นิพนธ์ต้นฉบับ

Effect of supplemented and nonsupplemented vancomycin in the intraocular irrigating solutions on the incidence of endophthalmitis after phcoemulsification : A pilot study

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Background : *Although prophylactic antibiotics are widely used, little evidence exists that they prevent postoperative endophthalmitis. More recently, antibiotic supplementation of intraocular irrigating solutions has received increasing publicity, leading to more widespread use. Incorporating supplemented vancomycin into the intraocular irrigating solutions offers the advantage of achieving bactericidal antibiotic levels in the anterior chamber peroperatively.These levels may not be maintained sufficiently to be therapeutic. In addition, a theoretical risk of toxicity exists if dosage errors occur.*

Objective : *To investigate the effect of supplemented and nonsupplemented vancomycin in the intraocular irrigating solutions on the incidence of postoperative bacterial endophthalmitis after routine uncomplicated phacoemulsification with intraocular lens implantation.*

Setting : *Department of Ophthalmology, Faculty of Medicine, Chulalongkorn University and Hospital, Bangkok 10330, Thailand.*

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Research design : *A prospective , non-randomized, controlled clinical trial*

Patients and Methods : *A group of 1060 eyes scheduled for routine elective cataract surgery using phacoemulsification was divided into two consecutive, nonrandomized groups. The first group (n=312) was a studied group; receiving vancomycin in the irrigating solution. The second group (n=748) was a controlled group; there was no antibiotic in the irrigating solution. The incidence of postoperative bacterial endophthalmitis was observed and compared among the two groups for 8 weeks after surgery.*

Results : *There was no single eye with clinically suspected postoperative bacterial endophthalmitis found in either group, using supplemented and nonsupplemented vancomycin in the intraocular irrigating solutions. There was no difference in the incidence of postoperative bacterial endophthalmitis in the two groups.*

Conclusion : *The prophylactic use of supplemented vancomycin in the irrigating solutions for patients who undergo cataract surgery inevitably results in many patients receiving apparently unnecessary treatment, with obvious financial implications. The use of vancomycin in this manner should be critically reassessed until further well designed studies with large populations become available.*

Key words : *Vancomycin, Phacoemulsification, Intraocular irrigating solution.*

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ปกิตติ ทยานิธิ. ผลของการใช้และไม่ใช้ยาแวนโคไมซินผสมในน้ำเกลือที่ใช้ชะล้างภายในตาขณะผ่าตัดต่ออุบัติการของการติดเชื้อภายในตาที่เกิดขึ้นภายหลังการผ่าตัดสลายต้อกระจกโดยใช้คลื่นเสียงความถี่สูง: การศึกษานำร่อง. จุฬาลงกรณ์เวชสาร 2541 พ.ค; 42(5): 339-51

ปัญหา : *มีการใช้ยาปฏิชีวนะเพื่อป้องกันการติดเชื้อภายในตาที่เกิดขึ้นหลังการ ผ่าตัดกันอย่างแพร่หลาย แต่ยังไม่มีหลักฐานที่เชื่อถือได้ยืนยันชัดเจนว่าการผสมยาแวนโคไมซินซึ่งเป็นปฏิชีวนะชนิดหนึ่งในน้ำเกลือที่ใช้ชะล้างภายในตาขณะที่ทำผ่าตัดภายในตาซึ่งกำลังเป็นที่นิยมปฏิบัติแพร่หลาย ปฏิบัติกันมากขึ้นเรื่อย ๆ จะช่วยป้องกันการติดเชื้อที่เกิดขึ้นหลังการผ่าตัดดังกล่าวได้เพียงใดการใช้ยาแวนโคไมซินในลักษณะนี้อาจเป็นการใช้ที่เกิดความจำเป็นหรือไม่ ทำให้ผู้ป่วยเพิ่มความเสี่ยงจากการได้รับยา เชื้อโรคมีการดื้อยาตามมา และเสียค่าใช้จ่ายจำนวนมากโดยไม่จำเป็น*

