

Development of Toxic Anterior Segment Syndrome Immediately after Uneventful Phaco Surgery

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Purpose: We report on 15 cases of suspected toxic anterior segment syndrome after uneventful phaco surgery.

Methods: We retrospectively reviewed the charts of patients who had developed toxic anterior segment syndrome (TASS) after uneventful phacoemulsification for senile cataracts between April and December of 2005. Clinical features and all possible causes were investigated including irrigating solutions or drugs, surgical instruments or intraocular lenses, sterilization techniques for instruments, or any other accompanying disease.

Results: The patients consisted of 2 males and 13 females with an average age of 64.7±10.9 years. Five different surgeons had performed their phaco surgeries. No abnormal preoperative or operative findings were reported. Nevertheless, all 15 patients developed a moderate degree of corneal edema. Ordinary treatments were not helpful. We suspect that lack of sterilization resulted in the development of the syndrome, because after ethylene oxide gas sterilization was replaced with autoclaving, no such incidents have occurred.

Conclusions: Toxic anterior segment syndrome requires special attention and thorough management, including sterilization of reused surgical instruments.

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Key Words: Corneal edema, Phacoemulsification, Toxic anterior segment syndrome

Recent technological developments have made the extraction of cataracts and intraocular lens implantations highly successful. However, temporary postoperative infections may be caused during these operations. The potential causes of such postoperative infections include intraoperative damage, a remnant of lens remaining in the eye, bacteria, sterile toxic substances, or preoperative uveitis.¹ Corneal edema may occur due to damage of the corneal endothelial cells. An increase in intraocular pressure, infection, or acute edema due to mechanical damage may also occur. If the endothelial cells retain normal function, they will recover completely over time.²

Since the 1980s, several cases of severe infections in the anterior segments have been reported. In addition, there have been cases of hypopyon caused by toxic substances as well as anterior segment damage to various degrees.³⁻⁶ At first, these cases were referred to as sterile endophthalmitis. However, with the symptoms of infection restricted to the anterior segments, Mondon et al.⁷ later renamed it "Toxic Anterior Segment Syndrome," or TASS. To be diagnosed as

TASS, serious anterior segment infection should occur in the early stages after anterior surgery, fibrosis should be observed, and corneal edema should be observed. In addition, the vitreous body of the eye should not be infected. In most cases, this syndrome occurs after an uneventful cataract operation, with symptoms usually showing on the same day or the day after the operation.

Corneal endothelial decompensation is known to be a very rare complication after cataract surgery, with incident rates of less than 1%.⁸ In Korea, however, corneal edema cases which have occurred due to the anterior chamber not being correctly irrigated with distilled water have been reported.^{9,10} In Gachon University Gil Medical Center, 15 cases occurred over a 9 month period with no known cause. Thus, the team decided to investigate the cause of those cases with a suspicion of TASS.

Materials and Methods

This study examines 15 eyes of 15 patients who were diagnosed with senile cataracts and underwent phacoemulsification and posterior chamber intraocular lens implantation at Gachon University Gil Medical Center. To analyze patient-related factors as well as factors related to operative conditions, we conducted a retrospective chart review and analysis on the pre- and post-operative conditions of those patients.

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Prior to the operation, all patients had tropicamide 1%, phenylephrine hydrochloride 2.5%, and cyclopentolate 1% for mydriasis applied to their eyes. Patients also had their skin and conjunctiva disinfected with betadine before the operation. The field was cleansed with normal saline, and then covered with a disposable sterilized surgical drape. The surgeon who performed the operation did a clear corneal incision with a 3.2 mm keratome. He then inserted viscoelastics into the anterior chamber and performed a continuous curvilinear capsulorrhexis, hydrodissection, phacomulsification, and placed an intraocular lens in the posterior chamber. After these steps were taken, dexamethasone and gentamicin sulfate were injected under the conjunctiva. All of the surgeries were uneventful. There were no complications during the operations.

Preoperative conditions which were evaluated included gender, age, preoperative visual acuity, history of systemic disease, history of ocular disease, corneal endothelial cell counts according to the specular microscopy, and medication used prior to the day of the operation. Intraoperative conditions were the operator, scrub nurses, operating room number, order of surgery, phaco machine, viscoelastics, intraocular lens, irrigating solution, and method used to sterilize the surgical instruments. Postoperative conditions included testing visual acuity after one week, final visual acuity at the last visit, notation of whether the cornea was transplanted, and testing to determine if glaucoma occurred. All figures for visual acuity used in this study are the best-corrected decimal acuity.

