

An Epidemic of Corneal Destruction Caused by Plasma Gas Sterilization

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Background: Toxic endothelial cell destruction (TECD) syndrome after intraocular ophthalmic surgery is rare and can result from exposure to a variety of toxins. During January 8 to 14, 1998, 6 patients developed TECD with corneal edema associated with unreactive or dilated pupils at Hospital A.

Methods: A case patient was any Hospital A patient with TECD within 24 hours after surgery during January 5 to 14, 1998 (epidemic period). A control was any hospital A ophthalmic surgery patient without TECD during the epidemic period. The medical records of hospital A ophthalmology surgery patients during the pre-epidemic (ie, September 1, 1997-January 4, 1998) and epidemic periods were reviewed. Inductively coupled plasma atomic emission spectrometry was used to detect trace inorganic elements on sterilized surgical instruments. Cannulated surgical instruments and laboratory rinsates were perfused directly to the corneal endothelium of isolated rabbit and human corneas. Corneal endothelial ultrastructure and swelling were assessed.

Results: The rate of TECD at hospital A was higher during the epidemic than pre-epidemic period (6/12 vs 0/118, $P < .001$). The only change during the periods was the introduction, on November 5, 1997, of a new sterilization method, AbTox Plazlyte, for sterilization of ophthalmic surgery instruments. Findings from spectrometry revealed that copper and zinc residues were higher in instruments sterilized with Plazlyte than in those sterilized with ethylene oxide (median copper value, 7.64 mg/L vs 0.14 mg/L, respectively, $P = .02$; median zinc value, 5.90 mg/L vs 1.35 mg/L, respectively, $P = .2$). Corneal endothelial perfusion of Plazlyte sterilized-instrument rinsates or laboratory solution with copper and zinc produced irreversible damage, similar to toxic corneal endothelial destruction, to rabbit and human corneas.

Conclusion: A new sterilization method degraded brass to copper and zinc on cannulated surgical instruments resulting in TECD of the cornea.

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TOXIC ENDOTHELIAL cell destruction (TECD) syndrome is a rare complication of intraocular surgery.¹⁻⁶ It is clinically manifest by unexpected profound corneal edema and opacification within 24 hours after surgery. Toxins implicated in TECD include detergent residues on ophthalmic instruments,³ topical antiseptic solutions,^{4,5} or preservatives in intraocular medications.⁶ Corneal endothelial cell toxic effects have been demonstrated experimentally with presurgical topical antiseptic solutions,⁵ intraocular irrigating solutions,⁷ high concentrations of intraocular medications,⁸ antibiotics in corneal storage media,^{9,10} preservatives in medications,^{3,6,8,11-13} detergent residues on instruments,¹⁴ hydrogen peroxide,¹⁵ or intraocular air.¹⁶ Corneal edema following ophthalmic surgery also can result from mechanical trauma, high intraocular pressure, or inflammation.¹⁷ Severe corneal endothelial decompensation can require corneal transplantation. Of 1.4

million cataract surgeries performed in the United States annually,¹⁸ it is estimated that 0.62% are complicated by corneal edema or corneal transplantation requiring rehospitalization.¹⁹

Because instruments routinely used in ophthalmic surgery often have small lumens, careful cleaning and sterilization are essential. Steam autoclaving and ethylene oxide (ETO) are two commonly used methods for sterilization of ophthalmic instruments. Each technique has its drawbacks. Deposition of rust on instruments and a decrease in sharpness can be seen with steam autoclaving. The National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention (CDC), Atlanta, Ga, consider ETO to be an occupational carcinogen and reproductive toxin.^{20,21} Because of this and the environmentally harmful effects of ETO, the Environmental Protection Agency, Washington, DC, is encouraging health care facility personnel to reduce use of this form of sterilization.

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METHODS

CASE AND CONTROL DEFINITION

We defined a case patient as any patient undergoing intraocular surgery from January 5 to 14, 1998 (epidemic period) at hospital A who had cornea edema and opacification (TECD) within 24 hours after surgery. We defined a control patient as any hospital A patient undergoing intraocular surgery during the epidemic period who did not develop TECD. To identify case patients and determine the background rate, we reviewed medical records of patients undergoing intraocular surgery at hospital A during the pre-epidemic (September 1, 1997-January 4, 1998) and epidemic periods.

ANALYTICAL EPIDEMIOLOGY AND STATISTICAL METHODS

A case-control study was conducted. Control patients were all patients who had an intraocular surgical procedure on the same day as the case patients. Data were collected on standardized forms, entered into a computer, and analyzed using Epi Info version 6.04 software (CDC) or SAS for personal computers (SAS Institute Inc, Cary, NC). Data collected included race; age; sex; dates of admission, surgery, and discharge; preoperative and postoperative vision assessment (≤ 24 hours and at 1-year follow-up); reason for eye surgery; type of surgery performed; type and model of intraocular lens (IOL) implant; type of anesthesia; all operative personnel including surgeons, anesthesiologists, and scrub or circulating nurses; medications used before, during, or after surgery; underlying disease; and instrument sterilization methods.

An ophthalmic surgical procedure (cataract removal) was observed. Infection control policies and procedures before, during, and after ophthalmic surgery were reviewed and observed, including the cleaning, rinsing, and packaging of surgical instruments.

LABORATORY STUDIES

To determine whether the method of sterilization may have been associated with adverse outcomes, we ran-

domly selected 16 ophthalmic surgery instruments (ie, scissors, forceps, cannulas, hooks) from a hospital A ophthalmic surgical kit for chemical evaluation. All 16 instruments were placed in Micropaks (Riley Medical Inc, Auburn, Me), a plastic microsurgical instrument tray, and sterilized (**Figure 1**). Then, 8 instruments were sterilized with the Plazlyte system and 8 with ETO at hospital A. Following sterilization, these instruments in trays were forwarded to CDC for chemical analysis. At CDC, the 16 instruments were removed from the trays and rinsed with water polished to 18 M Ω -cm resistance with a Milli-Q system (Millipore Corp, Bedford, Mass). The rinsates were then evaluated by inductively coupled argon plasma atomic emission spectrometry^{24,25} (JY 70 plus; Instrument SA Inc, Edison, NJ) to determine the presence of any trace elements. To determine the effect of instrument rinsing on residual trace element contaminants, 9 of 16 instruments were washed an additional 3 times with Milli-Q water and evaluated after each rinse by atomic emission spectrometry for residual trace elements.