วัตถุประสงค์ : *เป็นการศึกษานำร่องเพื่อศึกษาผลของการใช้น้ำเกลือที่ใช้ชะล้างภายในตาที่ผสมและไม่ผสมยาปฏิชีวนะแวนโคไมซินที่มีต่ออุบัติการของการติดเชื้อภายในตาเนื่องจากเชื้อแบคทีเรียที่เกิดขึ้นหลังการผ่าตัดสลายต้อกระจกโดยใช้คลื่นเสียงความถี่สูงร่วมกับการใส่เลนส์เทียม*

สถานที่ที่ทำการศึกษา : *ภาควิชาจักษุวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย*

รูปแบบการวิจัย : *การศึกษาแบบไปข้างหน้า แบบไม่สุ่มตัวอย่าง*

ผู้ป่วยที่ได้ทำการศึกษา : *ผู้ป่วยที่มารับการรักษาที่แผนกผู้ป่วยนอกจักษุวิทยา โรงพยาบาล--จุฬาลงกรณ์ ซึ่งได้รับการวินิจฉัยว่าเป็นต้อกระจกที่ไม่มีปัญหาแทรกซ้อนและได้รับการรักษา โดยการผ่าตัดสลายต้อกระจก โดยใช้คลื่นเสียงความถี่สูงร่วมกับการใส่เลนส์เทียม ผู้ป่วยเหล่านี้เป็นผู้ป่วยที่ไม่เคยได้รับการผ่าตัดตา และไม่มีโรคตาอย่างอื่นมาก่อนจำนวนทั้งหมด 1,060 ตา วิธีการศึกษาแบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มศึกษา จำนวน 312 ตา ใช้น้ำเกลือที่ใช้ชะล้างภายในตาขณะผ่าตัดที่ผสมยาปฏิชีวนะแวนโคไมซินส่วนกลุ่มควบคุม จำนวน 748 ตา ใช้น้ำเกลือที่ใช้ชะล้างภายในตาขณะผ่าตัดที่ไม่ได้*

ผสมยาปฏิชีวนะแวนโคไมซิน การรักษาทั้งสองกลุ่มเป็นการผ่าตัดสลายต้อกระจก โดยใช้คลื่นเสียงความถี่สูงร่วมกับใส่เลนส์เทียม ศึกษาเปรียบเทียบอุบัติการของการติดเชื้อภายในตาเนื่องจากเชื้อแบคทีเรียที่เกิดขึ้นหลัง การผ่าตัดเป็นเวลา 8 สัปดาห์

ผลการศึกษา : ไม่พบผู้ป่วยที่สงสัยหรือมีการติดเชื้อภายในตาเนื่องจากเชื้อแบคทีเรียที่เกิดขึ้นหลังการผ่าตัดเลยทั้งในกลุ่มทดลองและกลุ่มควบคุม อุบัติการของการติดเชื้อภายในตาเนื่องจากเชื้อแบคทีเรียที่เกิดขึ้นหลังการผ่าตัดของสองกลุ่ม ไม่แตกต่างกัน

วิจารณ์และสรุป : การลดอุบัติการของการติดเชื้อภายในตาเนื่องจากเชื้อแบคทีเรียที่เกิดขึ้นหลังการผ่าตัดควรจะให้ความสนใจในเรื่องการเลือกผู้ป่วย และวิธีทำให้ปราศจากเชื้อก่อนและระหว่างการทำผ่าตัดให้เคร่งครัด การใช้ยาปฏิชีวนะผสมในน้ำเกลือที่ใช้ชะล้างภายในตาขณะผ่าตัดในการทำผ่าตัดสลายต้อกระจก โดยใช้คลื่นเสียงความถี่สูงทุกรายเพื่อหวังผล ในการป้องกันการติดเชื้อภายในตาเนื่องจากเชื้อแบคทีเรียที่เกิดขึ้นหลังการผ่าตัดทำให้ผู้ป่วยได้รับยาและเสียค่าใช้จ่ายโดยไม่จำเป็น ควรสงวนยาแวนโคไมซินไว้ใช้เมื่อมีการติดเชื้อจริงเท่านั้น การศึกษานี้เป็นเพียงการศึกษานำร่องที่ยังมีจำนวนประชากรที่ทำการศึกษายังไม่มาก ควรจะต้องมีการศึกษาต่อไปที่มีจำนวนประชากรมากขึ้น เพื่อเป็นการยืนยันการศึกษานี้

