Graefes Arch Clin Exp Ophthalmol (2013) 251:81–87
DOI 10.1007/s00417-012-2098-1

CATARACT

Bag and chamber flushing: a new method of using intracameral moxifloxacin to irrigate the anterior chamber and the area behind the intraocular lens

Kazuki Matsuura · Chikako Suto · Junsuke Akura · Yoshitsugu Inoue

Received: 1 April 2012 / Revised: 9 June 2012 / Accepted: 15 June 2012 / Published online: 3 July 2012
© Springer-Verlag 2012

Abstract
Background Intracameral moxifloxacin is currently administered by injecting small doses (0.05–0.2 mL) of either undiluted or diluted solutions. It is difficult to ensure delivery of small amounts of antibiotic into the area behind the intraocular lens (IOL). Moreover, the anterior chamber pressure decreases as the tip of irrigation is removed, often leading to contaminated fluid flowing into the chamber. Conventional intracameral injection administers the diluted antibiotic without irrigating the recontaminated anterior chamber. Therefore, we developed a method of intracameral moxifloxacin delivery which flushes both the anterior chamber and the area behind the IOL immediately after surgery.
Methods Surgical technique (bag and chamber flushing = BC flushing): After removing the viscosurgical device, 1.5–1.8 mL diluted moxifloxacin was injected. Both the anterior chamber and the area behind the IOL were irrigated by lifting the IOL edge so that a stream of solution could circulate behind the IOL. Experiment 1 (pig): The anterior chamber was filled with condensed milk, and irrigated with 150-fold diluted moxifloxacin (33.3 μg/mL) in six eyes (BC flushing) to observe the irrigating effect. The anterior aqueous humor was sampled. Experiment 2 (human): A conventional intracameral injection (500 μg/mL) or BC flushing (33.3 μg/mL) was followed by sampling 0.1 mL of the anterior aqueous humor in six eyes each. High-performance liquid chromatography was performed to determine antibiotic levels.
Results Experiment 1: The antibiotic concentration in the anterior chamber was 33.0 μg/mL (99.0 % was displaced). The area behind the IOL was not effectively irrigated without inserting the cannula tip. Experiment 2: The final antibiotic concentration was 152.3 μg/mL using the conventional method and 29.4 μg/mL using the BC flushing (88.3 % was displaced).
Conclusion BC flushing technique enables surgeons to completely displace the anterior chamber including the posterior IOL surface, resulting in effective irrigation and a stable antibiotic concentration in virtually all cases.

Keywords Bag and chamber flushing · Intracameral injection · Moxifloxacin

K. Matsuura (✉)
Nojima Hospital,
2714-1 Sesaki-machi,
Kurayoshi-city, Tottori 682-0863, Japan
e-mail: i-mnys2001@za.ztv.ne.jp

K. Matsuura
e-mail: matsu224@ncn-k.net

C. Suto
Tokyo Women's Medical University,
8-1 Kawada-cho Shinjuku-ku,
Tokyo 162-8666, Japan
e-mail: chikakos@pastel.ocn.ne.jp

J. Akura
Kushimoto Rehabilitation Center,
259-6 Kushimoto Kushimoto-cho,
Higashimuro-gun, Wakayama 649-3503, Japan
e-mail: akura@bc4.so-net.ne.jp

Y. Inoue
Tottori University,
36-1 Nishi-cho,
Yonago-city, Tottori 683-8504, Japan
e-mail: yoinoue@med.tottori-u.ac.jp

Introduction

It has been reported that 10 %–20 % of eyes are contaminated immediately after surgery [1, 2], and it is important to initiate administration of antibiotic eye drops early during the postoperative period. Studies using rabbit endophthalmitis models indicate that when eye drops are administered immediately or within a few hours postoperatively, bacterial proliferation is suppressed, and the progress of endophthalmitis is limited [3]. There are also reports indicating that when eye drops are administered the day after surgery, the risk of developing endophthalmitis is 13 times higher than when administration is initiated on the day of surgery [4]. However, patients themselves often instill antibiotic ophthalmic solution after cataract surgery, indicating that patient compliance with surgeon instructions greatly affects the outcome. Additionally, shortage of staff results in insufficient patient education or insufficient assistance with administration of eye drops. Thus, only a few medical facilities can provide sufficient education and assistance to all patients early in the treatment cycle. Considering this situation, directly administering antibiotics into the anterior chamber immediately after surgery is the most reliable and effective method to supply sufficient amounts of antibiotics at the appropriate time.