Results

The patient group consisted of 2 male and 13 female patients with an average age of 64.7±10.9 years. Of the 15

eyes, 7 were right eyes and 8 were left. Eight patients had hypertension, five had type 2 diabetes mellitus, one had a history of tuberculosis, and four had no significant medical issues. Preoperative visual acuity varied from 0.1 to 0.6, and corneal endothelial cell counts shown in specular microscopy all exceeded 2,700 with normal cell density, coefficient of variation and hexagonality. Either ofloxacin or levofloxacin was used the afternoon before the surgery, once every hour for 7 hours. It seemed that there was no special clinical issue (Table 1).

The surgeries were performed by five different ophthalmologists (A~E). Four operating room nurses rotated to attend the operations. There were 801 cases of phacomulsification conducted in our hospital from April to December of 2005. The global incidence rate of TASS for these surgeries was 15/801 (1.87%). The incidence rate for each surgeon was as follows: A=4/285 (1.40 %), B=4/134 (2.99%), C=2/121 (1.65%), D=4/147 (2.72%), and E=1/79 (1.27%).

There was no correlation between the order of surgery and the operating room number. The cataract surgeries were conducted in two rooms. Six cases occurred in one room, and nine cases in the other. The phacomulsification times in all cases were under 10 minutes. Overall surgical time for each case did not exceed 30 minutes. All 15 cases developed at different times, and did not occur on the same day. Some surgeons preferred to use Sovereign® (AMO, California, USA) or Erbe® (GmbH, Tübingen, Germany) for the phaco machine. Intraocular lenses were hydrophobic or made of hydrophilic acrylic. All of the lenses were inserted into the posterior chamber. The viscoelastics used during the surgeries were Healon® (AMO, California, USA) or Heal Plus® (LG Life Sciences, Seoul, Republic of Korea). BSS® (Alcon, Hünenberg, Switzerland) was used as an irrigating solution (Table 2).

Table 1. Preoperative characteristics of TASS cases

Patient No.	Sex	Age	Side of eyes	Systemic disease	VA (Preop)	Specular microscopy	Topical Medication
1	F	52	L	HTN	0.4	2,983	ofloxacin
2	F	74	R	HTN	0.3	3,265	ofloxacin
3	F	72	L	DM, HTN	0.4	3,194	levofloxacin
4	F	51	L	DM	0.3	3,022	levofloxacin
5	F	81	L	DM	0.1	2,833	levofloxacin
6	F	59	R	DM, HTN	0.6	2,774	levofloxacin
7	F	70	R	Tbc	0.2	3,190	levofloxacin
8	M	64	L	DM, HTN	0.1	3,277	levofloxacin
9	F	47	R	(-)	0.4	3,019	levofloxacin
10	F	70	R	HTN	0.3	2,740	levofloxacin
11	F	65	L	HTN	0.4	2,865	ofloxacin
12	F	83	L	HTN	0.1	2,956	ofloxacin
13	F	62	R	(-)	0.6	3,138	ofloxacin
14	M	52	L	(-)	0.2	3,274	ofloxacin
15	F	68	R	(-)	0.2	3,015	levofloxacin

VA=visual acuity; DM=diabetes mellitus; HTN=hypertension; Tbc=tuberculosis.

Table 2. Intraoperative characteristics of TASS cases

Patient No.	Room No.	Order of surgery	Operator	Scrub nurse	Phaco machine	IOL	OVD
1	3	1	A	a	So	hydrophobic	H
2	3	2	A	a	So	hydrophobic	H
3	2	3	B	a	So	hydrophobic	H
4	2	1	C	b	So	hydrophobic	P
5	2	1	B	b	So	hydrophobic	P
6	2	2	B	b	So	hydrophobic	P
7	3	1	A	c	So	hydrophobic	P
8	2	2	B	b	So	hydrophobic	P
9	3	1	A	c	So	hydrophobic	P
10	2	2	C	c	So	hydrophobic	P
11	3	3	D	c	Er	hydrophilic	H
12	3	2	D	d	Er	hydrophilic	H
13	3	1	D	a	Er	hydrophilic	H
14	3	2	D	b	Er	hydrophilic	H
15	3	2	E	a	So	hydrophobic	P

So=Sovereign®; Er=Erbe®; H=Healon®; P=Heal plus®.