The goal of the ophthalmic surgeon is to perform sight-improving procedures using high quality techniques while minimizing adverse circumstances. Certain complications, such as postoperative bacterial infection, are difficult to anticipate; therefore, all patients must be covered by a consistent pattern of perioperative medication which is determined by patient requirements and physician preferences. Postoperative bacterial endophthalmitis is a devastating complication of intraocular surgery and remains a small but definite risk during all forms of intraocular surgery. Considerable effort has been and still is being expanded by ophthalmologists throughout the world, to minimize this risk because of the serious visual morbidity associated with such infection. Although the incidence of postoperative endophthalmitis has decreased in the past 30 years, it still occurs at an appreciable rate after cataract surgery, with the most accurate guide to its incidence (0.31%) coming from a prospective nationwide study performed between 1988 and 1989.[1] This incidence is higher than that reported in retrospective studies from teaching units[2,3] (0.072 to 0.10%) that do not represent national experience.[4,5] The difference may also be explained by selection bias from incomplete assessment. The majority of cases of postoperative bacterial endophthalmitis occur after cataract surgery,[6] with an incidence of between 0.072 and 0.58%.[1,2,4,5,7] Irrespective of its true incidence, as a quarter of the patients with postoperative endophthalmitis achieve a final visual acuity of worse than 20/200,[8] prevention of endophthalmitis is of great importance. Widespread adoption of self-sealing, small incision techniques in cataract surgery may further reduce the occurrence of endophthalmitis.

Evidence concerning the source of organisms responsible for endophthalmitis demonstrates that bacterial are frequently introduced into the eye during cataract surgery[9]. The origin of the infecting organisms is predominantly from commensals on the ocular surface[10] and, to a lesser extent, from airborne micro-organisms[11] or other endogenous sources such as the genitourinary tract. The most common infecting organism is Staphylococcus epidermidis.[12-15] However, in most cases, the source of the infecting organism cannot be identified with certainty. It has been clearly demonstrated that viable organisms are introduced into the eye during cataract surgery, and bacteria may be isolated from aqueous areas in a quarter or more eyes undergoing extracapsular procedures,[16] even where there has been surface disinfection with povidone-iodine or preoperative topical antibiotics have been administered.[17,18] These observations, together with the low rate of endophthalmitis (less than 1%), make it likely that endophthalmitis only develops after introduction of a sufficiently large or virulent inoculum. A variety of techniques have been proposed to minimize the risk of endophthalmitis, including meticulous aseptics in the operating theater,[10] conjunctival preparation with povidone-iodine,[19,20] small incision surgical techniques,[21] and administration of prophylactic antibiotics.

Although prophylactic antibiotics are widely used, little evidence exists that they prevent postoperative endophthlmitis. The prophylactic use of antibiotics to prevent postoperative bacterial endophthalmitis is controversial. In the past, antibiotics used in such a manner usually were given topically, subconjunctivally, or periocularly. It is difficult to properly evaluate the effect of peroperative antibiotics.[22-24]

While topical preoperative antibiotics alter the

patient's own conjunctival flora,[22] no reduction in the incidence of endophthalmitis[23] or the rate of culture-positive anterior chamber aspirates has been shown.[17] Similarly, subconjunctival antibiotics reach sustained therapeutic levels in the anterior chamber[24-26] without an effect on the incidence of postoperative endophthalmitis being proven.