A multicenter clinical trial conducted in 2006 by the Endophthalmitis Surgery Group, European Society of Cataract and Refractive Surgeons indicated a 5-fold reduction in infection rate following postoperative administration of cefuroxime within the anterior chamber [5]. Subsequent studies have indicated that intracameral administration of moxifloxacin, a fourth-generation fluoroquinolone, is both effective and safe [6–9].

However, intracameral administration refers to administering drugs within the anterior chamber and not behind the intraocular lens (IOL). Irrigation of the area between the IOL and posterior capsule is recommended. However, this procedure is not necessarily performed because of psychological resistance to reach the area close to the posterior capsule and lack of a simple technique. Moreover, when conventional irrigation is performed, anterior chamber pressure decreases as the tip of irrigation is removed, often leading to contaminated fluid outside the chamber flowing into the chamber. A conventional intracameral injection administers the diluted antibiotic without irrigating the recontaminated anterior chamber. Therefore, we devised an intraocular antibiotic administration method using a 5-ml syringe filled with diluted moxifloxacin to flush both the anterior chamber and the area behind the IOL. The goal of this study was to observe the irrigating effect and determine an appropriate moxifloxacin concentration for this procedure.

Material and methods

Drug preparation

The diluted moxifloxacin solution was prepared from commercially available self-preserved Vigamox™ (Alcon Inc., Hünenberg Switzerland) ophthalmic solution.

BC flushing (150-fold diluted moxifloxacin: 33.3 μg/ml): 0.2 ml Vigamox in 29.8 ml balance salt solution plus (BSS Plus, Alcon, Fort Worth, TX, USA) was prepared. This solution was delivered into the eye using a 5 ml syringe.

Conventional injection (10-fold diluted moxifloxacin: 500 μg/ml): 1.0 ml Vigamox in 9.0 ml BSS plus was prepared. A 0.1 ml dose (50 μg of moxifloxacin in 0.1 ml) was injected via the side port using a 1 ml syringe.

Surgical Technique: (Bag and chamber flushing = BC flushing)

After IOL implantation and removal of the viscosurgical device, 1.5–1.8 mL of diluted moxifloxacin was injected into the anterior chamber for approximately 15 s using a 5-ml hydration syringe. After the injection, both the anterior chamber and the area behind the IOL were thoroughly irrigated with solution. In practice, a cannula is inserted via a side port and used to lift the edge of the IOL so that a stream of solution can be circulated behind the IOL.

A cannula through which solution is already flowing was inserted via a side port, and the anterior chamber was flushed for several seconds (Fig. 1a and b). The opposite edge or the side edge of the IOL was lifted, and the stream of solution was directed behind the IOL. During this procedure, it was not necessary to insert the pointed cannula tip behind the IOL (Fig. 1c). Once the anterior chamber had been flushed for several seconds, the needle was removed while maintaining solution flow (Fig. 1d and e). Maintaining the solution flow throughout the procedure prevented posterior capsule rupture and allowed the surgeon to maintain positive pressure within the anterior chamber during the procedure. Paying close attention to leakage from the side port incision helped prevent an increase in anterior chamber pressure and led to more effective irrigation.

Experiment 1 (ex vivo porcine eyes)

BC flushing was performed in six eyes after implanting the IOL and removing the viscosurgical device. After a 2-min period, 0.1 mL of the anterior aqueous humor was sampled via the cornea with a 29-G needle and

