Toxic anterior segment syndrome: Common causes

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PURPOSE: To identify the most common risk factors associated with toxic anterior segment syndrome (TASS).

SETTING: Ophthalmic surgical centers in the United States, Argentina, Brazil, Italy, Mexico, Spain, and Romania.

METHODS: A TASS questionnaire on instrument cleaning and reprocessing and extraocular and intraocular products used during cataract surgery was placed on the American Society of Cataract and Refractive Surgery web site. A retrospective analysis of questionnaires submitted by surgical centers reporting cases of TASS was performed between June 1, 2007, and May 31, 2009, to identify commonly held practices that could cause TASS. Members of the TASS Task Force made site visits between October 1, 2005, and May 31, 2009, and the findings were evaluated.

RESULTS: Data from 77 questionnaires and 54 site visits were analyzed. The reporting centers performed 50 114 cataract surgeries and reported 909 cases of TASS. From January 1, 2006, to date, the 54 centers reported 367 cases in 143 919 procedures; 61% occurred in early 2006. Common practices associated with TASS included inadequate flushing of phaco and irrigation/aspiration handpieces, use of enzymatic cleansers, detergents at the wrong concentration, ultrasonic bath, antibiotic agents in balanced salt solution, preserved epinephrine, inappropriate agents for skin prep, and powdered gloves. Reuse of single-use products and poor instrument maintenance and processing were other risk factors.

CONCLUSIONS: The survey identified commonly held practices associated with TASS. Understanding these findings and the safe alternatives will allow surgical center personnel to change their practices as needed to prevent TASS.

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Toxic anterior segment syndrome (TASS) is a sterile inflammatory reaction of unknown incidence that can occur after anterior segment surgery. It typically presents within 12 to 48 hours of surgery. The most common finding is diffuse limbus-to-limbus corneal edema (Figure 1) secondary to damage from a toxic insult to the endothelial cell layer. Widespread breakdown of the blood–aqueous barrier is another hallmark of this condition, with fibrin in the anterior chamber and hypopyon present in 75% of cases (Figure 2). Damage to the iris may cause the pupil to dilate or become slightly irregular, and glaucoma secondary to trabecular meshwork damage may also occur.

Treatment with intense topical steroidal agents will eventually lead to resolution of the inflammation; however, in severe cases there may be lasting sequelae, such as permanent corneal edema, glaucoma, and other effects of chronic inflammation. Various entities have been shown to cause TASS. These include, but are not limited to, endotoxin; denatured ophthalmic viscosurgical devices (OVDs); preservatives such as benzalkonium chloride, bisulfites, and metabisulfites; heavy-metal residue, fine-matter particulates, and substances introduced into the anterior chamber that are at a pH or concentration that is toxic to the sensitive endothelial cells. In addition, residue of materials used in the cleaning and sterilization of ophthalmic instruments are an increasingly important source of TASS.

Members of industry and the American Society of Cataract and Refractive Surgery (ASCRS) have joined

to create a TASS task force. The goal of this task force is to educate anterior segment surgeons on the causes, symptoms, and treatment of TASS and to help investigate outbreaks of TASS.

Questionnaires are available on the ASCRS web site[A] to facilitate the reporting of TASS cases. The information entered into the questionnaires is reviewed by members of the TASS Task Force with the goal of identifying potential causes of TASS. Recommendations on preventative measures to stop recurrences are then made. This study will focus on common practices that may lead to TASS as well as alternative measures that will help protect patients having anterior segment surgery.

MATERIALS AND METHODS

The TASS questionnaires were posted on the ASCRS web site in 2007. A retrospective analysis was performed on questionnaires submitted between June 1, 2007, and May 31, 2009. The questionnaires address instrument cleaning and reprocessing practices and surgical protocols as well as substances and techniques used for cleaning phaco and irrigation/aspiration (I/A) handpieces. They also address products used extraocularly and intraocularly, such as medications, and the reuse of cannulas and other disposable items. Responses were analyzed, and commonly held practices that lead to cases of TASS are presented here.

