Toxic Anterior Segment Syndrome Outbreak after Cataract Surgery Triggered by Viscoelastic Substance

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Abstract:

PURPOSE: The purpose of this study is to present toxic anterior segment syndrome (TASS) outbreak at our clinic and discuss possible causes of TASS.

MATERIALS AND METHODS: Thirty-four eyes of 34 patients developed TASS in a consecutive 2 weeks period were included in this study. Both anterior segment and fundus examinations were performed before and after uncomplicated cataract surgery. During the follow-up period, clinical features and all possible causes were evaluated including perioperative products and processing such as sterilization technique of surgical instruments, irrigating solutions, drugs, viscoelastic substance (VES), and intraocular lens.

RESULTS: Patients had corneal edema, anterior chamber reactions, and decreased vision. No patient had purulent secretion, chemosis, lid involvement, and pain. At first 2 postoperative days, patients treated as infectious endophthalmitis by topical and oral antibiotics and then TASS was suspected, and patients treated completely with topical steroids. Suspected cause for TASS was VES substance, 2% sodium hyaluronate which had newly been used as VES product in phacoemulsification surgery. No new case has occurred after stopped usage of this VES product.

CONCLUSION: As far as we know, this is the largest report of TASS outbreak in the shortest period from the same clinic caused by VES. Suboptimal products of surgical materials can be the cause of TASS. Close monitoring of each surgical step and elimination of causative agent can prevent the outbreaks of TASS.

Keywords:
Cataract surgery, toxic anterior segment syndrome, viscoelastic substance

Introduction

Toxic anterior segment syndrome (TASS) is a rare but serious sterile postoperative inflammatory reaction due to contamination of noninfectious substance during operation that cause toxic damage in the intraocular tissues.[1] TASS usually occurs in clusters rather than single cases suggesting a common contamination of patient similar to series of endophthalmitis. The intense painless inflammation of the anterior segment typically presents within 24 h after surgery, in contrast to the longer presenting time of infectious endophthalmitis. Even infectious endophthalmitis can be diagnosed with the presence of periocular pain and accompanied by intense vitritis, in some cases with TASS differential diagnosis is not easy. Any surgical instruments or environmental conditions could be the cause of TASS, including some.[1–4]

Clinical outcomes of TASS are related toxic effect of causative agent on anterior segment tissues. Therefore, a careful investigation and elimination of the possible causative factors than immediately administer correct treatment can prevent irreversible
complications. The vast majority of TASS has been reported after uneventful cataract surgery, but there are some reports of TASS-like inflammation after penetrating keratoplasty, phakic lens implantation, posterior vitrectomy operation, and after intravitreal injection.

In the current study, we present an outbreak of TASS which appeared after an uneventful cataract surgery in a consecutive 2 weeks period caused by recently used two different concentration of viscoelastic substance (VES) and both of them were made of rooster comb, in which resident protein contents are high and special storage condition such as refrigerating between 2° and 8° is necessary to keep their chemical integrity. As far as we know, TASS outbreaks caused by uncontaminated, a pyrogen-free, sterile solution of sodium hyaluronate derived from rooster comb did not report until to date. Our report is the largest series of TASS occurred in a same clinic which is also present in the shortest period too.

**Materials and Methods**

Thirty-four eyes of 34 patients who had developed TASS in a consecutive 2 weeks were retrospectively analyzed. To achieve the correct diagnosis and to decide the type of treatment, patient-related factors as well as factors related to operative conditions were analyzed. Both ocular and systemic preoperative conditions such as gender, age, and history of ocular disease were evaluated. All patients underwent detailed ophthalmic examination, including measurement of visual acuity, intraocular pressure (IOP), slit lamp evaluation of anterior segment, and fundus examination as much as possible both preoperative period and during the follow-up. Prior the operation, all patients had received cyclopentolate 1%, phenylephrine hydrochloride 2.5%, and tropicamide 1% for mydriasis. The povidone-iodine solution was used for both skin, eyelids and conjunctival disinfection, and periocular area covered with a disposable sterilized surgical drape. All patients had undergone phacoemulsification surgery with the same technique in which after the clear corneal incisions VES’s (either 2.0% or 1.4% sodium hyaluronate) was inserted into the anterior chamber (AC) and continuous curvilinear capsulorhexis, hydro dissection, and phacoemulsification was performed. After filling AC with the same VES, an intraocular lens (IOLs) either made of hydrophilic (Ocuflex Polymer Technologies International, Gujarat, India) or hydrophobic (Acrysof Iol, Alcon Surgical Fort Worth, TX, USA) acrylic implanted into the posterior chamber. VES was removed by irrigation and aspiration as much as possible and incision ports closed by hydrating balanced salt solution (BSS). At the end of surgery, dexamethasone and gentamicin sulfate were injected under the conjunctiva.

