WORLD VIEW

An outbreak of endophthalmitis after extracapsular cataract surgery probably caused by endotoxin contaminated distilled water used to dissolve acetylcholine

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Aim: To study possible causes of an outbreak of severe endophthalmitis after planned extracapsular cataract surgery in Medan, Indonesia.

Methods: In a 3 week period in November 2001, 17 of 43 patients developed signs of endophthalmitis after planned extracapsular cataract surgery. A search for possible causes was undertaken 4 months later.

Results: In autoclaved stored distilled water used to dissolve acetylcholine (used in 16 of 17 patients with endophthalmitis) a high amount of endotoxin was detected in a human blood essay, as well as a small number of non-typeable *Pseudomonas* spp.

Conclusions: These findings suggest that distilled water used as solvent for acetylcholine was responsible for this outbreak of endophthalmitis. As a consequence, we now rely on solvents that are regularly checked for impurities such as an intravenous infusion fluid, rather than on vials with distilled water that is presumed to be sterile and kept for some time.

Pending vitreous biopsy results, severe postoperative inflammation is generally empirically treated as suspected bacterial endophthalmitis^{1,2}; several other non-infective causes, however, may give rise to postoperative inflammation.³⁻⁸ Fortunately this condition is rare and usually arises as a sporadic case of suspected postoperative bacterial endophthalmitis. An outbreak of multiple cases with this vision threatening complication is truly alarming and raises immediate concern about the correctness of the procedures used in the particular surgical setting.

During a period of cataract surgery in Medan, Indonesia, we were confronted with a series of patients with postoperative endophthalmitis. We went back for a second visit 4 months later and tried to identify the causes of this complication so as to improve on the procedures and prevent future occurrence of endophthalmitis. Our findings should be of interest to other ophthalmologists facing a series of postoperative endophthalmitis.

PATIENTS AND METHODS

In November 2001, 43 patients underwent planned extracapsular cataract extraction (ECCE) under retrobulbar anaesthesia on five consecutive days. Two surgeons experienced in ECCE performed the operations. Preoperative preparation consisted of cutting of the eyelashes, generous application of povidone-iodide 0.5% solution on the skin and conjunctiva for a minimum of 30 seconds before the start of surgery.

The patient's face was covered with an autoclaved drape and the surgeon and scrub nurse would wear a sterile surgical gown. During a single session, this gown was not changed between consecutive patients nor were the gloves, which were cleaned with acetone and alcohol between patients. The patients' draping material had been autoclaved at the local general hospital and was renewed after each operation; before each operation, instruments were sterilised in a table autoclave unit (Statim 5000), with the use of ISP steam emulating indicators to monitor correct temperature, pressure, and time.

Surgery was standardised as follows: after a corneoscleral incision, the lens capsule was opened with a canopener technique. The lens nucleus was expressed and remaining cortex was aspirated with a two way Simcoe canula, connected to a bottle of sterile saline. The same saline was used for several patients until the bottle was empty. No bacterial filter was interposed. Hydroxypropyl methylcellulose (HPMC) was used to help with intraocular lens (IOL) insertion, manufactured by the pharmacy of the Rijnland Hospital, Leiderdorp, Netherlands. Acetylcholine, dissolved with twice distilled water (Aqua Bidest, autoclaved, used within expiration date, and manufactured in Jakarta, Indonesia) was used to constrict the pupil after IOL insertion. One of the surgeon preferred to perform a peripheral iridectomy and to use HPMC sparingly, the other would not perform peripheral iridectomy and would use HPMC in all patients. Both surgeons would try to remove the HPMC at the end of surgery.

During November 2001 visit the following data were documented.

Preoperative visual acuity and ocular status and the following peroperative data: surgeon, assisting nurse, use of HPMC, use of acetylcholine, type of IOL and its expiration date, as well as the occurrence of capsular rupture or vitreous loss. Postoperative examinations were planned after 1 day, 4 days, and 1 week.

During the visit 4 months later, a team of two cataract surgeons, a sterilisation expert and a surgical theatre nurse specialised in ophthalmic surgery re-examined most of the patients operated during the November visit and screened surgical, procedural, and logistic procedures to try and find a possible preventable cause.