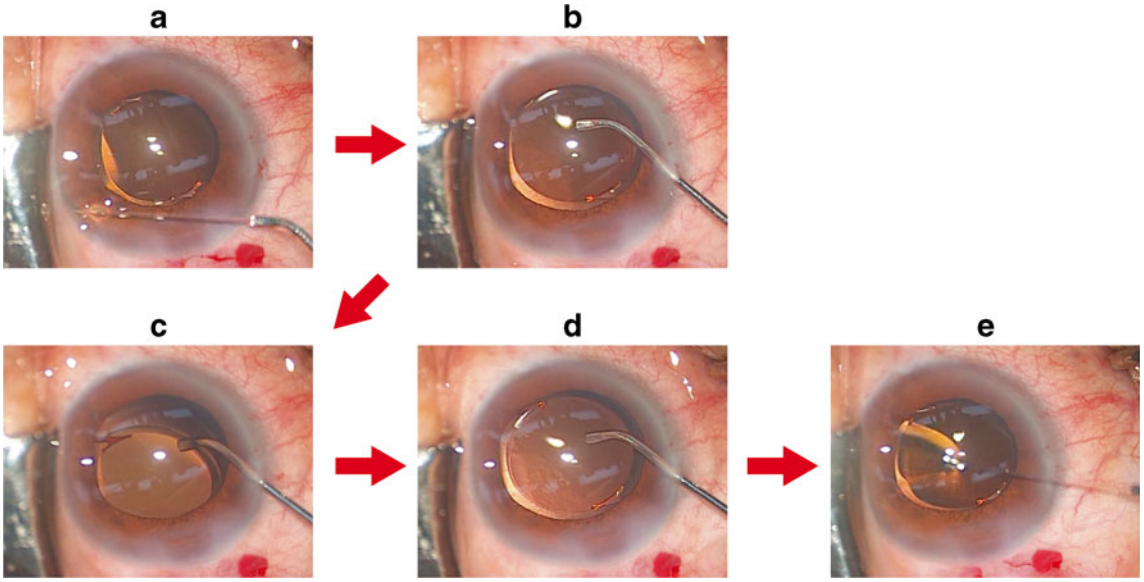

Fig. 1 A cannula is inserted via a side port, and the anterior chamber is flushed for several seconds (**a** and **b**). The opposite edge or the side edge of the intraocular lens (IOL) is lifted and the stream of solution is directed behind the IOL (**c**). Once the anterior chamber has been flushed for several seconds, the needle is removed while maintaining the solution stream (**d** and **e**)

then frozen. A high performance liquid chromatography (HPLC) analysis was performed to determine antibiotic levels. To make the dynamics of the solution visible, 0.3 mL of condensed milk was injected into the anterior chamber and behind the IOL. We observed the irrigating effect of the solution by inserting the tip of a flushing cannula behind the IOL.

Experiment 2 (humans)

This experiment was approved by the Tottori University Institutional Review Board and conducted under the guidelines of the Declaration of Helsinki. Written informed consent was obtained from each patient. Conventional intracameral injection (10-fold, 0.1 mL) or BC flushing was performed in six eyes each after the IOL was implanted and the viscosurgical device was removed uneventfully. After a 2-min period, 0.1 mL of the anterior aqueous humor was sampled via the cornea with a 29-G needle and then frozen. An HPLC analysis was performed to determine the antibiotic levels.

HPLC set up

The method employed a TSKgel ODS-80TM 5 μm column (250×4.6 mm) maintained at 40 °C and a mobile phase composed of a mixture of acetonitrile and citric buffer (pH=3.0) at a flow rate of 0.8 mL/min. Fluorescence detection was performed at an excitation wavelength of 290 nm and an emission wavelength of 470 nm.

Results

Experiment 1

The antibiotic concentration in the anterior aqueous humor was 33.0±4.1 μg/ml, i.e., 99.0 % of the anterior chamber volume was displaced. Our observation of porcine eyes revealed two completely different fluid dynamics depending on the self-sealing strength. When the eyes exhibited favorable self-sealing in the wound, aqueous humor easily flowed behind the IOL after aqueous humor was only injected into the anterior chamber. However, in eyes with weak self-sealing, in which anterior chamber formation was difficult (i.e. eyes in which the anterior chamber was barely formed after eager wound hydration), the milk behind the IOL hardly moved no matter how much the anterior chamber was irrigated (Fig. 2a, d, and e). We were able to effectively irrigate the area behind the IOL by inserting the tip of a cannula behind the IOL (Fig. 2a–c).