In addition, members of the TASS Task Force made site visits at the request of centers with TASS cases. The visits occurred between October 1, 2005, and May 31, 2009. During the visits, task force members observed preoperative, intraoperative, and instrument processing procedures to identify practices that could be associated with TASS. The data gathered from these visits are presented.

RESULTS

During the study period, 77 TASS questionnaires were submitted through the ASCRS web site, 9 of which were excluded from analysis. Of those excluded, 5 were duplicates, 2 did not report any TASS cases, and 2 were reporting cases of endophthalmitis. Of the centers included, 62 were in the United States; 6 international centers responded, with 1 each from Argentina, Brazil, Italy, Mexico, Spain, and Romania. Members of the TASS Task Force made 54 site visits, all in the United States. Overall, 909 cases of TASS were reported in 50 114 cataract surgeries performed concurrently at the reporting centers that submitted questionnaires. From January 1, 2006, to date, the 54 centers visited by a TASS Task Force member reported 367 cases of TASS in 143 919 procedures performed; 61% of them occurred in 2006.

Table 1 shows the cleaning procedures associated with TASS. Inadequate flushing of the phaco and I/A handpieces after surgery was the most commonly observed and reported behavior that can lead to TASS.

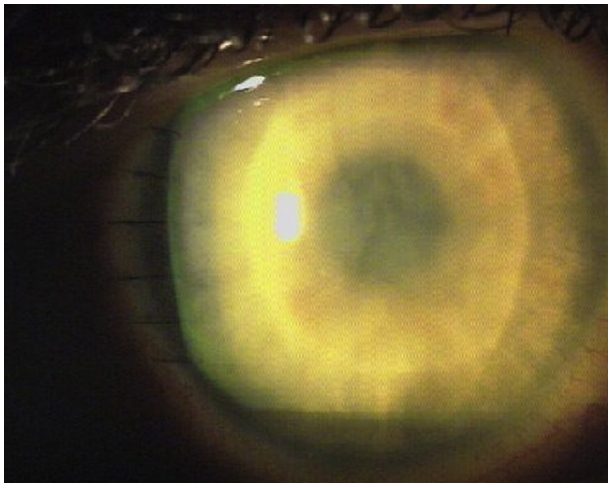

Figure 1. Toxic anterior segment syndrome after phakic IOL surgery. Note the limbus to limbus corneal edema.

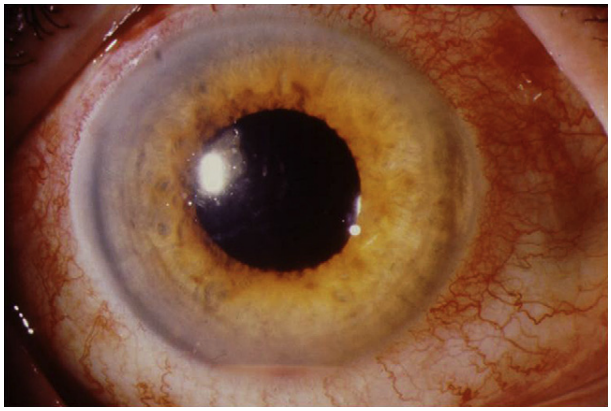

Figure 2. Hypopyon is seen in the anterior chamber of this patient with TASS.

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Of the 68 centers that filled out questionnaires, more than 60% used less than the recommended 120 cc per port (range 2 to 100 cc per port). Other factors were occluded I/A tips during surgery, a symptom of inadequate flushing.

Table 2 shows the observations made during site visits at centers with diagnosed cases of TASS. The top observations were inadequate flushing of phaco and I/A handpieces and cannulated equipment, use of enzymatic cleaners and detergents, use of reusable cannulas, and inadequate or no manual cleaning of instruments. Cleaned instruments were often left on towels that were not lint-free, and many centers did not train personnel regarding TASS and proper cleaning practices.