No one received ointment after surgery. All cataract surgeries were conducted in the same operation room and with the same surgical equipment.

**Results**

A total of 34 patients, 16 of females and 18 males, with the mean age of 66.9 years (minimum: 36 maximum: 85 years) were diagnosed as TASS. Twelve patients had hypertension, five had diabetes mellitus, one had meniere disease, and 16 had no systemic medical problem. Three patients have pseudoxefoliation (PEX) no one had history and sign of any other ophthalmic surgery or inflammation.

Nine patients developed a moderate degree of corneal edema, mild inflammation of AC in 24–48 h following surgery. No patient had purulent secretion, chemosis, lid involvement, and pain. Other ten patients underwent phacoemulsification surgery at the following day, all of them had corneal edema and AC inflammation. Four cases out of ten had severe corneal stromal edema extending from limbus to limbus combining with fibrin formation in the AC, and two cases had hypopyon, but conjunctival inflammation was minimal without discharge and chemosis. None of them had periocular pain. B-mode ultrasonography showed little inflammation in the anterior part of vitreous. According to this observation, we suspected the TASS outbreak clinically, but we did not exactly differentiate it yet from infectious endophthalmitis by the culture. Therefore, operations on the 3rd day were stopped. However, we mainly work as an outpatient clinic, and most of our patient could be examine the following day of surgery at 10 a.m. or later. Until we evaluate the previously operated patients which TASS outbreak was suspected, three other new cases had already undergone operation on the 3rd day. Unfortunately, all of them had TASS-like inflammation on the 1st postoperative day such as other patients.

Even there were still some doubts about the diagnosis of TASS and all patients regarded as having infectious endophthalmitis, no evidence of bacterial endophthalmitis was found on negative culture from surgical equipment. Because any surgical instruments or environmental conditions could be the cause of TASS, we investigated all possibilities of intraoperative and postoperative conditions. When we compared both inpatient underwent other intraocular surgeries such as pars plana vitrectomy in the same period, or patient underwent cataract operation previously, there were no significant differences in the operating room, operating personnel, including surgeons, nurses, type and length.
of surgeries, instruments, phaco machine, tubing sets, sterilization method of reused surgical devices, BSS, and type of IOL. There had been no changed in other surgical equipment and conditions. At that moment, expiration dates and lot numbers for all of the substances used were revised. Only a new VES of 2% sodium hyaluronate with same lot number which recently used in all patient underwent cataract surgery was found as a suspect agent and source of TASS. We thought inadequate washing and incomplete elimination of residues from high-concentrated VES that may end up TASS in our first 22 cases. Hence, the following week, we started the operations and change the VES from high concentration of 2% to low concentration of 1.4, with lower molecular weight. Both VES has same osmolarity, pH, and chemical vehicles. Both products made with rooster comb that refrigerating between 2° and 8° is necessary to keep them safe for surgery. Unfortunately, we observed TASS-like inflammation the following 12 patients with low concentrated VES were used too. However, the clinical conditions were not as serious as the first group no one had hypopyon or membrane, and corneal edemas were less severe. At 1st postoperative day, a total of eight patients had Grade 4 edema while seven patients had Grade 3, 12 had Grade 2, and 7 had Grade 1 edema. All of them had Grade 2-4 inflammation, four of them had fibrinous membrane, two cases had hypopyon.