Experiment 2

The conventional method using 500 μg/ml moxifloxacin resulted in an antibiotic concentration of 152.3± 32.3 μg/ml in the anterior aqueous humor, i.e., the anterior chamber was diluted about 3.3-fold. BC flushing using 33.3 μg/ml moxifloxacin resulted in an antibiotic concentration of 29.4±6.8 μg/ml in the anterior aqueous humor, i.e., 88.3 % of the anterior chamber volume was displaced.

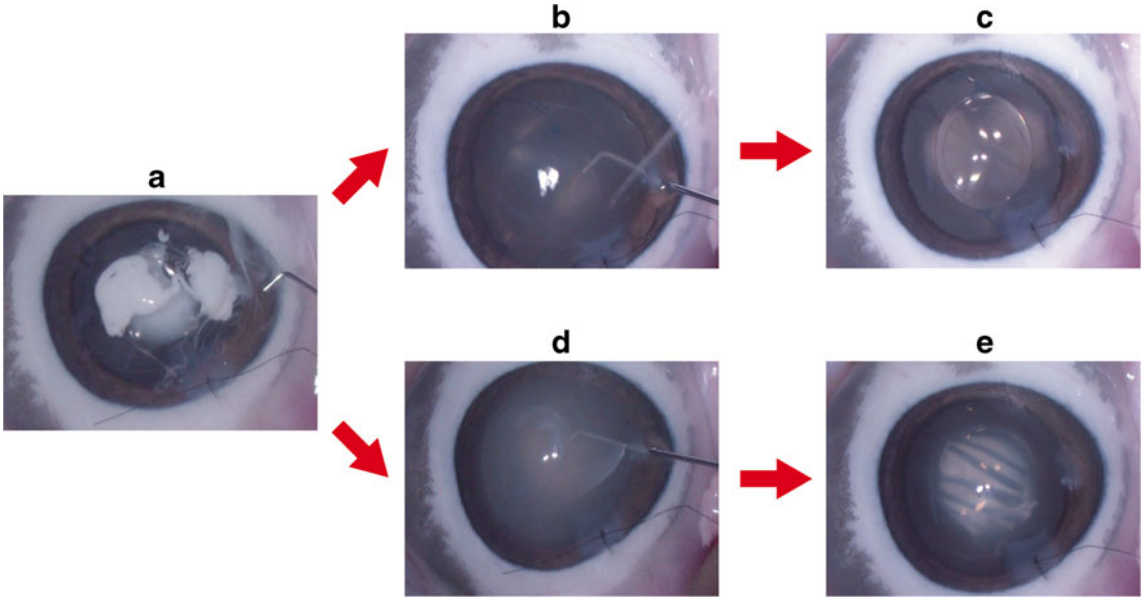

Fig. 2 Demonstration using condensed milk in the anterior chambers of the pig eye. We could effectively irrigate the area behind the intraocular lens (IOL) by inserting the cannula behind the IOL (**a**–**c**). Condensed milk was retained in the area behind the IOL in the case where the cannula was not inserted behind the IOL (**a**, **d**, and **e**)

Discussion

Our observation of porcine eyes revealed two completely different fluid dynamics depending on the self-sealing strength. That is, by injecting the solution into the anterior chamber in eyes with favorable self-sealing of the wound, the posterior capsule expanded easily and aqueous humor passed into the area behind the IOL (Fig.3a and b). In comparison, in eyes with poor anterior chamber formation due to reasons such as weak self-sealing, the posterior capsule could not expand even when aqueous humor was injected. As a result, the posterior capsule remained stuck to the back of the IOL (Fig. 4a). In eyes such as this, when the continuous curvilinear capsulorrhexis (CCC) is smaller than the IOL, the increase in intracameral pressure forces the CCC to press against the front surface of the IOL creating a seal. Thus, both the anterior capsule and the posterior capsule press against the IOL, causing a sealed space to form behind the IOL. Irrigating the anterior chamber then results in no flushing of the area behind the IOL (Fig. 4b). When the cannula tip is not inserted behind the IOL, the condensed milk behind the IOL is absolutely still during anterior chamber flushing. In actual clinical practice, viscosurgical device removal and irrigation of the IOL are often insufficient for cases with poor anterior chamber formation. Recontamination after tip removal is also likely to occur and the risk of endophthalmitis is considered high. This kind of case is not rare by any means. Anterior chamber administration is vital in cases where anterior chamber formation is difficult. However, a sealed space behind the IOL often occurs in cases such as these.