Medications given intracamerally or added to a balanced salt solution irrigant were another potential source of TASS. Table 3 shows the products associated

Table 1. Cleaning procedures associated with TASS.

Reported Practice	Centers Reporting Practice, n (%) (N = 68)
Amount of flush used for handpieces	
120 cc or more	18 (26)
<120 cc (range 2 100 cc)	42 (62)
Unknown	3 (4)
Not specified	5 (7)
Occluded I/A tips	
Yes	27 (40)
No	41 (60)
Final rinse water	
Deionized/distilled	30 (44)
Sterile/pyrogen free	22 (32)
Tap	12 (18)
Unknown	2 (3)
Not specified	2 (3)
Use of enzymatic cleaners	
Yes	36 (53)
No	28 (41)
Unknown	4 (6)
Use of US Bath	
Yes	43 (63)
No	25 (37)
Frequency of cleaning US bath	
After each use	8 (19)
More than once daily	31 (72)
Unknown	3 (7)
No cleaning protocol	1 (2)
Ophthalmic instruments separated for cleaning	
Yes	55 (81)
No	9 (13)
Don't know	4 (6)

I/A = irrigation/aspiration; US = ultrasonic

Table 2. Observations during site visits at centers with diagnosed cases of TASS.

Observation Category	Frequency of Observation, n (%) (N = 54)
Inadequate flushing of phaco and I/A handpieces and cannulated equipment	48 (89)
Use of enzymatic cleaners and detergents	43 (80)
Use of reusable cannulas	37 (69)
Inadequate or no manual cleaning of instruments	35 (65)
Use of preserved epinephrine	28 (52)
Reuse of single use devices, blades, tips, sleeves, etc.	28 (52)
Use of tap water with no sterile water final rinse	27 (50)
Inadequate personnel or trays to allow proper preparation of instruments	23 (43)
No immediate cleaning allowing OVD and surgical solutions to dry on devices	20 (37)
Use of preserved medicines in the eye	18 (33)
Reuse of tubing for flushing, latex bulb for irrigation, no training, no term sterilization, instruments stored on towels	20 (37)
Touching of IOL or patient contact areas of instruments with gloved hands	18 (33)
Off label use of lidocaine gel	17 (31)
Poor instrument maintenance, residual autoclave residue and instrument mild, rust, particulates, lint, etc.	15 (28)
Use of powdered gloves	15 (28)
Additives added to balanced salt solution against DFU	15 (28)
Improper use of prep solutions, detergents, and cleaners	14 (26)
Failure to follow manufacturer's DFU, including no air flush, use of unapproved enzymatics	11 (20)
Use of postoperative ointment in clear cornea cases	11 (20)
Povidone iodine placed in eye at end of procedure	9 (17)
Incorrect concentration of detergent and enzymatic cleaners used	4 (7)
Lack of routine cleaning of US	2 (4)

DFU = directions for use; I/A = irrigation/ aspiration; IOL = intraocular lens; OVD = ophthalmic viscosurgical device; US = ultrasound

Table 3. Products associated with TASS and their use.

Product Used	Centers Reporting Use, n (%)
Antibiotic added to BSS	
Vancomycin	16 (24)
Gentamicin	1 (1)
None	50 (74)
Unknown	1 (1)
Intracameral antibiotic agents	
Vancomycin	7 (10)
Cefuroxime	3 (5)
Moxifloxacin	3 (5)
Cefazolin sodium	1 (1)
None	54 (79)
Preserved epinephrine in BSS	
Yes	18 (36)
No	32 (64)
Preserved intracameral anesthetic agent	
Yes	3 (6)
No	44 (94)

BSS = balanced salt solution

with TASS. Antibiotic agents were the most common additives to balanced salt solution; some centers added epinephrine with preservatives or stabilizers. Slightly more than 20% of centers used intracameral antibiotic agents; 17 centers (31%) used preserved topical lidocaine gel preoperatively.