Next, to determine whether the type of packaging and the method of sterilization may have been associated with the adverse outcome, we resterilized 15 instruments, 8 of the initial 16 and 7 additional instruments (Figure 1). To determine if the adverse reactions could be associated specifically with hospital A sterilization (Plazlyte or ETO) machines, we sent instruments to be sterilized to hospital B in Dallas, Tex. Eight instruments were individually packaged in a Tyvek Mylar (DuPont, Wilmington, Del) paper and plastic pouch; 4 were sterilized in Plazlyte (2 at hospital A; 2, hospital B) and 4 in ETO (2 at hospital A; 2, hospital B). The remaining 7 instruments were sterilized at hospital A in Micropak trays—5 in Plazlyte and 2 in ETO. To determine if any trace elements were present, these 15 instruments were rinsed in balanced salt solution (BSS) (Cytosol Laboratories Inc, Braintree, Mass), and the rinsates were evaluated by atomic emission spectrometry.^{24,25}

To detect whether residual peracetic (peroxyacetic) acid and hydrogen peroxide were present on sterilized ophthalmic instruments, 10 mL of the rinsate was collected from the instruments. Then, an analytical titration method was performed in which hydrogen peroxide was titrated with ceric sulfate and the presence of peracetic acid was back titrated using starch indicator and sodium thiosulfate.²⁶

Recently, a new method of sterilization using plasma gas technology such as the AbTox Plazlyte sterilization system (AbTox Inc, Mundelein, Ill) has been introduced.^{22,23} This method sterilizes instruments by vaporization of a mixture of peracetic acid, acetic acid, and hydrogen peroxide in combination with low temperature (40°C) and an electromagnetic field; the vapor is removed with argon, oxygen, and hydrogen gas.^{22,23}

During January 8 to 14, 1998, 6 of 8 patients receiving elective intraocular surgery at one hospital (hospital A) developed endothelial cell destruction within 24 hours after surgery. When no source for the outbreak could be identified, CDC was invited to assist in the investigation.

RESULTS

DESCRIPTIVE AND ANALYTICAL EPIDEMIOLOGY

Six patients met the case definition. Toxic endothelial cell destruction after intraocular ophthalmic surgery was more frequent during the epidemic than pre-epidemic period (6/12 vs 0/118; $P < .001$). All case patients were men and ranged in age from 43 to 85 years (median age, 67 years). All had long-term systemic diseases, such as coronary artery disease, diabetes, or hypertension (**Table 1**).

IN VITRO EXPERIMENTS

An *in vitro* rabbit corneal endothelial perfusion model was used to evaluate the effects of the poststerilized instrument rinsates and various test solutions.^{15,27,28} Additionally, a human corneal endothelial perfusion model using Optisol GS–stored eye bank corneas (Chiron, Claremont, Calif) was used for evaluating laboratory-prepared solutions of 10-mg/L copper and 10-mg/L zinc (n=5).

New Zealand white rabbits weighing 2 to 3 kg were anesthetized with an intramuscular mixture of ketamine hydrochloride, 0.5 mL (30 mg/kg of body weight), and xylocaine hydrochloride, 0.5 mL (4 mg/kg of body weight). The rabbits were euthanized with an intracardiac injection of pentobarbital sodium, 324 mg/mL (1.0 Euthanasia-5 solution [1 mg/2.5-kg rabbit]; Henry Schein Inc, Fort Washington, NY), and the eyes were enucleated with the conjunctiva and eyelids intact. All experiments were conducted under the Association for Research in Vision and Ophthalmology, Bethesda, Md, guidelines for animal research.

The rabbit corneas were mounted in an *in vitro* specular microscope. The test solutions were perfused directly to the corneal endothelium (rabbit and human) after a 1-hour stabilization perfusion period with a control solution (BSS Plus; Alcon Laboratories Inc, Ft Worth, Tex). Temperature was maintained at 37°C, perfusion pressure at 15 mm Hg, and perfusion rate at 30 µL per minute. There were 31 solutions used; 9 were rinsates from Plazlyte-sterilized instruments; 5, rinsates from ETO-sterilized instruments; 6, laboratory-prepared solutions of 10-mg/L copper or 10-mg/L zinc; 4, 10-mg/L copper only; and 7, 10-mg/L zinc only. Each of 31 rabbits had 1 cornea perfused with a test solution and the other cornea perfused with a BSS Plus control solution. We measured the change in corneal thickness (micrometers) over time (hours) and calculated a swelling rate (micrometers per hour) by linear regression analysis. At the end of perfusion, the corneas were fixed in 2.5% glutaraldehyde (Electron Microscopy Sciences, Fort Washington, Penn) in 0.1 mol/L cacodylate buffer and examined by scanning electron microscopy (SEM) and transmission electron microscopy (TEM) to determine if TECD had occurred.²⁷ The tissue parameters for human corneas stored in Optisol GS were as follows: age 60.0±11.4 years; time from death to enucleation, 3.2±0.7 hours; and storage time, 5.5±0.5 days.

Two case patients had extracapsular cataract extraction and a posterior chamber IOL implant; 2, cataract removal by phacoemulsification and a posterior chamber IOL implant; 1, repositioning of a previously implanted anterior chamber IOL; and 1, a trabeculectomy for glaucoma. Case patients had corneal edema associated with visual loss within 24 hours of postoperative examination. At 1-year follow-up, 3 of 6 case patients had received a corneal transplant for persistent corneal edema. Of 3 remaining case patients, corneal edema has resolved in 2, and 1 has slowly resolving corneal edema (**Table 2**).

When we compared case with control patients, there were no significant differences in the following preop-

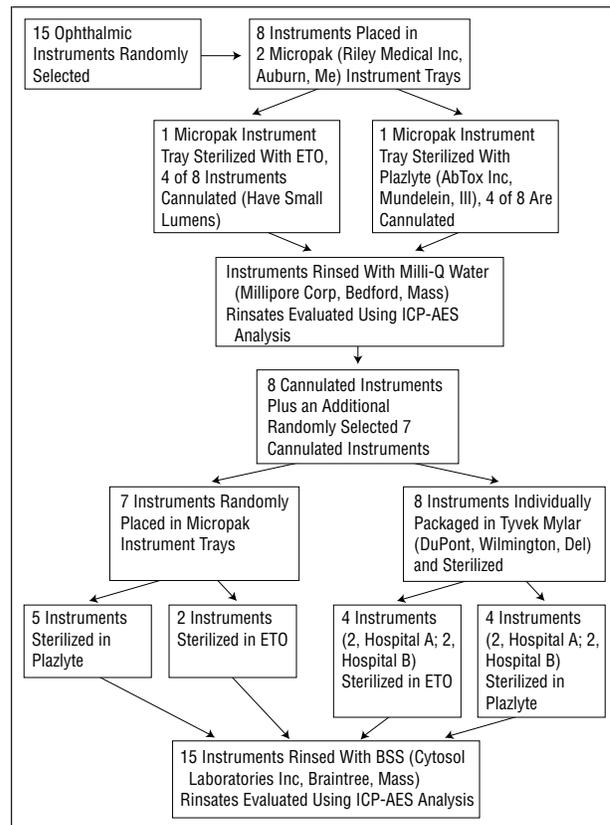


Figure 1. Assessment methods for ophthalmic instrument sterilization. ICP-AES indicates inductively coupled argon plasma atomic emission spectrometry; ETO, ethylene oxide; and BSS, balanced salt solution.

erative, intraoperative, or postoperative conditions: medications, including local or general anesthesia; operating room; operative personnel, including surgeons, anesthesiologists, and scrub or circulating nurses; preoperative vision; length of surgery or time under anesthesia; type of surgery; or brand of lens implant. In contrast, case patients had poorer vision and greater postoperative corneal thickness than controls (Table 1).