Because moxifloxacin has a high maximum aqueous concentration and a wide antibacterial spectrum, it is one of the best available antibiotics for the eyes. However, there is no guarantee that sufficient quantities remain in the

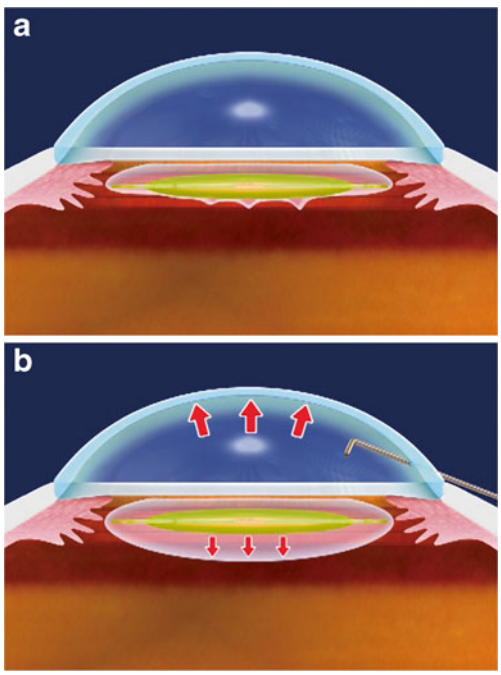

Fig. 3 **a** A case in which the pharmaceutical effectively reaches the area. The posterior capsule contacts the IOL back surface. **b** Administration to the anterior chamber causes the anterior chamber pressure to rise, and pressing the posterior capsule downward allows the fluid to flow to the area behind the IOL

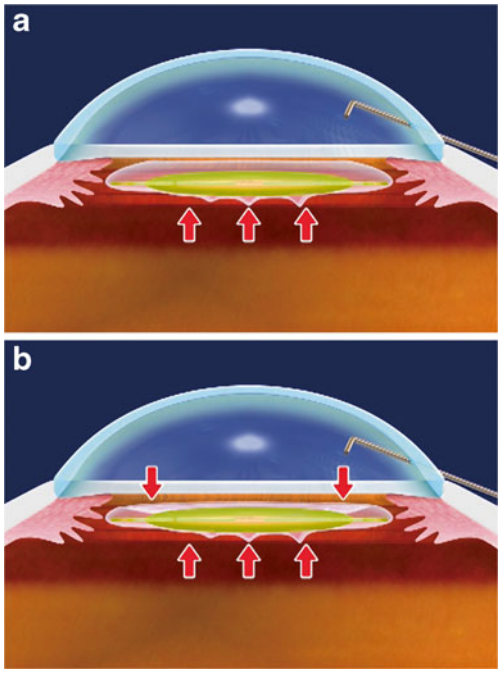

Fig. 4 **a** Incidentally, for eyes in which the formation of the anterior chamber after surgery is difficult due to reasons such as insufficient self-closure, with high pressure on the vitreous body, even when a pharmaceutical fluid is administered to the anterior chamber, the back cannot be extended and the posterior capsule remains adhered to the lens. **b** The increase in intracameral pressure forces the CCC edge to press against the IOL surface, creating a seal. Thus, a sealed-off space forms behind the IOL and irrigation of the anterior chamber results in no flushing of the area behind the IOL

conjunctival sac in the presence of edema, inflammation, hemorrhage, or lacrimation. Furthermore, there is no guarantee that intracameral antibiotic concentrations can be maintained in practice because they are under experimental conditions. Furthermore, because many patients undergoing cataract surgery are elderly, it is difficult to adequately educate them regarding the correct method of eye drop administration. Thus, patients and paramedics who do not have a thorough understanding of the procedure may present additional risk factors against early eye drop administration. In contrast, an intracameral injection of moxifloxacin [5–9] allows the surgeon to be certain that a sufficient concentration of antibiotic reaches the anterior chamber.