Poor instrument maintenance was also pervasive. Autoclaves were found to have autoclave residue, instrument milk, rust, particulates, or lint at more than a quarter of the sites. Other sites failed to follow manufacturer's directions for use when cleaning instruments; this included omitting an air flush of cannulated equipment, although this had been recommended, or using enzymatics during processing when this was not approved.

In centers in which non-ophthalmologic surgeries were performed, ophthalmic instruments were processed along with instruments from other types of surgeries at 9 (13%) centers responding by questionnaire; 4 (6%) respondents did not know whether instruments were separated at the time of processing.

DISCUSSION

The data in this analysis were self-reported in the case of the questionnaires or the result of self-referrals for site inspection in relation to TASS cases. The data from the site visits were taken from written reports submitted at the end of the visit. Although there is motivation on the part of surgical centers to obtain assistance when cases of TASS occur, in an effort to prevent future cases, not all cases of TASS may be recognized or centers may choose not to report cases if only a small percentage of their cataract surgeries result in TASS and a problem is not perceived. Because we do not have a tally of all TASS cases that occur in the United States, and because those reporting cases all reported various timeframes in which the reported cases occurred for each center, we cannot calculate the incidence of TASS from our data.

The most frequently identified practice associated with TASS is inadequate cleaning of phaco and I/A handpieces after use. To be most effective, the manufacturer's directions for use should be strictly followed and handpieces should be wiped with a lint-free cloth, immediately immersed in sterile water until they are flushed, or both.[1–3] This was not done at 89% of centers visited. This practice is imperative to prevent residual OVD and debris from drying within the handpiece and tips before they are flushed. This is especially important because dried OVD denatures after sterilization at high temperatures and if this or other particles or debris are irrigated into the anterior chamber, TASS may result.[4] While instruments are still moist, they must be flushed with 120 mL of fluid per port, or more if indicated in the manufacturer's directions for use. This can be performed with tap water as deionized water. However, the final flush must then consist of sterile distilled or sterile deionized water. If cleaned instruments are stored on towels, the towels should be lint free.[3,5,6]

In addition to addressing the problem of inadequate flushing, it is important to address some of the reasons it occurs. Even if an adequate cleaning protocol is in place, if surgical centers are understaffed or there are too few surgical trays to allow proper cleaning of instruments between cases (as observed at 43% of centers visited), time constraints will lead to insufficient flushing and patients will be placed at risk for TASS. The reuse of tubing for flushing and latex bulbs for irrigation is also a potential issue. These items are difficult to clean and hard to sterilize, which can lead to improper processing between cases.

It is imperative that surgical centers ensure that there are adequate numbers of personnel and surgical trays to allow all steps of cleaning and sterilization to be completed between uses of ophthalmic instruments. It is also crucial that personnel are trained sufficiently in the causes of TASS and the proper steps of cleaning and sterilization.[2,3,7–9]

Eighty percent of surgical centers visited and 53% of those responding via questionnaire were using enzymatic detergents in the processing of their ophthalmic instruments. The benefit of using enzymatic detergents to clean ophthalmologic instruments has not

been established and may actually be prohibited in the manufacturer's directions for use for specific products. Furthermore, the use of detergents mixed at the wrong concentration has been linked to TASS outbreaks.[10] Seven percent of centers visited were using the wrong concentration of detergents, putting their patients at risk for TASS as a result of residual detergents and incomplete rinsing.