All of the patients had severe corneal stromal edema ranging from limbus-to-limbus to Descemet's membrane folds on the day after surgery. Their visual acuity was limited to hand motion or light perception. There were inflammatory cells and fibrous exudate in the anterior chamber. In addition, the pupils showed irregular, unreactive features and mydriasis in various degrees. However, B-scan ultrasonography showed little inflammation in the vitreous, and the inflammation was confined mainly to the anterior segment. Compared to severe anterior chamber inflammation, conjunctival inflammation is less severe. This includes conjunctival or ciliary injection, discharge, and conjunctival edema.

Because any surgical instruments or machine can be the cause of intractable postoperative corneal edema, we investigated the possibility that the intraocular lenses or viscoelastics were inferior products. We asked the manufacturing company about this possibility. They informed us that there were no cases like ours reported for materials

with similar lot numbers. In addition, we received no information from the company regarding the phaco machine, tubing line, cassette, and inappropriate phaco power. Even though the phaco machine may malfunction due, for example, to incorrect power, the surgeon can almost always detect this. We therefore regarded malfunctioning of the phaco machine to be an unlikely cause of the TASS.

We suspected TASS clinically and differentiated between it and infectious endophthalmitis. In general, anterior segment inflammation caused by infectious endophthalmitis develops 2-3 days postoperatively, accompanies inflammation in the vitreous, and shows inflammation in the conjunctiva or eyelid.

Visual acuity after 1 week ranged between hand motion and 0.1 (Fig. 1). Steroids and 5% NaCl solution were used as treatment. Five out of 15 patients stopped coming to the Medical Center within a month after the surgery. Another 5 of the 15 patients underwent penetrating keratoplasty (Fig. 2

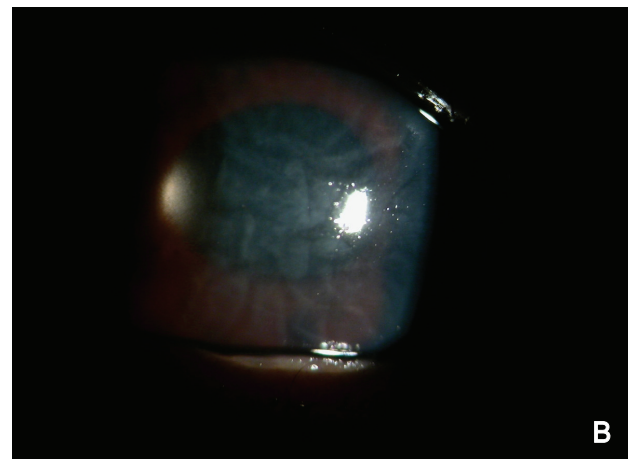
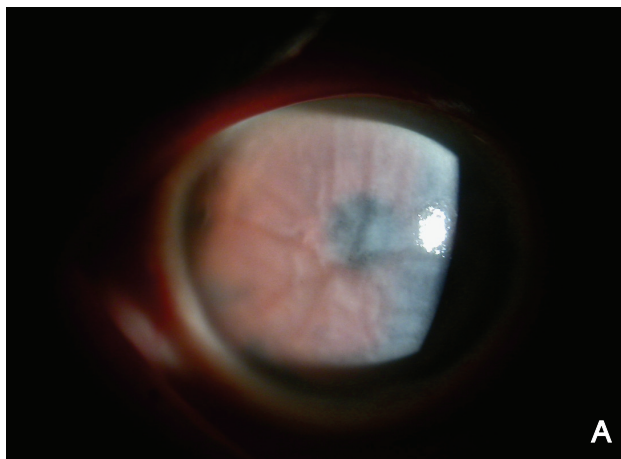


Fig. 1. A, B, Postoperative corneal edema was evident in patient 10 (A) and 13 (B). Note the marked limbus to limbus edema and an irregular, unreactive pupil.

and 3) with a donated cornea. The final visual acuity of these patients improved to between 0.1 and 0.5. However, one patient suffered from graft rejection which made visual acuity close to light perception. Four patients showed an increase in intraocular pressure and had to receive topical treatments for glaucoma. The increased intraocular pressure of one patient in this group was not controlled with medication. This patient received a trabeculectomy. Malignant glaucoma developed and visual acuity was not restored (Table 3).