Initially, all patients regarded as having infectious endophthalmitis and intense topical antibiotics applied every 15 min, systemic antibiotics administered two times a day and topical 5% NaCl applied every hour on the first 2 postoperative days. As we found no evidence of bacterial endophthalmitis on the negative culture, we favored sterile endophthalmitis, resembling TASS, therefore, did not continue systemic antibiotic treatment and we changed the topical treatment regime from antibiotic to mainly topical steroids. Most cases respond rapidly to topical steroids given 30 min for the first 2 days with gradual tapering to eight times a day at the end of the 1st week, following five times a day for a month. Subconjunctival injection of dexamethasone performed once a day for 5 days and 60 mg of methylprednisolone acetate administered orally per a day for 10 days in patient with hypopyon and fibrous membrane formation.

Most cases respond rapidly to intense steroid treatments. In all 34 cases, the AC inflammation diminished within 48 h and disappeared gradually at the end of 1st week. However, sterile membrane formation was persisted in two eyes with PEX and yttrium-aluminum-garnet (YAG) laser membranotomy was performed. None of them had recurrent membrane formation and AC inflammation after YAG membranotomy. Corneal edema significantly decreased to Grade 1 or 2 within a week, 12 corneas regain transparency, 17 eyes had G: 1 and five had G: 2 edema at the end of 1st week. Two eyes had persisted G: 2 edema during 1-year follow-up period. Fortunately, no one had endothelial decompensation and no one underwent corneal transplantation surgery. Eight cases in whom intense AC inflammation was observed had increased IOP in 1st week, which controlled with topical antiglaucoma medication (dorzolamide-timolol combination and brimonidine) for 1 month, then only brimonidine two times a day was continued. No one underwent any glaucoma surgery during follow-up of 1 year. Visual acuities ranged between hand motion on 10 cm to 0.7 in snellen chart with the average of 0.184 ± 0.178 on 1st postoperative day and gradually increased to mean 0.46 ± 0.22 (minimum: 0.1 to maximum: 0.8) in 1st week; 61.8% of cases had more than 0.5 visual acuity. At the end of 1st month, visual acuities of patients underwent YAG membranotomies increased to 0.3 and 0.4 too. The lowest visual acuities were mainly due to retinal pathology such as age-related macular degeneration. The suspected VESs made of rooster comb were substituted by VES derived from bacterial fermentation, and no cases of TASS have occurred for more than 1 year.

Discussion

TASS is an intense early sterile inflammation of anterior segment of the eye after intraocular surgery that can present as sporadic cases or in outbreaks. Its incidence is considered to be changed from 0.1% to 2%, but the mild cases can recover spontaneously in a short period so usually most of the TASS cases unnoticed and fortunately the serious cases are very rare.[3,8-11] Duffy et al. observed six patients with TASS after cataract surgery, reposition of a previously implanted AC IOL, or trabeculectomy in a 1 week period.[12] Choi and Shyn reported 15 cases of TASS between April and December 2005 after phaco surgery and Breebaart et al. presented 18 cases with TASS, 16 of them underwent operation in 8 weeks period.[2,13]

We observed a total of 34 patients had TASS all of them had undergone uneventful phacosaurgery in a 2 consecutive weeks period. As far as we know, our report is the largest cluster of TASS reported due to any reason which was also observed in the shortest period. Diagnosis of TASS and differentiation from infectious endophthalmitis is critical and identifying the causative agent in this syndrome can be a difficult process. Symptoms occurred in the 1st postoperative day in all of our patients, which was earlier presentation time of infectious endophthalmitis that peaks between typically 3–5 days postoperatively. Even with diffuse severe degree corneal edema and significant AC inflammation with the face of hypopyon in some of them, no one had pain, conjunctival discharge, eyelid swelling, and significant vitreous involvement which
are typically appear in infectious endophthalmitis and important criteria for differential diagnosis of TASS.\(^{[5-7]}\)