After introduction of the AbTox Plazlyte system, some ophthalmology personnel noticed blue-green residues on some of the instruments and commented that they smelled a pungent odor similar to acetic acid when opening instrument packs. Therefore, we next reviewed intraocular surgery procedures, including instrument cleaning and reprocessing. There had been no changes in surgical procedures. In contrast, surgery instrument sterilization practices had changed with the introduction of the AbTox Plazlyte sterilization system in November 1997. Postoperatively, instruments were washed with sterile water, placed in a solution of Klenzyme (Steris Co, St Louis, Mo) and tap water for 10 minutes, rinsed with tap water, washed by hand in a solution of Klenzyme and tap water, and rinsed again with tap water. Next, they were hand-rinsed sequentially with tap water, deionized water, and distilled water. Then, all instruments were hand-dried; the smaller instruments and those with lumens were blown dry with compressed air. All ophthalmic surgery instruments to be sterilized were placed in Micropaks and sterilized in the Plazlyte machine.

Table 1. Comparison of Case and Control Patients, Hospital A, January 5-14, 1998*

Variable	Case Patients (n = 6)	Control Patients (n = 6)	P
Continuous			
Age, y	67 (43-85)	67 (47-82)	NS
Length of surgery, min	52 (17-119)	63 (38-92)	NS
Length of anesthesia, min	120 (85-185)	129 (85-163)	NS
Anesthesia severity score	2.8 (1-4)	2.8 (2-4)	NS
Preoperative vision, range	20/40-20/200	20/40-hand motions	.02
Postoperative vision ≤24 hours postoperatively, range	20/400-hand motions	20/25-20/400	.02
Postoperative corneal thickness ≤24 hours postoperatively	3 (2+-4+)	0 (clear-trace)	.002
Categorical (No.)			
Race			
White	5	4	NS
Nonwhite	1	2	
Sex, M	6	6	NS
Underlying disease			
Cataracts	4	5	NS
Lens dislocation	1	...	NS
Glaucoma	1	...	NS
Bullous keratopathy	...	1	NS
Type of surgical procedure			
Extracapsular cataract extraction or phacoemulsification with posterior chamber intraocular lens	4	5	NS
Lens reposition	1	...	NS
Glaucoma filtering procedure	1	...	NS
Corneal transplant	...	1	NS

*Values are given as median (range) except where indicated. NS indicates not significant; ellipses, not applicable.

Table 2. Case Patients, Corneal Edema, Visual Acuity, and Pupillary Examination Preoperatively, Within 24 Hours, and at 1-Year Follow-up, Hospital A, 1998 and January 1999*

Case Patient	Surgical Procedure	Corneal Edema		Visual Acuity			Pupillary Examination Findings	
		≤24 h Postoperatively	1-y Follow-up	Preoperatively	≤24 h Postoperatively	1-y Follow-up	≤24 h Postoperatively	1-y Follow-up
1	AC IOL repositioning	2+	Corneal edema resolved	20/40	Hand motions	Hand motions†	Nonreactive, dilated pupil	Nonreactive, dilated pupil
2	Trabeculectomy	3+	Corneal transplant (performed 7 months postglaucoma filter)	20/40	Hand motions	Counting fingers‡	Nonreactive, small pupil	Nonreactive, small pupil
3	ECCE with PC IOL	3+	Slowly resolving cornea edema	20/200	Counting fingers	20/150	Partially reactive, dilated pupil	Partially reactive, dilated pupil
4	ECCE with PC IOL	3+	Corneal transplant (performed 9 months postcataract surgery)	20/200	Counting fingers	20/300	Reactive, dilated pupil§	Nonreactive, dilated pupil
5	Phacoemulsification with PC IOL	4+	Corneal transplant (performed 4 months postcataract surgery)	20/70	Counting fingers	20/30	Nonreactive, dilated pupil	Nonreactive, dilated pupil
6	Phacoemulsification with PC IOL	3+	Corneal edema resolved	20/60	20/400	20/40	Nonreactive, dilated pupil	Nonreactive, dilated pupil

*AC IOL indicates anterior chamber intraocular lens; ECCE, extracapsular cataract extraction; and PC IOL, posterior chamber intraocular lens.

†Vision with the development of optic atrophy and an afferent pupillary defect.

‡Advanced glaucomatous atrophy and afferent pupillary defect noted prior to filtering procedure.

§Three days postoperatively.

LABORATORY STUDIES

Next, we evaluated the relationship between sterilization method and residual inorganic metals (copper and zinc), including the influences of packaging materials on metal residuals and the importance of rinsing. First, we assessed the relationship between sterilization method (Plazlyte vs ETO) and presence of residual trace elements. Eight of 16

instruments sterilized in Micropaks by using either ETO or Plazlyte had measurable amounts of copper and zinc by atomic emission spectrometry; all 8 were cannulas with brass hubs and very small lumens, which are placed directly into the eye during surgery (Figure 1). Of 8 cannulated instruments sterilized, the 4 sterilized in the Plazlyte machine had higher levels of copper and zinc than the 4 sterilized in ETO, although the latter did not reach statistical significance (me-

Table 3. Levels of Copper and Zinc in Cannulated Intraocular Surgery Instrument Rinsate by Type of Packaging and Sterilization Method, Hospital A, December 1997 and April 1998

Packaging Type	Sterilization Method	No. of Cannulas	Copper, mg/L	Median P	Zinc, mg/L	Median P
Micropak*	Ethylene oxide	6	0.050	.002	0.83	.03
	AbTox-Plazlyte†	8	9.160		7.16	
Individual	Ethylene oxide	4‡	0.060	.04	0.15	.06
	AbTox-Plazlyte	4‡	0.280		0.89	
Micropak	AbTox-Plazlyte	8	9.160	.006	7.16	.006
Individual	AbTox-Plazlyte	4‡	0.028		0.89	
Micropak	Ethylene oxide	6	0.050	.90	0.83	.10
Individual	Ethylene oxide	4‡	0.055		0.15	

*Riley Medical Inc, Auburn, Me.

†AbTox Inc, Mundelein, Ill.

‡Two cannulas from hospital A and 2 from hospital B.

dian copper values: 7.64 vs 0.14 mg/L, respectively, $P = .02$; median zinc values: 5.90 vs 1.35 mg/L, respectively, $P = .20$).