We investigated the possibility of an abnormality in the viscoelastics or intraocular lenses used during surgery, but could not find any problem. Additionally, the possibility that antibiotic eyedrops or ointment flowed into the anterior chamber immediately after surgery was very low because the anterior chamber was well maintained on the first post-operative day.

While conducting this study, we investigated the technique used to sterilize the surgical instruments used during cataract surgeries and found that all sterilization procedures for the phaco handpiece, insertion device for the intraocular lens, and

tubing line had been done using EO gas. All of the tubing lines used in these cases were reused after EO gas sterilization. EO gas sterilization was later replaced with autoclaving for the phaco handpiece and the insertion device for intraocular lens. Sterrad® (Johnson & Johnson, Miami, USA) was used for the tubing line. No cases of TASS have occurred since the sterilization technique was changed.

Discussion

TASS is an acute sterile inflammation of the anterior segment which may occur after surgery on the anterior segment. The most distinctive characteristic of TASS is the timing of the symptoms. Symptoms usually have an onset 12 to 48 hours after the surgery. This syndrome recently came under the spotlight as multiple incidents were reported across the United States. The inflammation is restricted to the anterior segment, and does not involve the vitreous. It can be partially alleviated with frequent topical administration of steroids.¹¹

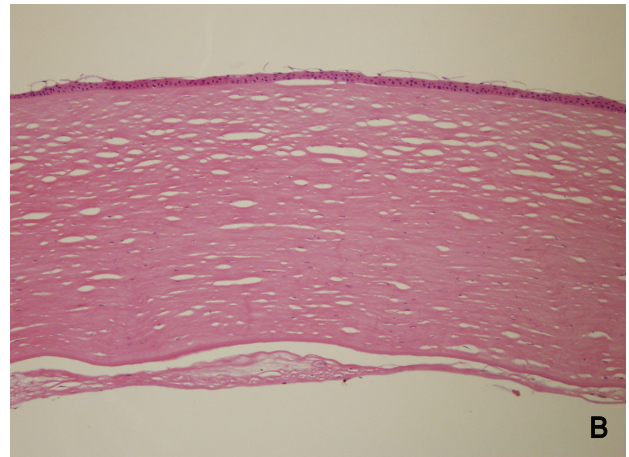
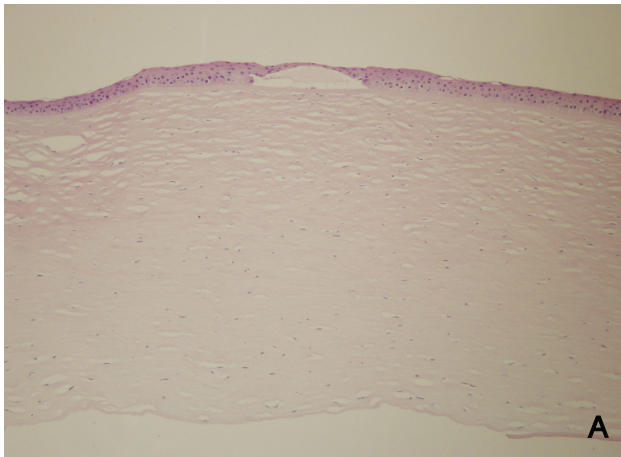


Fig. 2. A, B, Hematoxylin and eosin-stained sections of the corneal button obtained at the time of penetrating keratoplasty. The lack of endothelial cells was noted in (A) (patient 10) and subendothelial fibrosis was noted in (B) (patient 13). $\times 100$.