Suzuki et al. indicated that the bacteria trapped behind the IOL disrupt the posterior capsule, thus causing endophthalmitis in the eyes after uneventful cataract surgery [10].

Through experiments with porcine eyes, we realized that there are some cases in which pharmaceuticals that are administered to the anterior chamber do not effectively reach the area behind the IOL. Depending on the self-sealing state, it has been indicated that endophthalmitis is more likely to occur even if drugs are administered only into the anterior chamber, as it may be difficult for them to reach the area behind the IOL in some cases.

Even if the anterior chamber is contaminated, cells such as macrophages exist, and the anterior chamber is displaced by physiological flow, which reduces the number of bacteria. Appropriate use of antibiotic eye drops increases the antibiotic concentration in the anterior chamber. However, when the anterior chamber is incompletely formed, the space behind the IOL might be isolated from the anterior chamber, which results in no reduction of bacteria and no antibiotic flow from the anterior space. After removing the viscosurgical device, we occasionally observe blood outside the chamber flowing into the anterior chamber. Conventional irrigation often causes a decrease in anterior chamber pressure when the tip is removed, possibly leading to recontamination at the conclusion of surgery. Diluted moxifloxacin is merely injected into the recontaminated anterior chamber without irrigating the target area in conventional intracameral injections. To overcome this drawback, we developed a method of flushing both the anterior chamber and the area behind the IOL with diluted moxifloxacin immediately at the conclusion of surgery. It is obvious that maintaining the anterior chamber during the final stage of surgery is essential to prevent recontaminating the irrigated area.

This technique will enable surgeons (1) to deliver antibiotics to the anterior chamber and the area behind the IOL, (2) to displace that area totally, resulting in effective irrigation and scheduled antibiotic concentration, and (3) to create instant self-sealing and avoid hypophthalmis followed by recontamination at the conclusion of surgery.

Subsequent studies have indicated that the intracameral administration of moxifloxacin, a fourth-generation fluoroquinolone, is both effective and safe [6–9]. In these studies, 0.1 mL moxifloxacin stock solution (5000 μg/mL) or 10-fold diluted moxifloxacin was injected into the anterior chamber. Assuming that this was further diluted 5-fold in the anterior chamber, the final concentration was 1000 μg/mL or 100 μg/mL respectively. Kernt et al. reported that prophylactic intracameral use of moxifloxacin at concentrations up to 150 μg/mL may be safely used to prevent endophthalmitis after intraocular surgery [11]. Moxifloxacin at a concentration of 150 μg/mL dose exceeds the mutant prevention concentration by at least five times [12–14]. We believe that a final concentration of 150 μg/mL is appropriate, effective, and safe.

The final concentration was 152.3 μg/mL after using the conventional method with 10-fold diluted moxifloxacin. After BC flushing using 150-fold diluted moxifloxacin (33.3 μg/mL), the final concentration was 33.0 μg/mL (99.0 % displaced) in the pig and 29.4 μg/mL (88.3 % displaced) in the human. Assuming that 90 % of the anterior chamber was displaced, it is presumed that BC flushing using 30-fold diluted moxifloxacin (166.7 μg/ml) resulted in a final concentration of about 150 μg/mL.

We believe that approximately 90 % of the anterior chamber was displaced based on the fluid dynamics of condensed milk in suspension. In other words, even if the anterior chamber were contaminated with bacteria, irrigation diluted the aqueous humor 10-fold. It was assumed that the concentration in the anterior chamber reaches 100–150 μg/mL with the usual 0.1-mL intracameral injection of 10-fold diluted moxifloxacin or in the case of antibiotics placed in the irrigating bottle, the solution can be circulated into the area behind the IOL. But in cases where there is a large amount of hydration due to poor self-sealing, the final intracameral concentration cannot be determined. However, because flushing results in a 90 % displacement, a stable intracameral concentration can be achieved.