Possible sources of the spread of bacteria were investigated by taking a culture (using contact impression wipes) from the floor and tables of the operation room, the autoclave unit

Abbreviations: ECCE, extracapsular cataract extraction; HM, hand movements; HPMC, hydroxypropyl methylcellulose; IOL, intraocular lens; LP, light perception; NLP, no light perception

(Statim), and the air conditioning unit. We also tested the room air by placing bowls with sterile distilled water as sedimentation dishes for 24 hours on the table lining the window, on the operation theatre floor, and on the operation table. For comparison, we placed similar bowls outdoors, in the vicinity of the operation room. Finally, the saline used for cortical material removal and rinsing of the cornea was cultured, as were the HPMC and vials of Aqua Bidest used to dissolve acetylcholine. The culture material was transported in Uricult medium, kept at 35°C and plated on return in the Netherlands.

To additionally test for the presence of endotoxins the vials of Aqua Bidest, HPMC, and saline were examined for its inflammatory potential as described.

Blood of healthy controls was collected in endotoxinfree tubes (Endotube ET; Chromogenix) and diluted one in five in RPMI fluid culture medium. Next, to the whole blood tubes was added either 250 µl Aqua Bidest, HPMC, and saline, 250 µl endotoxin free aquadest from the Leiden University Medical Center pharmacy, or 100 ng/ml lipopolysaccharide and next incubated overnights. To compensate for the addition of Aquadest, the Aquadest was initially diluted in phosphate buffered saline with double strength electrolytes. Supernatants were collected after 18 hours and assayed by commercial enzyme linked immunosorbent assay for the presence TNF- α , IL-1 β , and IL-10 (Sanquin Research, Amsterdam, Netherlands).

The Aqua Bidest, HPMC, and saline were additionally cultured on sheep blood agar and in aerobic and anaerobic blood culture bottles (Bactec, Dickinson). Determinations were performed by standard ViTek.

RESULTS

Patients

In five of the 43 patients posterior capsular rupture occurred, in four with vitreous loss. In one patient an IOL was inserted in the sulcus, in one an iris fixated lens. In three patients no IOL was inserted because of aphakia in the fellow eye. In another four patients without peroperative complications no lens was inserted, because of aphakia in the fellow eye. Surgical time did not exceed 40 minutes in any of the patients.

Although record keeping had not been complete for uneventful patients, in all 16 patients with endophthalmitis the use HPMC had been noted, as well as the use of acetylcholine in 15 of 16 with endophthalmitis. The first patients with excessive postoperative inflammation were diagnosed on their first postoperative day, which was not until the fifth day of surgery. Further surgery that day was cancelled, but three patients had already undergone surgery. Six of 13 patients of the previous day were involved. During the rest of the 3 week visit, in all 16 patients were diagnosed with endophthalmitis: nine developed signs after 1 day, seven had signs found on the fourth postoperative day.

Pain was not a prominent presenting symptom in these patients. Signs in the 16 initial patients included an opaque corneal epithelium in six, corneal stromal oedema in eight, excessive fibrin in all, posterior synnechia in 15, a fibrotic cyclitic membrane in 15, and a hypopyon in 11.

Table 1 Culture results of Uricult wipes

Instruction manual on counter	22 cfu*
Condenswater AIRCO	>50 cfu
Window casing	>50 cfu
On top of cupboard	>50 cfu
Operating room table	15 cfu
Floor	>50 cfu

*Colony forming units.

Table 2 Culture results of sedimentation bowls

Sample at the window:	<i>Penicillium</i> species <i>Aspergillus nigr</i> <i>Cladosporium</i> species <i>Curvularia</i> species <i>Fusarium</i>
Sample on the operation table:	<i>Chrysonilia sitophila</i>
Sample left up front:	<i>Aspergillus nigr</i> <i>Aspergillus clavatus</i> Mould
Sample left in the back:	<i>Chrysonilia sitophila</i>
Account collected on operating room:	<i>Penicillium</i> species Mould <i>Cladosporium</i>
Outdoor samples	<i>Aspergillus nigr</i> <i>Cladosporium</i> species
Distilled water in Statim	<i>Proteus</i> spp

In one patient an aqueous tap was performed and a fibrotic membrane was cut in the pupil, revealing a clear vitreous behind the pupil. No bacterial growth was detected on culturing of the anterior chamber fluid of one patient. Six patients were treated with intravitreal antibiotics (1 mg vancomycin and 0.1 mg gentamicin), 10 patients received subconjunctival gentamicin (20 mg) and betamethasone (5 mg).

Findings during the second visit after 4 months

One additional patient (37) was diagnosed with endophthalmitis, thus raising the total number of patients in this outbreak to 17.