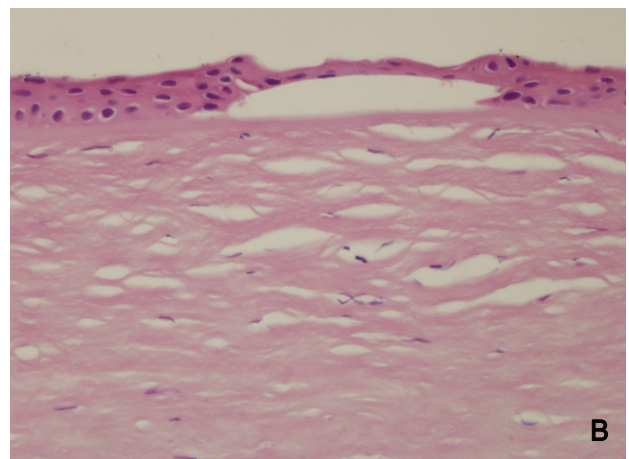
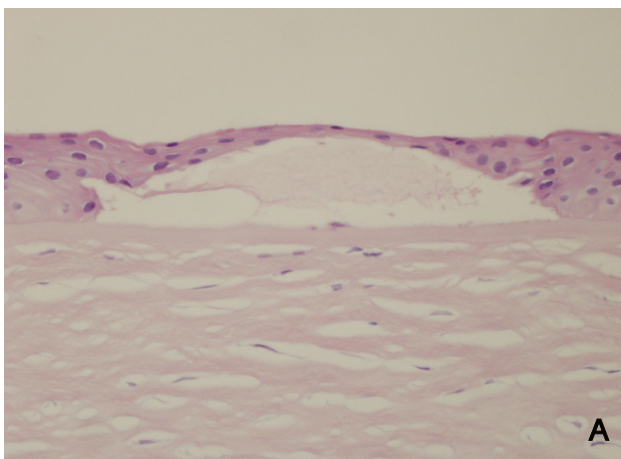


Fig. 3. A, B, Hematoxylin and eosin-stained sections of the magnified anterior portion of the corneal button obtained at the time of penetrating keratoplasty in patient 10 (A) and 13 (B). Both show epithelial cysts and irregular epithelial cell proliferation consistent with bullous keratopathy. $\times 400$.

Table 3. Postoperative characteristics and clinical courses of TASS cases

Patient No.	VA (POD#7)	PKP	VA (Final)	Glaucoma medication	Follow-up
1	0.08	done	0.2	(-)	
2	0.1	(-)	0.1	done	loss
3	0.1	(-)	0.1	(-)	
4	HM	(-)	NLP	done	
5	0.08	(-)	0.08	(-)	loss
6	0.04	(-)	0.04	(-)	loss
7	HM	(-)	HM	(-)	loss
8	HM	(-)	HM	done	
9	HM	(-)	HM	done	Malignant glaucoma
10	0.04	done	0.1	(-)	
11	HM	done	0.5	(-)	
12	HM	(-)	HM	(-)	loss
13	HM	done	0.2	(-)	
14	HM	done	LP	(-)	rejection
15	0.1	(-)	0.2	(-)	

VA=visual acuity; PKP=penetrating keratoplasty; NLP=no light perception; HM=hand motion; LP=light perception.

When the damage is restricted to corneal endothelial cells, TASS cases are classified as toxic endothelial cell destruction syndrome, or TECD.¹²⁻¹⁴ TECD is a rare complication of intraocular operations. According to clinical reports, it causes unexpected severe corneal edema and opacity within 24 hours after surgery.¹²⁻¹⁷ Toxic substances associated with the development of TECD include remnants of cleaning solutions used in sterilizing surgical instruments,¹⁴ topical disinfectants,^{15,16} or preservatives included in medicine which is injected into the anterior segment.¹⁷ The following toxic substances have been shown in studies to cause damage to corneal endothelial cells: preoperative disinfectant, intraocular irrigating solution, highly concentrated intraocular medicine, preservatives, remnants of cleaning solutions for surgical devices, hydrogen peroxide, or the insertion of air into the anterior segment.¹⁸⁻²¹

The most common symptom of TASS is blurry vision. TASS is not painful in most cases, but some patients do complain of some degree of pain. TASS is an acute syndrome with most patients reporting symptoms on the same day of the surgery, or within 24 hours after the surgery. This differentiates TASS from acute infectious endophthalmitis as the pain or visual conditions from endophthalmitis develop around 4-7 days after surgery. The most common clinical feature is edema in the cornea. Infection in the anterior segment is severe, and fibrous exudate or hypopyon is observed due to damage to the blood-aqueous barrier. In addition, the iris may be damaged due to mydriasis, or it may show an irregular, unreactive pupil. Secondary glaucoma may occur as well, which is caused by damage to the trabecular meshwork.¹ In this study, severe diffuse edema in the entire cornea and folding of Descemet's membrane was observed in all 15 patients on the day after the cataract surgery. This corneal edema was notably different from the temporary and local edema which may normally appear after surgeries. Additionally, flare and fibrinous exudate was observed in the

anterior segment. Pupils were irregularly dilated, and showed no response to light (Fig. 1).

