was Hydroxy Propyl Methyl Cellulose (APPAVISC®), and partially left in the AC at the end of the cases. Even though we could not find any literature on Hydroxy Propyl Methyl Cellulose and TASS, the possible correlation cannot be ruled out.

**Conclusion**

To date, no cases of TASS after trabeculectomy has been reported, but we must keep in mind that TASS is possible after any intraocular surgery. There is no diagnostic tool but as soon as TASS is suspected, it should be treated, carrying out a meticulous investigation of all the potential causes and remedial measures instituted. Based on the postoperative courses of our 2 patients, the rapid onset, response, and good visual recovery, the authors conclude that TASS was the most likely diagnosis. Changes to the instruments cleaning protocols have been adopted in our center to adhere to the ASCRS and manufacturer’s recommendations for cleaning and sterilizing instruments, as failures in the same can lead to serious infectious or inflammatory complications.
Statement of Ethics

This study protocol was reviewed and the need for approval was waived by the Bioethical Committee of Dr. Luis Razetti University Hospital, in Barcelona Venezuela. Written informed consent was obtained from the subjects to use details of their medical cases and accompanying images for publication purposes.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Tatiana M. Gil-Martínez, María J. Herrera, and Vanessa Vera participated in the research, writing, and revision of the manuscript.

Data Availability Statement

All data that support the findings of this study are included in this article.

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