More recently, antibiotic supplementation of intraocular irrigating solutions has received increasing publicity, leading to more widespread use. To reduce the risk for postoperative bacterial endophthalmitis , the use of supplemented antibiotics, such as vancomycin, in the intraocular irrigation solutions during routine cataract surgery has been recommended.[27-31] Incorporating supplemented vancomycin into the intraocular irrigating solutions[32] has yielded promising results. Although it offers the advantage of achieving bactericidal antibiotic levels in the anterior chamber peroperatively, these levels may not be maintained sufficiently to be therapeutic.[33, 34] In addition, a theoretical risk of toxicity exists if dosage errors occur.

This study was undertaken to investigate the effect of supplemented and nonsupplemented vancomycin in the intraocular irrigating solutions on the incidence of postoperative bacterial endophthalmitis after routine uncomplicated phacoemulsification with intraocular lens implantation.

Patients and Methods

Selection of Patients

The study included 1060 consecutive eyes having routine elective cataract surgery and intraocular lens implantation (from June 1,1994. to November 30, 1995). Patients were excluded if there was a history or evidence of previous surgery or penetrating injury to the eye, local or systemic infection at the time of surgery, or a perioperative complication (e.g. posterior capsule rupture). All types of cataracts (posterior subcapsular, nuclear sclerosis, dense brunescent, etc.) were included in this study.

The eyes were prospectively divided into two consecutive, nonrandomized groups: in the studied group of 312 eyes (from June 1,1994 to November 30, 1995), 10 mg. of vancomycin hydrochloride (Vancocin CP, Eli Lilly, Indianapolis, IN) were added to 500 ml. of preservative-free, balanced salt solution (BSS, Alcon Laboratories Inc., Forth Worth, TX), resulting in a vancomycin concentration of 20 microgram/ml. (20 mg./ L) in the intraocular irrigating fluid:In the controlled group of 748 eyes (from December 1, 1995 to February 28, 1998), there was no supplemented vancomycin in the intraocular irrigation solution.

Surgical Procedure

All cataract procedures were performed by one surgeon (P.T.), using the same technique of topical corneal tunnel phacoemulsification with injectable or foldable intraocular lenses. The operative eye was prepared for surgery with 1% tropicamide (Mydriacyl, Alcon Laboratories Inc., Forth Worth, TX) and 10% phrenylephrine hydrochloride (Neo-Synephrine, Sanofi Wintrope,New York, NY) starting 30 minutes before surgery. Topical 0.5% proparacaine hydrochloride (Ophthetic, Allergan Westport Co., Mayo, Ireland) was instilled 5 minutes before surgery and repeated at the start of the preparation. Ocular preparation in the operating room included cleaning of eyelids and lashes with 10%

povidone-iodine solution (Betadine 10%, Escalon, Lakewood, NJ) allowing the antiseptic solution to contact the conjunctiva and conjunctival fornices. Lashes were not cut and no prophylactic topical or systemic antibiotics were used. Patients were draped with a sterile, disposable, self-adhesive plastic drape (Opsite, Smith & Nephew) to keep the lashes away from the field of the surgery. The head and body were draped with a sterile clothes drape. A wire speculum was in placed. No rectus bridle suture was used. Two stab incision were made for performing capsulorhexis and insertion of a second instrument at the 2 clock position away from the incision on each side using a disposable 15 degree metal stab knife (Stab Knife, Alcon Surgical, Alcon Laboratories, Inc., Forth Worth, TX, and and Sharpoint, Surgical Specialities Corporation, PA). A 3-mm, two-plane, clear corneal incision was made in the steepest corneal meridian and temporally in case of round cornea, and guided by preoperative keratometry, using 3 mm. disposable metal keratome (Slit Knife, Alcon Surgical, Alcon Laboratories Inc., Forth Worth, TX, and Sharpoint, Surgical Specialities Corporation, PA). The anterior chamber was filled with viscoelastic substances (Amvis Plus, Chiron Vision, Claremont, CA, Ophthalin, Ciba Vision, Hettlingen, Switzerland). A 5.5-mm diameter continuous curvilinear capsulorhexis was performed with a bent 27-gauge hypodermic needle. Hydrodissection and hydrodeleniation were performed with the same balanced salt solution used for intraocular ocular irrigation during phacoemulsification. The modified stop and chop type technique of phacoemulsificston was used. After all cortical material was removed by irrigation and aspiration, viscoelastic was injected to fill the capsular bag. The incision was enlarged to 3.2-3.5 mm in width straddling the steepest corneal meridian using a disposable metal keratome. Injectable or foldable intraocular lens implants were inserted into the capsular bag. The intraocular lenses included injectable, one-piece, plate haptic silicone lenses (Chiron Vision , model C10UB and C11UB, Chiron Vision, Claremont, CA), three-piece foldable silicone lenses (Soflex, model LI41U, and model C31UB, Chiron Vision, Claremont, CA) and three-piece foldable acrylic lenses (Acrysof, model MA 60 BM, Alcon Laboratories Inc., Forth Worth, TX). All viscoelastic was removed with irrigation and aspiration and the anterior chamber was filled with the irrigating balanced salt solution. The incision was not sutured. No intracameral antibiotics or miotics were used. Topical combined antibiotics (neomycin-polymyxin B, Spersapolymyxin, Dispersa, Switzerland) were instilled at the end of the surgery. No subconjunctival injection, eye ointment, or topical miotics was used. The operated eye had no patch applied but was shielded at the end of the procedure.