We observed little inflammation confined mainly to the anterior part of the vitreous in two cases similar to Choi and Shyn’s observation which may due to secondary involvement of immunologic reaction from anterior segment. According to clinical findings and no evidence of microbes by negative cultures, we consider them TASS and changed the initial treatment regimen from antibiotics to intense anti-inflammatory therapy as recommended. Because TASS is caused by toxicity and not sterility, it responds well to intense steroid treatment as it observed in most of our cases. In cases of TASS, the corneal endothelium has more significantly damaged because it is the most sensitive anterior segment tissue to toxic agents. Clinical outcomes are related to toxic effect of causative agent.\(^{[8-12]}\)

The possible source of TASS in our cases may lower toxic effect than other chemicals such as sterilization residues. Therefore, fortunately with adequate treatment and close monitoring, no one requires a penetrating keratoplasty during 1-year follow-up. In Duffy et al.\(^{[12]}\) series, three of six cases had received a corneal transplant, and in Choi and Shyn\(^{[13]}\) series, 5 of 15 patients underwent penetrating keratoplasty. Despite intense treatment, two severe cases with membrane formation in the AC showed only a moderate reduction in corneal edema and some improvement in vision. Both patients with persistent membrane formation had PEX too, which had been implicated in blood-aqueous barrier disruption and subsequently heavy leakage of protein and fibrinoid substance from iris vessels causing membrane formation in the AC. These patients with persistent membrane formation treated successfully by YAG laser. Because AC washout and surgical membranectomy have not been shown to improve the prognosis and also has potential complication of endothelium which may lead to corneal decompensation, we prefer to perform noninvasive YAG membranotomy.\(^{[3,4,10,11]}\) None of these patients had recurrent membrane formation and severe AC inflammation and persistent corneal edema after YAG membranotomy. When the outbreak had been recognized to prevent TASS in other patient thorough investigation was done to identify the possible cause of our series. We reviewed intraocular surgery procedure, including sterilization protocol, equipment usage, expiration dates, and lot numbers for all materials. As reused tubing lines and cannules never used in any of our cases, phaco handpiece and I/A tips are sterilize by prolonged high-temperature sterilization instead of ethylene oxide or short cycle sterilization and all reusable instruments are rinsing with sterile distilled water, the sterilization technique could not be the reason of our cases in contrast to other series in contrast to other series reported in the literature.\(^{[14-17]}\) Andonegui et al.\(^{[9]}\) observed five cases with TASS, caused by BSS, prepared in the hospital pharmacy but as commercial BSS has been using in our clinic, BSS could not be the reason of TASS either. At the end of surgery, subconjunctival injection was given instead of intracameral antibiotics and/or ointments. In addition, the possibility that antibiotic eye drops flowed into the AC following surgery was very low because all ACs were well maintained on the 1\(^{st}\) postoperative day in each cases. There had been no changes in most of surgical materials. In contrast, recently, a new VES of 2% sodium hyaluronate was used in the first 22 cases TASS may caused by inadequate irrigation of this VES with high-molecular weight and viscosity. Therefore, 2% VES substituted by another VES with lower concentration of 1.4% sodium hyaluronate which has also lower molecular weight and viscosity. Although less severe than that of with the previous VES, TASS was occured with the lower concentrated VES too.

VES related TASS, may caused by some variation in the manufacturing, transport or storage process which is unrecognized by inspection during surgery other than different concentration and viscosity. Both VES has same osmolarity, pH, and chemical properties none of them were outside the tolerable physiological limit for maintaining viability to anterior segment tissues. Both products were sterile pyrogen-free solution made with rooster comb, in which resident protein contents are high, in contrast to sodium hyaluronate derived from bacterial fermentation. Refrigerating between 2\(^{\circ}\) and 8\(^{\circ}\) is necessary for VES made of rooster comb to keep them safe for surgery, because storage at room temperature or exposure to heat may change its integrity and cause TASS as we observed in our series. Because even paying attention to keep them in proper condition, we did not have any information about storage and transport environment before arriving our hospital.\(^{[18]}\) When the possible cause of TASS detected, these VESs were substituted by different VES derived from bacterial fermentation, and no cases of TASS have occurred for more than 1 year. To the best of our knowledge, this is the first report of TASS outbreak caused by VES made of rooster comb and the largest series of presented in the same clinic that well treated without necessity of any further surgery or left any significant sequel. TASS may have catastrophic and irreversible complications.