Even in human eyes with favorable self-sealing, when active irrigation was discontinued, the posterior space immediately reduced its volume and the posterior capsule closely attached to the IOL. After surgery, a wrinkle from one end of the lens loop to the other is often observed. Slit-lamp observation directly after surgery indicates that the posterior capsule adheres over a wide area to the back surface of the IOL, leaving space for the tiny wrinkles (Fig. 5). Though bacteria are carried by surgical instruments, the IOL, the backflow of contaminated fluids, and other means, many are eliminated by the physiological flow inside the anterior chamber. However, the IOL back surface might be closed, enabling bacteria to remain. Also, unlike the anterior chamber, it is difficult for immune system cells and pharmaceutical fluids to reach the IOL back surface. This can turn it into a breeding ground for bacteria.

Thus, the area behind the IOL and the anterior chamber should be circulated intentionally at the conclusion of surgery.

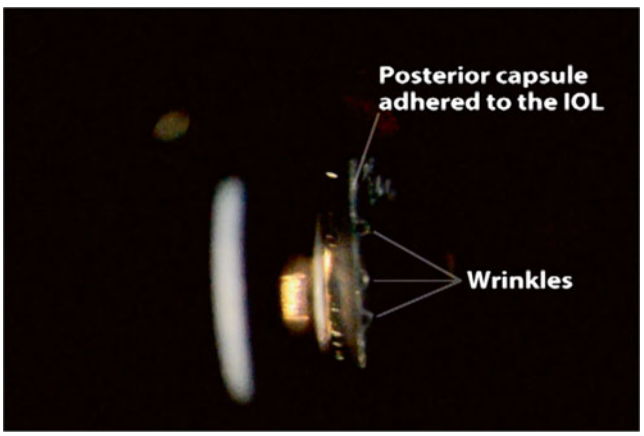

Fig. 5 Slit-lamp view two hours after surgery (human). The posterior capsule adheres over a wide area to the back surface of the IOL, and wrinkles can be seen in the posterior capsule. Sealed space exists, in which bacteria might exist. It seems that flow of antibiotic from the anterior chamber to the posterior space was obstructed

A method adding low dose antibiotic into the irrigating solution has been shown to be ineffective [15]. In contrast, markedly high antibiotic concentrations can be injected via the intracameral route.

BC flushing, which is used during the final phase of surgery, involves injecting antibiotics into the anterior chamber as well as irrigating and sealing off the anterior chamber, including the area behind the IOL. Thus, BC flushing has a number of advantages that are not associated with antibiotic administration via the irrigation bottle.

If the antibiotic is placed in an irrigating bottle, although sufficient antibiotics should remain in the anterior chamber, the anterior chamber can be recontaminated after removing the viscosurgical device. In addition, as previously mentioned, BC flushing attains the stable concentration even if self-sealing is poor during the final phase of surgery, and much hydration must be performed.

Irrigating the area behind the IOL is recommended in the removal of the viscosurgical device, however psychological resistance to reach the area close to the posterior capsule exists. At the very least, flushing is easier to perform than conventional irrigation of the area behind the IOL.

The conventional intracameral injection of a moxifloxacin stock solution or a 10-fold diluted moxifloxacin requires a syringe not normally used for such a procedure. BC flushing only requires the use of a 5-mL syringe normally used for hydrodissection and hydration. Loading the syringe with 4.8 mL of artificial aqueous humor containing 4 drops (1 drop=0.04 mL) of 0.5 % moxifloxacin is an easy way to prepare a 30-fold dilution. BC flushing is simply an additional step to the hydration that is ordinarily performed at the end of surgery. This method reduces both the required effort and risk of contamination.

We have successfully used BC flushing for approximately 800 cases without any complications such as endophthalmitis, posterior capsule rupture, markedly decreased corneal endothelium or toxic anterior segment syndrome (data not shown). In future studies, the complication rates and endophthalmitis incidence rates need to be assessed with experiments using endophthalmitis models and investigation of the clinical results of a large number of cases. Further studies are needed to determine the clinical implications of these findings in reducing the incidence of post-operative endophthalmitis associated with IOL implantation.

Conclusion

The IOL back surface, with its poor self-cleaning capability, is extremely susceptible to endophthalmitis. It has become clear that, depending on the case, there is a possibility that pharmaceuticals will not sufficiently reach this IOL back surface.