Postoperative Procedure

Patients were started on topical combined chloramphenical - dexamethasone solution (Spersadexoline, Dispersa, Switzerland) on the day of the procedure, 1 drop into the operated eye every hour for 4 hours and then four times a day for three weeks. No other topical or oral medications were prescribed except analgesic tablets (paracetamol tablets). Patients were asked to refrain from eye rubbing and swimming during the first two postoperative weeks; otherwise, their activities were not restricted.

Patients were seen during the first three days after surgery, at 2 weeks, 4 weeks and 8 weeks postoperatively unless circumstances necessitated more frequent visits an each postoperative visit each patient

underwent measurements of uncorrected visual acuity, slit-lamp examinations looking for postoperative bacterial endophthalmitis as defined in the inclusion criterias, autorefractokeratometery and tonometry. The best corrected visual acuity was recorded on the last postoperative examination during the study period.

Inclusion criterias for postoperative bacterial endophthalmitis

1. postoperative ocular pain more severe than expected
2. tearing and photophobia
3. unexplained decreased visual acuity
4. hypopyon, vitritis
5. formation of fibrinous anterior reaction coating the iris, intraocular lens or forming a pupillary membrane
6. conjunctival hyperemia ,chemosis and lid swelling
7. corneal edema and cloudiness

Results

There was no single eye with clinically suspected postoperative bacterial endophthalmitis found in either the control group (no antibiotics) or the test group (with vancomycin). There was no difference in the incidence of postoperative bacterial endophthalmitis despite using supplemented or nonsupplemented vancomycin in the intraocular irrigating solutions.

Discussion

The rate of postoperative bacterial endophthalmitis decreased to 0.1 to 0.3% with the introduction of new cataract surgical techniques that provided correct wound closure and improved aseptic preparations of the patients.[1,35] To reduce bacterial contamination of the anterior chamber during phacoemulsification and thus minimize the risk of postoperative endophthalmitis, several authors[31,36] have recommended the use of antibiotics in the intraocular irrigating solution. This could be controversial because there have been no randomized prospective studies that evaluated the effect of antibiotics in the irrigating solution on the incidence of postoperative ocular infection.

The author investigated the association of using supplemented vancomycin and nonsupplemented vancomycin in the irrigating solutions on the incidence of postoperative bacterial endophthalmitis in the patients having routine phacoemulsification. Despite the limitations of this study because of the small population group, there appeared to be no difference in the incidence of postoperative endophthalmitis when vancomycin was not used. Because few patients develop endophthalmitis, a randomized, controlled trial of preoperative prophylactic antibiotics would require a large number of patients approximately 100,000 cases, to demonstrate a modest reduction in incidence.[37] This study has been only a pilot study. Additional studies are required to judge the clinical relevance of the my observations in this study.