Second, we assessed the influence of type of packaging (Micropaks vs Tyvek Mylar) and method of sterilization (Plazlyte vs ETO) on instrument copper or zinc residuals. Also, we evaluated whether copper or zinc would be found on cannulas after sterilization in hospital B's machines (Plazlyte vs ETO). The 8 cannulas placed in Micropaks and sterilized by using the Plazlyte method had rinsates with significantly higher levels of copper and zinc than rinsates from instruments sterilized in Micropaks and ETO (**Table 3**). All rinsates from Plazlyte-sterilized cannulas individually packaged in Tyvek Mylar had lower levels of copper and zinc than the rinsates from cannulas sterilized in plastic Micropaks. The copper and zinc residuals were significantly lower in ETO-sterilized instruments whether in Tyvek Mylar or Micropaks. Ophthalmic surgical instruments sterilized with Plazlyte at hospital A and at hospital B had similar copper and zinc levels.

Third, we determined if sequential rinsing of sterilized ophthalmic surgical instruments would affect the residual amount of copper or zinc. Nine instruments, 2 of which were cannulas, sterilized in the Plazlyte machine, rinsed once, were rinsed 3 additional times. Findings from atomic emission spectrometric analysis of these 2 cannula rinsates showed a rapid decrease in the trace elements in the first 5 mL wash, with very low levels of copper and zinc in the subsequent washes (**Table 4**). The other noncannulated instruments had little to no initial measurable amounts of copper and zinc. When we examined the Plazlyte-sterilized cannulas for residual sterilant (ie, peracetic acid or hydrogen peroxide), neither was detected.

Rabbit Experiments

Next, we performed in vitro rabbit corneal endothelial perfusions to assess whether the rinsates from the instruments would cause TECD. Nine rabbit corneas were perfused with rinsates from Plazlyte-sterilized cannulas (ie, BSS Plus rinsed through the sterilized cannulas); 5 were infused with rinsates from ETO-sterilized cannulas. Additionally, 6 were perfused with a laboratory-made solution of 10-mg/L copper, 10-mg/L zinc, and BSS Plus; 4 with 10-mg/L copper only; and 7 with 10-mg/L zinc only.

Table 4. Residual Copper and Zinc in Plazlyte-Sterilized Cannulated Intraocular Surgery Instruments After Sequential Rinsing

Rinse No.	Cannula Levels 1		Cannula Levels 2	
	Copper, mg/L	Zinc, mg/L	Copper, mg/L	Zinc, mg/L
First	5.790	3.460	20.100	8.36
Second	0.097	2.210	0.016	1.00
Third	0.006	0.009	0.005	0.04
Fourth	0.005	0.009	0.002	0.01

The rabbit corneas perfused with ETO cannula rinsates or BSS Plus alone (controls) showed minimal corneal swelling ($7.0 \pm 1.1 \mu\text{m/h}$ vs $3.8 \pm 1.7 \mu\text{m/h}$, respectively) (**Figure 2**) with no significant differences between the two. Findings from SEMs and TEMs revealed no structural damage with a normal hexagonal mosaic (SEM), intact borders, and normal intracellular organization (TEM) with no evidence of endothelial cell edema (**Figure 3**).

In contrast, rabbit corneas perfused with Plazlyte cannula rinsates swelled at 35.5, 38.0, and 16.6 $\mu\text{m/h}$, vs BSS Plus, $11.2 \pm 1.5 \mu\text{m/h}$, and corneas exposed to the laboratory-made solutions of copper and zinc swelled at $34.0 \pm 3.0 \mu\text{m/h}$ vs BSS Plus, $8.5 \pm 1.8 \mu\text{m/h}$, $P < .001$ (**Figure 4** and **Figure 5**). Rabbit corneas perfused with either 10-mg/L zinc only ($24 \pm 2.7 \mu\text{m/h}$ vs BSS Plus, $13.1 \pm 2.0 \mu\text{m/h}$, $P < .01$) or 10-mg/L copper only ($21 \pm 4.2 \mu\text{m/h}$ vs BSS Plus, $5.9 \pm 2.9 \mu\text{m/h}$, $P < .03$) showed less corneal swelling than those perfused with both (Figure 5). Electron micrographs of Plazlyte rinsate-perfused endothelial cells demonstrated marked endothelial cell destruction (SEM) with cell borders pulling apart and endothelial cell edema (TEM) compared with normal-appearing controls (**Figure 6**). Findings from SEM and TEM of endothelial cells perfused with laboratory-made solutions of copper and zinc showed endothelial cell damage (SEM) with intracellular vacuolization and disorganization (TEM) compared with normal-appearing controls (**Figure 7**).

Human Experiments

We performed in vitro corneal endothelial perfusions with Optisol GS-stored human corneas to assess how human

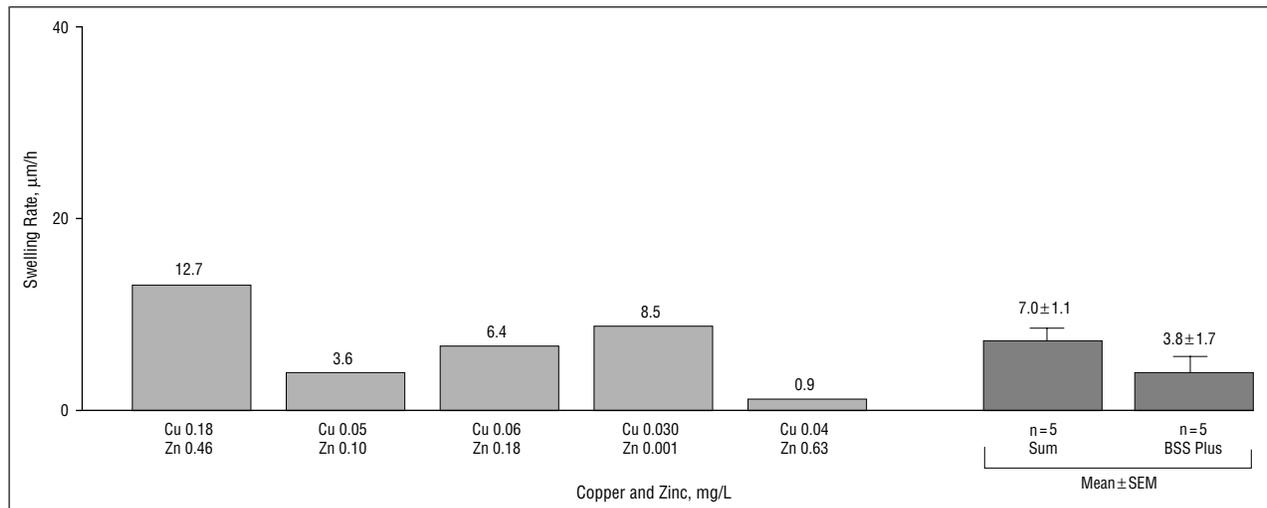


Figure 2. Corneal swelling rates in rabbit corneas following endothelial perfusion of ethylene oxide rinsates compared with balanced salt solution (BSS) Plus (Cytosol Laboratories Inc, Braintree, Mass) control. This graph represents 5 individual rinsates with corresponding copper (Cu) and zinc (Zn) levels indicated. The sum (mean±SEM) represents an average of the 5 rinsate perfusions.