Enzymatic detergents often have the exotoxin subtilisin or α-amylase enzymes as their active ingredients. These are only deactivated at temperatures higher than 140°C, and most autoclaves do not reach temperatures higher than 120°C to 130°C. Thus, it is likely that residue from enzymatic detergents will build up on reused instruments.[11] Human and rabbit studies evaluating the effect of enzymatic detergents on the anterior chamber showed dose-related corneal swelling; ultrastructural damage to the endothelial layer, leading to increased corneal permeability; and an increased inflammatory response in the iris.[12]

The purpose behind the use of enzymatic detergents is to rid ophthalmic instruments of debris. If instruments are kept moist immediately after use before flushing and if proper flushing with an adequate volume is performed, there should be no adherent debris and thus no need for enzymatic detergents. If detergents are used, it is imperative that strict attention is paid to the dilution and expiration date. Furthermore, instruments processed with detergents must be rinsed with copious amounts of fluid according to the manufacturer's directions for use. Recommended volumes should be considered a minimum volume, and the final rinse should be performed with sterile distilled or sterile deionized water.[1]

Sixty-three percent of reporting facilities used an ultrasonic bath as part of the processing of their ophthalmologic instruments. This has been associated with the accumulation of heat-stable endotoxins produced by bacteria in the bath water.[13] Endotoxin remaining on instruments after cleaning and sterilization can induce the inflammatory reaction of TASS.

As with enzymatic detergents, the purpose of the ultrasonic bath is to dislodge dried debris from instruments, particularly OVDs. Again, if instruments are kept moist after use and then properly flushed with an adequate volume of water, there should be no adherent debris and thus no need for an ultrasonic bath.

If an ultrasonic bath is used, the manufacturer's directions for use for instruments should be verified because some instruments should not be processed in this manner. In addition, the ultrasonic bath should be designated for medical use only and the manufacturer's directions for maintenance should be strictly followed. Furthermore, all gross material should be completely removed from instruments before they are immersed in bath water. Then, after each use, and if in accordance with the manufacturer's directions for use, the bath water should be emptied and the tub cleaned with an Environmental Protection Agency–registered facility-approved disinfectant. This should be followed with a rinse using volumes of sterile or tap water adequate to remove the cleaning agent completely. Then, 70% to 90% ethyl or isopropyl alcohol should be used to clean the tub if this is in accordance with the manufacturer's directions for use and not associated with a risk of fire. Endotoxin can be removed from the walls of the bath by wiping the walls with ethyl or isopropyl alcohol.[1,14] The tub should then be dried completely with a lint-free cloth and refilled immediately before use.

This process of cleaning must be followed after each use to prevent endotoxin buildup. However, only 19% of centers responding to the questionnaire cleaned the ultrasonic bath after each use as recommended and 4% of centers visited had no protocol for routine cleaning of the ultrasonic bath.

Of centers reporting via questionnaire, 25% added antibiotic agents to the balanced salt solution irrigant and 21% used intracameral antibiotic agents. The use of antibiotic agents may be associated with toxicity when they are included in anterior chamber irrigant and when injected intracamerally at the end of a case.[7] If antibiotic agents are improperly mixed, the concentration may be too high or the pH incorrect, both of which can prove toxic to the anterior chamber tissues.

The use of vancomycin and gentamicin sulfate in anterior segment surgery has been described for prophylaxis against endophthalmitis.[15] However, the use of these products is associated with concerns over vancomycin-resistant organisms as well as aminoglycoside-related macular toxicity, respectively. Furthermore, the concentration used in irrigating solution and the time of contact with a possible contaminant is inadequate for their bacteriostatic or bacteriocidal properties to function.

Studies to evaluate intraocular cefotaxime for endothelial toxicity have been performed. A prospective randomized masked study of 66 patients by Kramann[16] found no toxicity with 0.4 mL of 0.25% cefotaxime in the anterior chamber. Other studies evaluating the use of cefuroxime[17,18] found no toxicity and a role for the agent in endophthalmitis prevention.

These findings were strengthened with the results in a prospective randomized partially masked study in which 1.0 mg cefuroxime in 0.1 mL normal saline injected into the anterior chamber after surgery decreased the risk for endophthalmitis (0.05% incidence rate when counting all endophthalmitis cases)

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