**Conclusion**

Therefore, special attention needs to be pay on each step to prevent the syndrome. Once it occurs, combining with thorough management, all possible risk factors, especially newly introduced medical devices such as VES, its storage, and transport conditions, as we observed in our series must analyze to identify and eradicate causative agent.
Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Maier P, Birnbaum F, Böhringer D, Reinhard T. Toxic anterior segment syndrome following penetrating keratoplasty. Arch Ophthalmol 2008;126:1677-81.
2. Breebaart AC, Nuyts RM, Pels E, Edelhauser HF, Verbraak FD. Toxic endothelial cell destruction of the cornea after routine extracapsular cataract surgery. Arch Ophthalmol 1990;108:1121-5.
3. Holland SP, Morck DW, Lee TL. Update on toxic anterior segment syndrome. Curr Opin Ophthalmol 2007;18:4-8.
4. Mamalis N, Edelhauser HF, Dawson DG, Chew J, LeBoyer RM, Werner L. Toxic anterior segment syndrome. J Cataract Refract Surg 2006;32:324-33.
5. Andonegui J, Jiménez-Lasanta L, Aliseda D, Lameiro F. Outbreak of toxic anterior segment syndrome after vitreous surgery. Arch Soc Esp Oftalmol 2009;84:403-5.
6. Sarobe Carricas M, Segrelles Bellmunt G, Jiménez Lasanta L, Iruin Sanz A. Toxic anterior segment syndrome (TASS): Studying an outbreak. Farm Hosp 2008;32:339-43.
7. Sato T, Emi K, Ikeda T, Bando H, Sato S, Morita S, et al. Severe intraocular inflammation after intravitreal injection of bevacizumab. Ophthalmology 2010;117:512-6.e1-2.
8. Ozcelik ND, Eltutar K, Bilgin B. Toxic anterior segment syndrome after uncomplicated cataract surgery. Eur J Ophthalmol 2010;20:106-14.
9. Kim SY, Park YH, Kim HS, Lee YC. Bilateral toxic anterior segment syndrome after cataract surgery. Can J Ophthalmol 2007;42:490-1.
10. Mamalis N. Anatomy of a TASS outbreak. J Cataract Refract Surg 2007;33:357-8.
11. Meltzer DW. Sterile hypopyon following intraocular lens surgery. Arch Ophthalmol 1980;98:100-4.
12. Duffy RE, Brown SE, Caldwell KL, Lubniewski A, Anderson N, Edelhauser H, et al. An epidemic of corneal destruction caused by plasma gas sterilization. The Toxic Cell Destruction Syndrome Investigative Team. Arch Ophthalmol 2000;118:1167-76.
13. Choi JS, Shyn KH. Development of toxic anterior segment syndrome immediately after uneventful phaco surgery. Korean J Ophthalmol 2008;22:220-7.
14. Whitby JL, Hitchins VM. Endotoxin levels in steam and reservoirs of table-top steam sterilizers. J Refract Surg 2002;18:51-7.
15. Parikh C, Sippy BD, Martin DF, Edelhauser HF. Effects of enzymatic sterilization detergents on the corneal endothelium. Arch Ophthalmol 2002;120:165-72.
16. Liu H, Routley I, Teichmann KD. Toxic endothelial cell destruction from intraocular benzalkonium chloride. J Cataract Refract Surg 2001;27:1746-50.
17. Glasser DB, Schultz RO, Hyndiuk RA. The role of viscoelastics, cannulas, and irrigating solution additives in post-cataract surgery corneal edema: A brief review. Lens Eye Toxic Res 1992;9:351-9.
18. Bissen-Miyajima H. Ophthalmic viscosurgical devices. Curr Opin Ophthalmol 2008;19:50-4.