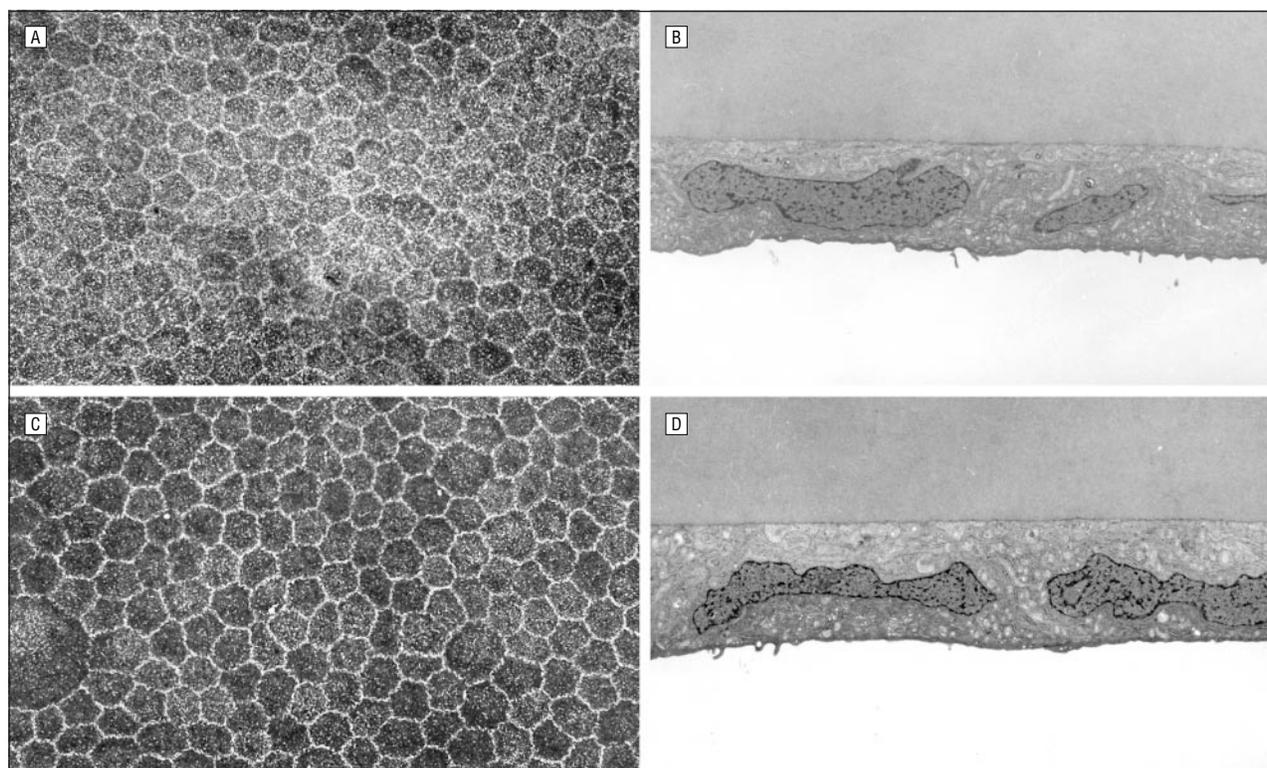


Figure 3. A, Scanning electron micrograph (SEM) of corneal endothelium perfused with balanced salt solution (BSS) Plus (Cytosol Laboratories Inc, Braintree, Mass) for 3 hours. The endothelial cells are hexagonal with tight junctions (original magnification $\times 540$). B, Transmission electron micrograph (TEM) of corneal endothelium perfused with BSS Plus, which shows endothelial cells with intact borders and normal intracellular organization (original magnification $\times 4495$). C, An SEM of corneal endothelium perfused with ethylene oxide rinsate, which is very similar to control (original magnification $\times 540$). D, A TEM of corneal endothelium perfused with ethylene oxide rinsate, which reveals normal intracellular organization (original magnification $\times 4495$).

corneas perfused with laboratory-prepared samples of 10-mg/L copper and 10-mg/L zinc would compare with results of the perfused rabbit corneas of 10 mg/L-copper and 10 mg/L-zinc. Similar to results seen in the rabbit, the human corneas swelled significantly ($28.2 \pm 0.9 \mu\text{m/hr}$ vs BSS Plus, $14.2 \pm 0.9 \mu\text{m/hr}$, $P < .001$). Electron micrographs reveal endothelial cell destruction (SEM) with large vacuolization and endothelial cell edema (TEM) (**Figure 8**).

COMMENT

We investigated an outbreak of profound corneal endothelial decompensation observed within 24 hours after surgery. Our initial epidemiologic investigation failed to identify any risk factors for adverse outcome. The recent changes that occurred in ophthalmic surgery instrument sterilization methods led us to evaluate the relationship between