The clinical course had been severe: no light perception (NLP) in four, LP in 11, hand movements (HM) in one; only one patient (35) recovered function to 0.25.

Hypotony was present in nine patients; physis had developed in five of those.

The pupil was occluded by a fibrotic membrane in 12 patients. The fundus could be visualised in none, because of vitreous opacities (one), occluded pupil (12), opaque cornea (four).

Active inflammation was present in four patients. In three of these a vitreal biopsy was taken and cultured for bacterial growth; vancomycin (1 mg) and gentamicin (0.1 mg) were injected intravitreally.

Of note, we found no association between the surgeon, scrub nurse, or circulating nurse or use of HPMC and the inflammation. Acetylcholine had been used definitely in 16 of 17 patients with endophthalmitis as well as in an undocumented number without endophthalmitis.

Culture results

The four vitreous biopsies taken at the 4 month visit were inadvertently cultured for 1 day only, and had not yet revealed bacterial growth.

Culture of different fluids used during surgery

Samples of HPMC and saline used during surgery were cultured but revealed no bacterial growth.

At a later stage, extended culture of samples taken out the Aqua Bidest vials yielded two types of non-fermenting Gram

negative rods, non-typeable *Pseudomonas* spp, at a low concentration of about 50–100 micro-organisms per ml fluid.

Test for non-infective pyrogens

Whereas the control fluid from the Leiden University Medical Center hospital pharmacy, saline, or HPMC did not elicit any release of the cytokines TNF- α , IL-10, or IL-1 β (all at or below detection level of assay), incubation of whole blood with Aqua Bidest stimulated the release of both TNF- α , IL-1 β , and less so of IL-10, in a concentration dependent manner. This demonstrated that the solution contained immunostimulatory components that could elicit an inflammatory response in the host. Given the subsequent culture of low numbers of water *Pseudomonas* spp from this fluid, the major immunostimulatory compound probably is the endotoxin of this Gram negative non-fermenter.

Culture of the sedimentation dishes and autoclave taken after 4 months

Contact impression wipes indicated the abundant presence of bacteria in the operating theatre (table 1).

Also, cultures of sedimentation bowls from the surgery room and outdoors yielded different and abundant micro-organisms. Culture of distilled water taken from the Statim autoclave yielded *Proteus mirabilis* (table 2).

DISCUSSION

Since 1990 a group of Dutch ophthalmologists has been involved in a project to reduce preventable blindness through cataract surgery in Medan, north Sumatra, Indonesia, in close collaboration with a resident ophthalmologist, who recruits and screens the patients before each visit. Four times a year during a 3 week visit, a team consisting of two Dutch ophthalmologists perform cataract surgery in a nursing home in Medan. From 1990 up to April 2002 planned extracapsular cataract surgery was performed in 4235 patients.

During the reported November 2001 visit 17 patients operated upon developed postoperative endophthalmitis. In the acute stage, an aqueous tap was performed in only one patient and yielded no bacterial growth. Otherwise, no comprehensive effort was made to detect or exclude a bacterial aetiology of the endophthalmitis. Because we suspected initially that the postoperative inflammatory reaction was an excessive fibrin reaction rather than a bacterial endophthalmitis, at the time we did not perform vitreous biopsies or administer an adequate treatment for suspected bacterial endophthalmitis. As a consequence, only six of 17 patients received intravitreal antibiotics.

As the investigation 4 months later revealed, a varied and abundant microbial load had probably been present in the surgical theatre's air and on the surfaces at the time of the operations, and airborne contamination of instruments or bowl of saline used to rinse the cornea on the instrumentation table could be among the causes for this outbreak of acute onset postoperative endophthalmitis. However, an intense bacterial or fungal contamination is not likely, because none of the fluids used intraocularly had been in contact with air.

The non-infective toxic anterior segment inflammation or toxic cell destruction syndrome⁹ has been described as a syndrome with different suggested aetiologies: no clear cause from intraocular lens material,³ remaining detergent of an ultrasonic bath solution detergent,^{7 8 10} or endotoxins caused by a cleaning bath agent infected by *Klebsiella*⁶ (which resembles our finding of *Proteus* spp in the distilled water of the autoclave unit). All reports, however, have in common that the endophthalmitis was mainly restricted to the anterior segment and that patients recovered useful vision, albeit in one patient requiring a corneal transplant.⁸

Thus, another cause for this outbreak had to be considered, such as contamination of irrigation fluids, viscoelastics like the HPMC used, and the distilled water used to dissolve intraocular medications.