It is difficult but important to distinguish TASS from infectious bacterial endophthalmitis. There are some very useful clinical clues which can be used to make this differential diagnosis. TASS usually develops within 24 hours after surgery. Symptoms are limited to the anterior segment, and respond to steroid treatment. Bacterial endophthalmitis usually occurs 4-7 days after an operation. Signs are also seen in the vitreous. It often causes lid edema, conjunctival injection and edema, eye discharges, and pain.²¹ In the cases reported in this study, corneal edema and anterior infection developed within 24 hours after surgery. No conjunctival injection, eye discharge, or pain was reported. The most common symptom in the 15 cases was decreased visual acuity.

Corneal endothelial cells reproduce quite slowly. If damage from disease or an ocular operation occurs, the cell count reduces significantly. At the time of birth, most people have about 5,000 cells/mm². This lowers to 2,500-3,000 cells/mm² by the time people reach their twenties. The number then stabilizes, and if there are no external injuries, it slowly goes down by 0.6% every year. If the density falls to about 800 cells/mm², the patient will develop decompensation. This will lead to a loss of transparency due to edema.²²

The histopathological characteristic of TASS is toxic damage in the anterior segment. Cells undergo necrosis and extracellular matrix is destroyed due to a severe acute inflammatory immune reaction. Corneal endothelial cells are located within the anterior segment, and this area is particularly sensitive to toxic substances, thus the cornea is vulnerable in the event that such damage occurs. There are various factors that can cause damage. These include preservatives in the irrigating solution, antibiotics or anesthetics injected into the anterior segments, mitomycin C,

sterilizers or cleansing solutions for instruments, or viscoelastics. The preservative that is most well known and commonly used in topical medications, benzalkonium chloride, is known to be safe at a concentration of less than 0.001% (the highest safe intraocular concentration). Doses higher than this safe concentration which are injected into the eyes can be fatal to endothelial cells.²³ In addition, according to Pastor et al.²⁴ mitomycin C used during a trabeculectomy may decrease the endothelial cell count by 4.7-20%. Out of the 15 cases, the team performed penetrating keratoplasty on five patients. Corneal tissues from these patients were stained and observed under a microscope. A decrease in the number of corneal endothelial cells was observed. Fibrosis was also noted on the corneal endothelial cells which in turn affected the corneal stroma and epithelium. An irregular increase and fibrosis in the epithelium, which led to bullous keratopathy, was also observed (Fig. 2, 3).

Corneal toxic reactions caused by sterilizing agents have become a recent focus of attention for ophthalmologists and operating room staff. Subtilisin and α -amylase, which are found in some enzymatic detergents, are disabled only when the temperature goes over 140°C. However, most autoclave systems only reach 120~130°C. This may introduce some problems. In an experiment involving men and rabbits, Parikh et al.²⁵ found a correlation between the dose of sterilizing agents and an increase in corneal thickness, as well as histological damage to the endothelial cells. This leads to the recommendation that the cannula, I/A tip, and insertion devices for intraocular lenses, as well as other reusable instruments, should be replaced with disposable instruments.

In addition to the remnants of surgical instrument cleansers, bacterial endotoxin contamination during sterilization can be related to the development of TASS. Gram-negative bacteria may proliferate if the water reservoir in the phaco machine or inside the autoclave is not replaced on a regular basis. Gram-negative bacteria are typically destroyed during the autoclaving procedure; however, heat-stable lipopolysaccharide (LPS) endotoxin may remain behind. Endotoxin deposits are removed only by acetone or alcohol if operative instruments are dry. If heat-stable lipopolysaccharide (LPS) endotoxin gets into the eye during the operation, it may cause severe anterior segment inflammation.²⁶ The team in this study was not able to carry out a chemical toxin analysis after cleansing instruments and sterilizers were used in the surgeries. They were also unable to inject such toxin into animal eyes to compare the symptoms with those of TASS. Therefore, it will be beneficial to carry out further studies to investigate this hypothesis if similar cases may occur in the future.