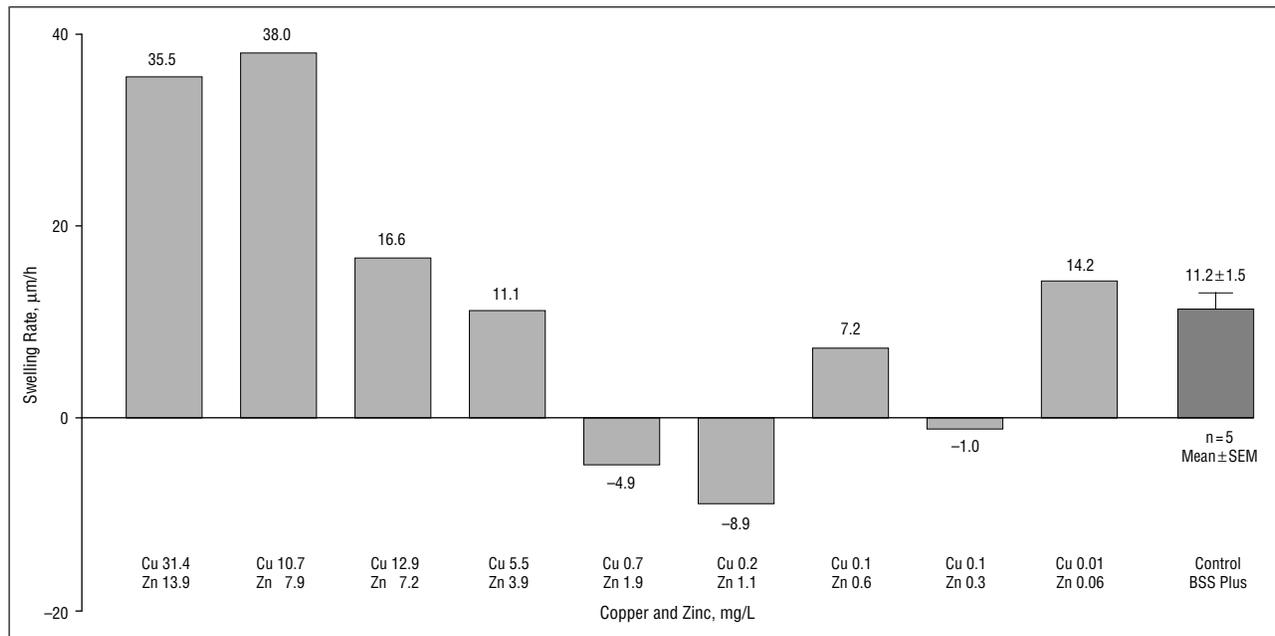


Figure 4. Swelling rates in rabbit corneas following endothelial perfusion of Plazlyte rinsates (AbTox Inc, Mundelein, Ill) compared with balanced salt solution (BSS) Plus (Cytosol Laboratories Inc, Braintree, Mass) control. This graph represents 9 individual rinsates with corresponding copper (Cu) and zinc (Zn) levels for each rinsate. The last bar graph is the mean ± SEM of the BSS Plus control perfusions. (Four corneas used for controls were damaged during the mounting procedure.)

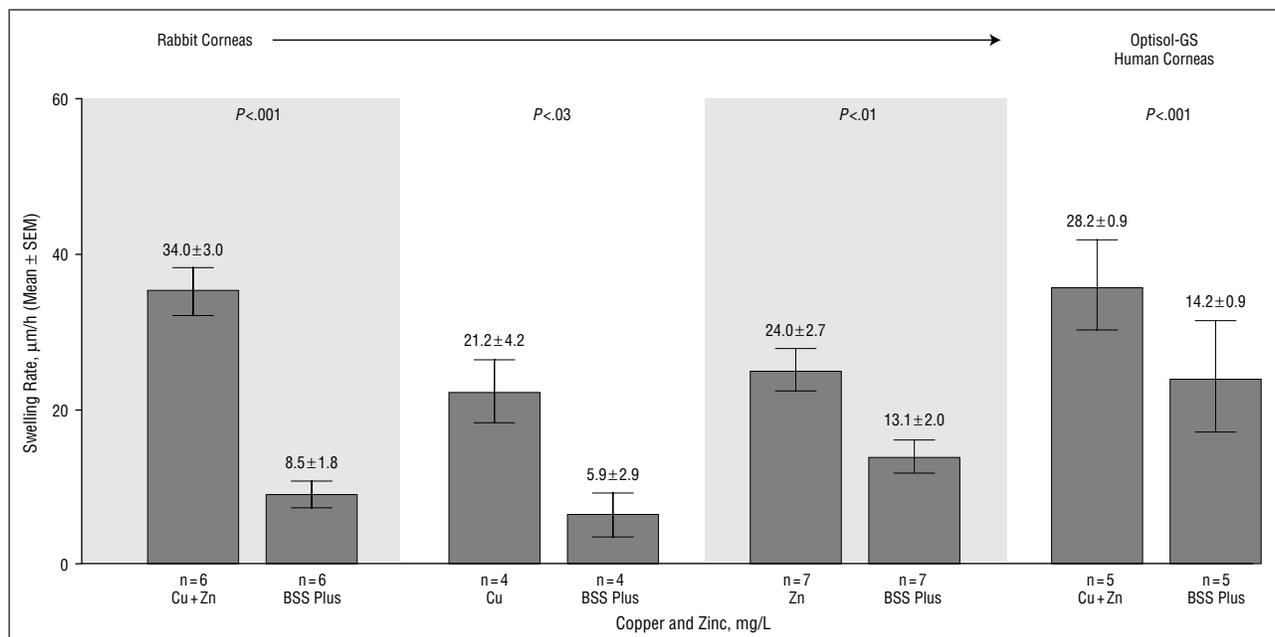


Figure 5. Corneal swelling rates (mean ± SEM) following endothelial perfusion of rabbit corneas of laboratory-prepared 10-mg/L copper (Cu) plus 10-mg/L zinc (Zn) combined and separately compared with balanced salt solution (BSS) Plus (Cytosol Laboratories Inc, Braintree, Mass) control. All concentrations are 10 mg/L for copper and zinc. The last 2 bars represent corneal swelling (mean ± SEM) of human Optisol GS-stored corneas (Chiron, Claremont, Calif) following endothelial perfusion of 10-mg/L copper plus 10-mg/L zinc compared with BSS Plus control.

these changes and the adverse outcomes. We found that rinsates of cannulated sterilized ophthalmic surgery instruments with small lumens had measurable copper and zinc levels. Regardless of the packaging, our laboratory experiments showed that rinsates from cannulas sterilized with the Plazlyte system had elevated levels of both copper or zinc compared with instruments sterilized in ETO; these levels were elevated whether the instruments were

sterilized at Hospital A or Hospital B, suggesting that the method of sterilization rather than specific hospital practices was responsible. Rinsate from cannulas sterilized with Plazlyte in surgical kits had the highest levels of copper and zinc.

Since the Plazlyte sterilization machine was introduced for instrument sterilization in November 1997, it is unclear why more patients have not developed TECD.