Despite the numerous departures from best accepted aseptic techniques and the lack of air treatment in our surgical setting, we, nevertheless, suggest that the most likely culprit in our patients was the vials of distilled water used to dissolve acetylcholine. Why would this fluid have caused such a severe endophthalmitis?

At least three mechanisms may have been active. Firstly, we observed that the distilled water induced in a dose dependent fashion a strong inflammatory response in peripheral blood mononuclear cells that was comparable with that induced by about 10 ng/ml endotoxin. That endotoxin probably induced the release of the cytokines was confirmed by the culture of a low number of water type Gram negative non-fermenter *Pseudomonas* spp in samples of the distilled water. Secondly, the immunostimulants in the distilled water would have been administered at a rather high concentration because the particular solution was injected directly into the anterior chamber. Thirdly, the injected *Pseudomonas* spp may have contributed to tissue destruction. Although the circumstances in which this outbreak occurred were far from optimal to perform a definitive and conclusive study into its causes, we propose, nevertheless, that our findings underscore the necessity to critically evaluate the surgical procedures, exclude direct contamination of fluids and instruments with large numbers of micro-organisms, and next scrutinise other ways in which surgery may bring about an inflammatory reaction in the host. For instance, by using materials that contain remnants of heat inactivated and very low numbers of living bacteria. As such a contamination with strongly immunostimulatory compounds cannot be evaluated easily, it is preferable to only use fluids and materials for intraocular use that are under daily quality control and have a high turnover rate, rather than rely on once sterile vials that have no further continuous quality test directly before use in the operation theatre. As a response to the outbreak described, for intraocular fluids we now rely on the stock of a local general hospital's intravenous saline, which is used on daily basis and subject to a continuous quality monitoring (that is, by its lack of pyrogenic activity in patients with intravenous lines). We have also changed the supplier of the distilled water for the autoclave unit: we now use the sterile distilled water stock of the local general hospital's pharmacy, that is also used daily for patients and thus monitored. With such measures, since 2001 a further series of 1563 cataract surgeries have been performed without a single case of postoperative endophthalmitis.

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REFERENCES

- 1 **Callegan MC**, Engelbert M, Parke DW, *et al.* Bacterial endophthalmitis: epidemiology, therapeutics, and bacterium-host interactions. *Clin Microbiol Rev* 2002;**15**:111–24.
- 2 **Gan IM**, van Dissel JT, Beekhuis WH, *et al.* Intravitreal vancomycin and gentamicin concentrations in patients with postoperative endophthalmitis. *Br J Ophthalmol* 2001;**85**:1289–93.
- 3 **Jehan FS**, Mamalis N, Spencer TS, *et al.* Postoperative sterile endophthalmitis (TASS) associated with the memorylens. *J Cataract Refract Surg* 2000;**26**:1773–7.
- 4 **Monson MC**, Mamalis N, Olson RJ. Toxic anterior segment inflammation following cataract surgery. *J Cataract Refract Surg* 1992;**18**:184–9.
- 5 **Nelson DB**, Donnenfeld ED, Perry HD. Sterile endophthalmitis after sutureless cataract surgery. *Ophthalmology* 1992;**99**:1655–7.
- 6 **Kreisler KR**, Martin SS, Young CW, *et al.* Postoperative inflammation following cataract extraction caused by bacterial contamination of the cleaning bath detergent. *J Cataract Refract Surg* 1992;**18**:106–10.
- 7 **Nuyts RM**, Boot N, van Best JA, *et al.* Long term changes in human corneal endothelium following toxic endothelial cell destruction: a specular microscopic and fluorophotometric study. *Br J Ophthalmol* 1996;**80**:15–20.
- 8 **Nuyts RM**, Edelhauser HF, Pels E, *et al.* Toxic effects of detergents on the corneal endothelium. *Arch Ophthalmol* 1990;**108**:1158–62.
- 9 **Parikh CH**, Edelhauser HF. Ocular surgical pharmacology: corneal endothelial safety and toxicity. *Curr Opin Ophthalmol* 2003;**14**:178–85.
- 10 **Breebaart AC**, Nuyts RM, Pels E, *et al.* Toxic endothelial cell destruction of the cornea after routine extracapsular cataract surgery. *Arch Ophthalmol* 1990;**108**:1121–5.