Another possible cause of TASS during the sterilization process is the presence of precipitated remnants of oxidized metal which are generated in the reusable tubes or metal parts of the cannula. A cannula with a small internal caliber, or one which is covered with chrome, is commonly used in ocular surgery. If it is not thoroughly rinsed and sterilized,

a very small number of metal ions may cause a toxic response on the corneal endothelial cells or uvea. Smith et al.²⁷ found that the chrome covering the inside of the cannula may be oxidized during plasma gas sterilization. This would leave behind traces of copper or zinc, which can in turn get into the anterior segment of the eye and cause TASS. Meanwhile, Duffy et al.²⁸ also showed that a solution which was used to rinse the surgical instruments after plasma gas sterilization could cause TASS if it was injected into the anterior segments of rabbit eyes.

Currently, sterilization of surgical instruments is mostly done using an autoclave or EO gas. An autoclave has the disadvantage of potentially leaving rust inside devices with a small internal caliber. It may also wear down the instruments. However, the U.S. Centers for Disease Control and Prevention (CDC) pointed out that EO gas is a carcinogen and can be toxic to reproductive cells.²⁸ This indicates that sterilization using EO gas should be avoided whenever possible. Autoclaving should be the technique of choice to sterilize surgical instruments. The use of disposable instruments will help make operative conditions safer for patients.²⁸ In this study, the team found that all patients who developed TASS had surgeries which used instruments that were sterilized with EO gas. Therefore, it is highly likely that development of TASS was related to the sterilization technique. In addition, if metal remains are not removed from the surface or interiors of surgical instruments, they may be toxic to corneal endothelial cells during an operation.

The first step in treating TASS is differentiating the symptoms from bacterial endophthalmitis. Topical steroids are then used frequently while the inflammation in the anterior segment and the severity of the corneal edema is monitored. Additional intraocular pressure measurements and treatments may be necessary because the inflammation and destruction in the trabecular meshwork may lead to increased intraocular pressure and the development of glaucoma. As the corneal edema start showing signs of improvement, a gonioscopic examination should be conducted to identify peripheral anterior synechiae of the iris. Specular microscopy to check for damage to the endothelial cells should also be done.

Despite these treatments, TASS can progress unfavorably. Minor cases may improve over several days to weeks with the use of topical steroid treatments. However, severe cases will show only a slight reduction in corneal edema or no improvement at all. These cases will eventually require a penetrating keratoplasty. Some cases may need a trabeculectomy or glaucoma valve implant due to the development of uncontrollable glaucoma.²⁹ In this study, the team was able to track the progress of these patients and conducted penetrating keratoplasty for five patients who consented. These patients later showed minor improvement in vision (Table 3). An additional four patients required treatment with anti-glaucoma medication. One of these four had a trabeculectomy (Table 3).

Once it occurs, TASS can be fatal to the cornea and the eye. Therefore, it is best to prevent the syndrome using all possible precautions. First, ophthalmologists and operating room staff need to pay careful attention to all drugs and irrigating solutions which are injected into the anterior chamber. All fluid injected into the anterior chamber can be toxic to the corneal endothelium. It is essential that the types and concentrations of drugs be checked precisely. Second, it is recommended that reusable instruments be replaced with disposable ones. The inside of the phaco tip and handpiece need to be thoroughly washed and rinsed with sterilized deionized water. An autoclave is preferable to the use of EO gas for sterilization of surgical instruments if possible. In addition, the water reservoir for the phaco devices needs to be replaced daily. If it is not, gram-negative bacteria will grow and cause the release of heat-stable endotoxins. The water bath used for the autoclaved devices also has to be replaced at least once a week to suppress bacterial growth or endotoxin proliferation.⁵

If TASS develops despite these preventive steps, additional surgeries should be stopped. A complete check of all surgical instruments and staff involved is necessary before any new surgeries can be performed. In general, corneal edema due to TASS is rarely resolved with topical steroid or hypertonic NaCl treatments. The prognosis in this situation is very bad. A penetrating keratoplasty is the only choice of treatment.

The continuous occurrence of TASS in a short period of time, and the fact that a similar syndrome did not occur for 2 years after the sterilization technique for surgical instruments changed from the use of EO gas to autoclaving, indicates that the EO gas sterilization technique was the most likely cause of TASS. The limitation of this study is that we could not directly prove causality.

In summary, the overall operative conditions, including sterilization and reuse of surgical instruments, requires special attention as well as continuous and thorough management. In addition, it is recommended to check for bacteria and endotoxins in the sterilization system on a regular basis.

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