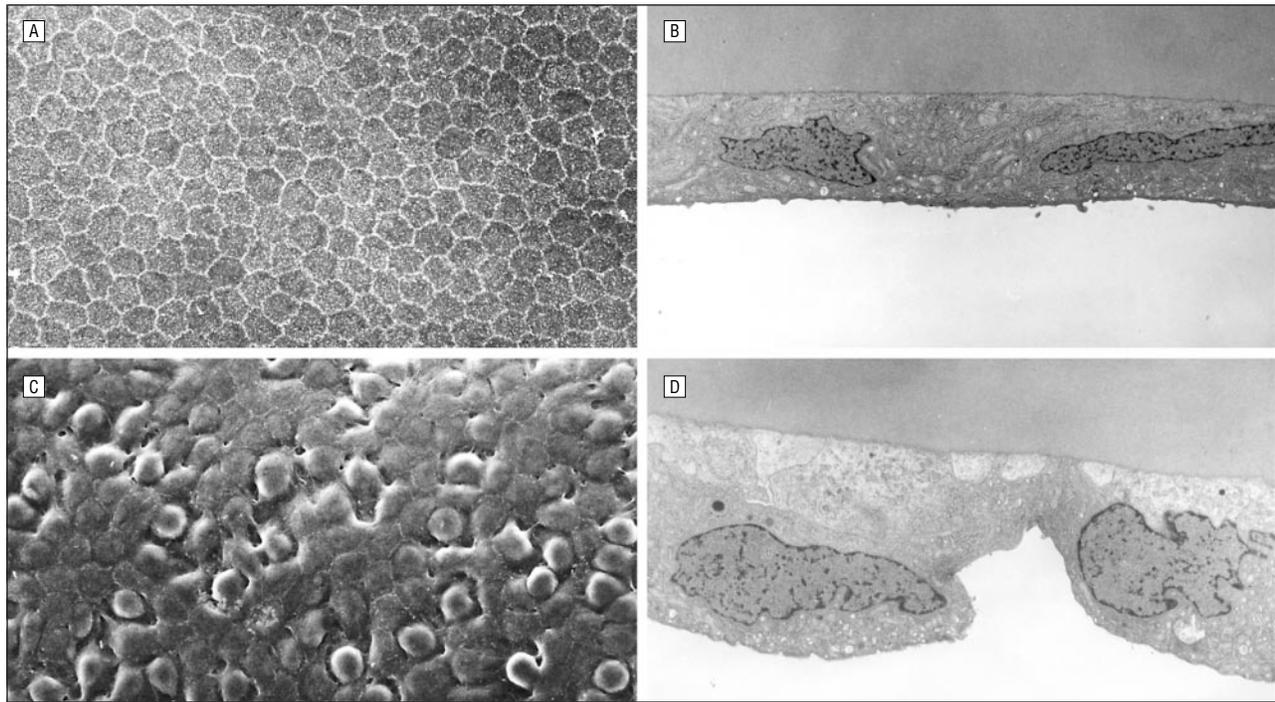


Figure 6. A, Scanning electron micrograph (SEM) of corneal endothelium perfused with balanced salt solution (BSS) Plus (Cytosol Laboratories Inc, Braintree, Mass) for 3 hours. The endothelial cells show a regular hexagonal pattern with tight junctions (original magnification $\times 540$). B, Transmission electron micrograph (TEM) of corneal endothelium perfused with BSS Plus, which shows endothelial cells with intact borders and normal intracellular organization (original magnification $\times 4495$). C, An SEM of corneal endothelium perfused with Plazlyte rinsate (AbTox Inc, Mundelein, Ill), which demonstrates marked endothelial cell destruction (original magnification $\times 540$). D, A TEM of corneal endothelium perfused with Plazlyte rinsate, which shows cell borders pulling apart and endothelial cell edema (original magnification $\times 4495$).

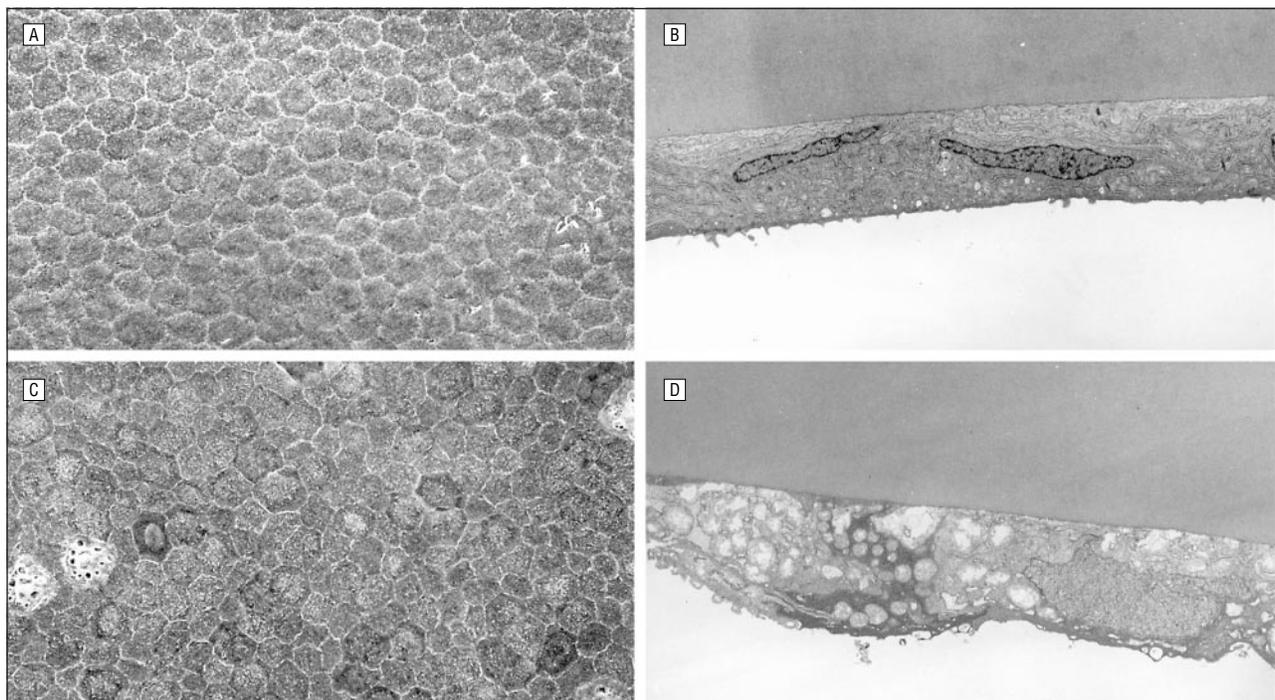


Figure 7. A, Scanning electron micrograph (SEM) of corneal endothelium perfused with balanced salt solution (BSS) Plus (Cytosol Laboratories Inc, Braintree, Mass) for 3 hours. The endothelial cells show normal hexagonality with intact borders (original magnification $\times 540$). B, Transmission electron micrograph (TEM) of corneal endothelium perfused with BSS Plus, which shows endothelial cells with tight junctions and regular intracellular organization (original magnification $\times 4495$). C, An SEM of corneal endothelium perfused with laboratory-made solution of 10-mg/L copper plus 10-mg/L zinc, which shows endothelial cell damage (original magnification $\times 540$). D, A TEM of corneal endothelium perfused with laboratory-made solution of 10-mg/L copper and zinc, which reveals intracellular vacuolization and disorganization (original magnification $\times 4495$).