Using our Back and Chamber Flushing procedure to flush the anterior chamber, including the IOL back surface, allows an antibiotic with the desired concentration to reach the intended area in virtually all cases. Additionally, since surgery is self-closing with positive pressure, there is no concern of recontamination.

Acknowledgment The authors would like to thank Mr. Mitsuharu Ikeda and Dr. Shinichi Sasaki for assistance with the manuscript.

Author disclosure statement No competing financial interest exists.

References

1. John T, Sims M, Hoffman C (2000) Intraocular bacterial contamination during sutureless, small incision, single-port phacoemulsification. J Cataract Surg 26:1786–1792
2. Tervo T, Ljungberg P, Kautiainen T, Pusk P, Leht I, Raivio I, Järvinen E, Kuusela P, Tarkkanen A (1999) Prospective evaluation of external ocular microbial growth and aqueous humor contamination during cataract surgery. J Cataract Refract Surg 25:65–71
3. Wada T, Kozai S, Tajika T, Sakai H, Suzuki T, Ohashi Y (2008) Prophylatic efficacy of ophthalmic quinolones in experimental endophthalmitis in rabbits. J Ocul Pharmacol Ther 24:278–289
4. Wallin T, Parker J, Jin Y, Kefalopoulos G, Olson R (2005) Cohort study of 27 cases of endophthalmitis at a single institution. J Cataract Refract Surg 31:735–741
5. Endophthalmitis Surgery Group, European Society of Cataract & Refractive Surgeons (2007) Prophylaxis of postoperative endophthalmitis following cataract surgery: result of the ESCRS multicenter study and identification of risk factors. J Cataract Refract Surg 33:978–988
6. Espiritu CR, Ramon CG, Caparas VL, Bolinao JG (2007) Safety of prophylactic intracameral moxifloxacin 0.5 % ophthalmic solution in cataract patients. J Cataract Refract Surg 33:63–68
7. Kim SY, Park YH, Lee YC (2008) Comparison of the effect of intracameral moxifloxacin and cefazolin on rabbit corneal endothelial cells. Clin Experiment Ophthalmol 36:367–370
8. Lane SS, Osher RH, Masket S, Belani S (2008) Evaluation of the safety of prophylactic intracameral moxifloxacin in cataract surgery. J Cataract Refract Surg 34:1451–1459
9. O'Brien TP, Arshinoff SA, Mah FS (2007) Perspectives on antibiotics for postoperative endopthalmitis prophylaxis: potential role of moxifloxacin. J Cataract Refract Surg 33:1790–1800
10. Suzuki T, Wada T, Kozai S, Ike Y, Gilmore MS, Ohashi Y (2008) Contribution of secreted proteases to the pathogenesis of postoperative Enterococcus faecalis endophthalmitis. J Cataract Refract Surg 34:1776–1784
11. Kernt M, Neubauer AS, Liegl RG, Lackerbauer CA, Eibl KH, Alge CS, Ulbig MW, Kampik A (2009) Intracameral moxifloxacin: In vitro safety on human ocular cells. Cornea 28:553–561
12. Mather R, Karenchak LM, Romanowski EG, Kowalski EG (2002) Fourth generation fluoroquinolones: new weapons in the arsenal of ophthalmic antibiotics. Am J Ophthalmol 133:463–466
13. Blondeau JM (1999) A review of comparative in-vitro activities of 12 antimicrobial agents, with a focus on five new respiratory quinolones. J Antimicrob Chemother 43(suppl B):1–11
14. Kowalski RP, Dhaliwal DK, Karenchak LM, Romanpwski EG, Mah FS, Ritterband DC, Gordon YJ (2003) Gatifloxacin and moxifloxacin; an in vitro susceptibility comparison to levofloxacin, ciprofloxacin, and ofloxacin using bacterial keratitis isolates. Am J Ophthalmol 136:500–505
15. Kodjikian L, Renaud FN, Roques C, Garweg JG, Pellon G, Freney J, Burillon C (2005) In vitro influence of vancomycin on adhesion of a *Staphylococcus epidermidis* strain encoding intracellular adhesion locus *ica* to intraocular lenses. J Cataract Refract Surg 31:1050–1058