Vancomycin, a glycopeptide that inhibits cell wall biosynthesis, is highly active against gram-positive cocci. Its antibacterial activity is slow and time dependent; it begins in vitro after 6 hours and becomes complete after 24 to 28 hours.[38] For antibiotics to exert the desired inhibitory and bactericidal effect, an appropriate antibiotic must be present in either bacteriostatic or bacteriocidal concentrations over a significant period of the cell cycle.

In fact, a standard suspension of Staphylococcus aureus or Staphylococcus epidermidis incubated in balanced salt solution containing vancomycin (20mg./L) showed no decrease in the number of viable organisms for up to 120 minutes.[33] Phacoemulsification time is usually 15 to 30 minutes. At the end of an actual surgical procedure, the anterior chamber is reformed with irrigating solution with supplemented vancomycin. Some of the antibiotic diffuses into the surrounding tissues, including the vitreous. This may act as a depot, extending the antibiotic exposure, but the overall effect is not known. Probably more important in the anterior chamber's pharmacokinetics are the aqueous humor dynamics. It is difficult to measure the aqueous turnover during the first 24 hours after surgery. It is known that in a normal, noninflamed, unoperated eye, approximately 1% of the aqueous volume turns over per minute.[39] That would mean that concentration of a drug in the anterior chamber would decrease by one half in 70 minutes. The aqueous dynamics are more likely greatly accelerated in the immediate postoperative period due to inflammation. If allowing less than 1 hour for the surgical procedure and a dilution of the vancomycin concentration within a few hours because of aqueous turnover, the effective duration of the vancomycin activity after intraocular irrigation is fewer than 48 hours, insufficient to kill bacteria.[40]

Endophthalmitis can occur in spite of using antibiotics in the irrigating fluid. In an invitro model, it was demonstrated that exposure to antibiotics for a short time generally has no effect on organisms commonly responsible for endophthalmitis.[41] Towsend-Pico and associates[42] reported a patient with endophthalmitis secondary to coagulase-negative Staphylococcus after phacoemulsification with vancomycin containing irrigating solution. Despite the organism's in vitro susceptibility to vancomycin, the presence of vancomycin in the irrigating solution did not prevent this case of endophthalmitis.

Manipulation of irrigating solution, such as during the addition of antibiotics, opens an opportunity for errors or contamination that could have untoward effects. The surgeon must recognize that the use of these antibiotics in the irrigating fluid is not always protect on against postoperative endophthalmitis and that the risks may outweigh the possible benefits.

Another significant issue is the additional cost of adding antibiotics to the irrigating fluid. A standard bottle of vancomycin (500 mg., Vancocin CP, Eli Lilly) will cost the patient up to 845 baht per dose if an individual bottle is used for each patient.

The US Department of Health and Human Services, Center for Disease Control and Prevention, has published recommendations for the appropriate use of vancomycin.[43] These recommendations stem from the increasing prevalence of vancomycin-resistant enterococci and methicillin-resistant Staphylococcus aureus.[44] Reports in the medical literature point to the need to discourage the use of vancomycin for routine surgical prophylaxis and the use of vancomycin solution for topical application and irrigation.[45] In view of the warning of emerging bacterial resistance to vancomycin, it seems prudent that ophthalmologists carefully consider alternatives in the routine use of vancomycin in the irrigating fluid and for subconjunctival or topical administration.

In conclusion, the risk-benefit ratio of using supplemented vancomycin in the intraocular irrigating fluid is unknown. The considerations for reducing the risk for postoperative endophthalmitis must focus on the

identification of the high-risk patient preoperatively, routine use of povidone-iodine on the lids and conjunctiva, plastic barrier drapes to cover the lid margins, and adherence to a standard sterile protocol during surgery. The prophylactic use of supplemented vancomycin in the irrigating solutions for all patients who undergo cataract surgery inevitably results in many patients receiving apparently unnecessary treatment, with obvious financial implications. Additional large-population well-designed studies are needed to provid address the conclusion. The author recommends that ophthalmologists reserve vancomycin to treat infections only when they occur.

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