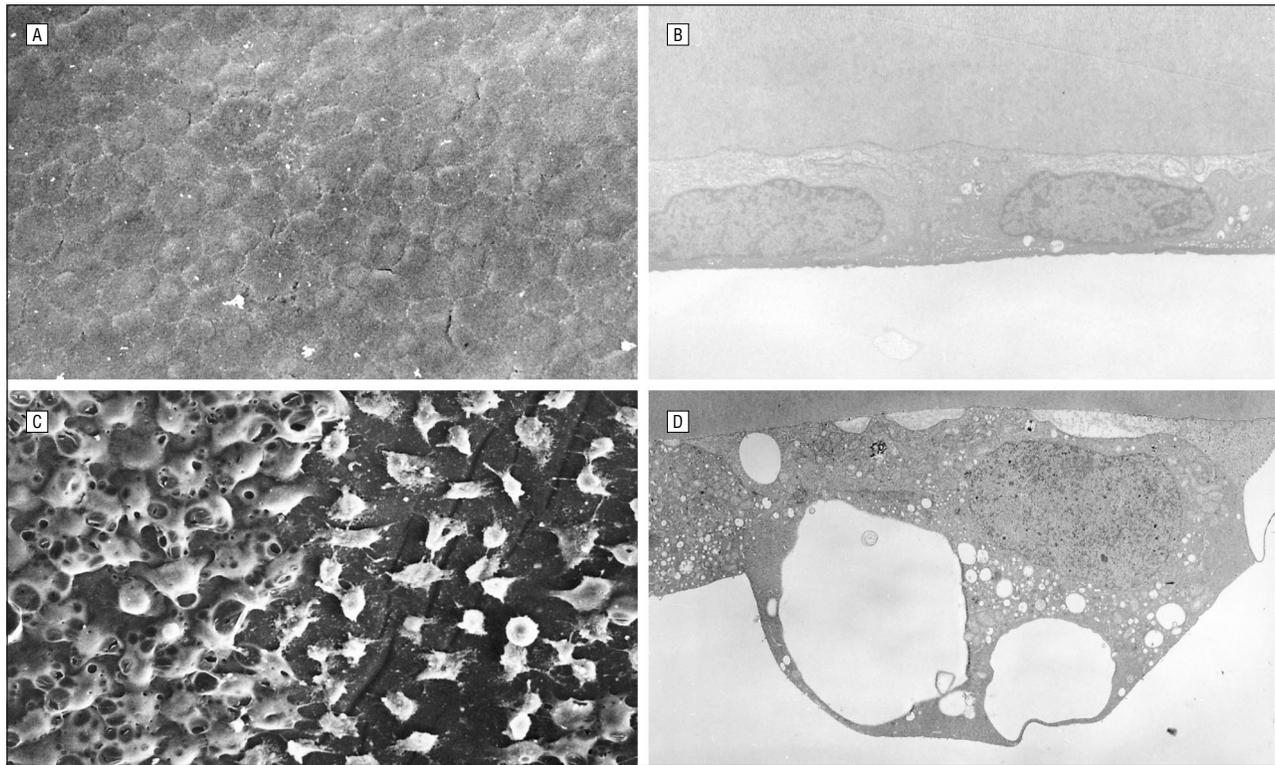


Figure 8. A, Scanning electron micrograph (SEM) of human corneal endothelium perfused with balanced salt solution (BSS) Plus (Cytosol Laboratories Inc, Braintree, Mass) for 3 hours. The endothelial cells show a normal mosaic with intact borders and no evidence of edema. B, Transmission electron micrograph (TEM) of human corneal endothelium perfused with BSS Plus, which shows normal intracellular organization (original magnification $\times 4495$). C, An SEM of human corneal endothelium perfused with laboratory-made solution of 10-mg/L copper plus 10-mg/L zinc, which reveals endothelial cell destruction (original magnification $\times 540$). D, A TEM of human corneal endothelium perfused with laboratory-made solution of 10-mg/L copper and zinc, which shows large vacuoles and endothelial cell edema (original magnification $\times 4495$).

We hypothesize that cannulated instruments that were manufactured with chrome-covered brass hubs may have been oxidized by the acetic and peracetic acids from the Plazlyte sterilization machine. The chrome's degradation, through repeated reprocessing, exposed the brass; then, brass decomposed into its primary elements, copper and zinc. It also is possible that the acetic and peracetic acids, used during the Plazlyte sterilization process, did not quickly dissipate, especially in those cannulas sterilized in Micropaks. The increase in contact time of the acetic and peracetic acids on the instruments may have allowed oxidation of the brass to occur, each time exposing more and more of the brass. This process may have been repeated each time the cannulas were sterilized. Following the sterilization, copper and zinc would have remained in the cannula channel and then flushed into the patient's eye during the surgical procedure, producing TECD.

Since the oxidation process would have occurred over time, the breakdown of the brass by the acetic and peracetic acids may have been related to the number of times the cannulas were sterilized in the Plazlyte machine or the age of the cannulas. Hospital personnel did not always record which kit instrument was used or how many times it was previously used or sterilized. Hospital personnel did not perform many (<5 per day) intraocular ophthalmic surgery procedures, so it is possible that some surgical kits were used rarely and not repeatedly resterilized; thus, little oxidation of the cannula brass hubs of these instruments may have occurred. These later instruments may have been

used during the eye procedures of those patients who did not develop TECD. Alternatively, the copper and zinc residuals were water soluble. Sufficient rinsing before the procedure could reduce or eliminate the copper and zinc residuals, reducing or diminishing the risk of their infusion into the eye. Hospital A personnel noted that it was their policy to rinse routinely the instruments and irrigate cannulas before their use in the eye.

Contamination of instruments with the trace metals copper and zinc would allow the formation of free hydroxyl and peroxy radicals within the eye. Any of these reactive elements would indiscriminately combine with intraocular tissues, resulting in the unexpected TECD. Additionally, the smell of acetic acid on some instruments suggests that residual hydrogen peroxide was present, although we were not able to detect it.

The AbTox Plazlyte machine had not been approved by the Food and Drug Administration (FDA), Washington, DC, for instrument sterilization. The FDA had approved an earlier design of the Plazlyte machine for use on stainless steel items but not instruments with small lumens or hinges, such as many intraocular surgery instruments. Furthermore, instruments sterilized in the AbTox Plazlyte machine require careful cleaning and drying before sterilization to avoid residual chemicals or water, which can react with the Plazlyte chemicals or gas to produce by-products.

The results of this investigation led to a CDC *Morbidity Mortality Weekly Report*²⁹ and an FDA safety alert

about the use of AbTox Plazlyte Sterilization System in sterilizing eye instruments.²⁹⁻³¹ Until the FDA approves its use, cannulated instruments should not be sterilized in the Plazlyte machine.

Corneal endothelial cells are a sensitive indicator of potential toxins inadvertently introduced during ophthalmic surgery. Our case patients demonstrated the potentially catastrophic effect that copper and zinc contamination can have on intraocular tissues. This investigation documented the importance of active post-market surveillance for complications associated with newly introduced medical devices or sterilization methods. Furthermore, it emphasizes that medical personnel should ensure that the FDA has approved a medical device or sterilization method before it is used on patients or patient equipment. As new sterilization methods and devices are developed and implemented, health care personnel must be aware of and determine whether changes in practice are safe to avoid adverse patient outcomes.

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