• Clinical Research •

Risk factors for endophthalmitis after cataract surgery in diabetic patients: a case control study

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Abstract

• AIM: To identify risk factors associated with post-cataract surgery endophthalmitis (PCE) in type 2 diabetic patients.

• METHODS: A hospital-based retrospective case-control study was conducted on 194 type 2 diabetic patients undergoing cataract surgery in Rajavithi Hospital from January 2007 to December 2015. Fifteen patients with PCE were included as the case group and 179 patients without PCE were included as the control group. Potential factors associated with PCE among both groups including demographics, pre-operative characteristics, surgical settings and complications, were statistically analyzed using Chi-square testing and a logistic regression model.

• RESULTS: Within the case group, 53% were females and the median age was 68y. Univariate analysis of pre-operative characteristics, surgical settings and complications revealed that recent pre-operative fasting plasma glucose, insulin therapy, presence of diabetic retinopathy, and severe non-proliferative or proliferative diabetic retinopathy were significantly associated with PCE. In a multivariate analysis adjusting for blood glucose level, insulin treatment was the only significant factor associated with an increased risk of PCE (OR 3.9, 95%CI 1.0-15.0, *P*=0.04) compared to patients without insulin treatment. The most common causative organisms were gram-positive bacteria (89%). *Staphylococcus* species represented the most common group (67%). Median best corrected visual acuity at 1-month and 3-month follow-up was equal at 0.7 logMAR (20/100).

• CONCLUSION: The authors identify insulin treatment as the only risk factor associated with endophthalmitis after cataract surgery in type 2 diabetic patients. Further studies with serum levels of pre-operative glycated hemoglobin (HbA_{1c}) and post-operative fasting plasma glucose level are essential to truly demonstrate the role of peri-operative glycemic markers as a risk factor for PCE.

• **KEYWORDS:** endophthalmitis; cataract surgery; diabetic patients; insulin; fasting plasma glucose
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INTRODUCTION

Cataract surgery is the most common intraocular surgery in ophthalmology practice. The technological advancement of surgical machinery and intraocular lenses (IOLs) have made this maneuver easier, faster and safer. In addition, patients with cataract problems can gain better vision and recovery after the surgery. However, the most serious complication of cataract surgery is post-operative endophthalmitis which can deteriorate vision and cause blindness[1]. Diabetes mellitus is a very common metabolic illness that detrimentally affects the microvascular system. Many previous studies conducted in the various surgical specialties, including ophthalmology, have found that diabetes is associated with a significantly higher risk of post-operative or surgical site infection years[2-7]. Nonetheless, in the field of ophthalmology, there has been no research conducted demonstrating the risk of developing post-operative endophthalmitis after cataract surgery in the diabetic group specifically. The Endophthalmitis Vitrectomy Study, the landmark study of post-cataract surgery endophthalmitis (PCE), investigated different responses between diabetic and non-diabetic patients and recommended early vitrectomy for diabetic patients. However, this study did not specifically examine the risk factors for developing PCE in diabetic patients[8].

This work focuses on diabetic patients and aims to identify risk factors including demographics, pre-operative characteristics, surgical settings and complications associated with PCE.

SUBJECTS AND METHODS

Ethical Approval A case-control study was initiated by retrospectively reviewing medical charts of patients developing PCE at the Department of Ophthalmology, Rajavithi Hospital,

Bangkok, Thailand from January 2007 to December 2015. The study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Rajavithi Hospital. Informed consent was waived due to the retrospective nature of the study.

Study Design and Data Collection Individuals were considered to have endophthalmitis if hypopyon or vitritis was present or if the patient received an intravitreal injection of antibiotics for presumed endophthalmitis[9-10]. PCE was defined as an endophthalmitis occurring after uncombined cataract surgery. In the present study, exclusion criteria were any of the following: 1) PCE developing in non-diabetic patients; 2) missing laboratory or operative data (any patients); 3) records indicating non-compliance with drug treatment or less than 1mo of follow-up (any patients). The remaining type 2 diabetic patients who did not fulfill any exclusion criteria were included in the study. The case group consisted of diabetic patients who developed PCE post cataract surgery, whereas the control group consisted of type 2 diabetic patients undergoing cataract surgery who did not develop PCE. For each case, 10 control patients were randomly selected from the surgical logbook of patients who underwent cataract surgery within 14d before or after each case.

Data collected included variables typically associated with PCE, which mostly involved diabetic control and operative profile. Diabetes was defined as a fasting plasma glucose level ≥126 mg/dL (or a glucose level ≥200 mg/dL for those not fasting), the use of insulin or oral hypoglycemic drugs, or a reliable self-reported history of diabetes. Preoperatively, patients had fasting plasma glucose measured as a part of routine pre-operative testing, which occurred on average 6wk (1-12) before the operation. Measurements performed more than three months before the operation were not accepted. If plasma glucose was measured multiple times before an operation, the most recent result was used. Glycated hemoglobin (HbA_{1c}) was also gathered, although it was not included in our pre-operative laboratory routine. All diabetic treatments documented in the study were employed by primary care physicians or endocrinologists at the time surgery was appointed.

In regards to operative profile, operative risk factors collected included antiseptic technique, eyelash removal, type of cataract surgery, type of IOL used, complications, the presence of stitches and different operating rooms occupied. In addition, microbiologic profiles, treatment modalities and visual outcomes of PCE cases were collected. Presenting acuity was defined as the acuity at the first visit for endophthalmitis. Snellen visual acuity of the affected eye was converted to the logarithm of the minimum angle of resolution (logMAR). The following scale was applied to logMAR values: counting fingers, 2.00; hand motion, 2.30; light perception, 2.60; and no light perception, 2.90[11-12].

The preoperative evaluation and preparation for endophthalmitis prophylaxis included an absence of periocular and ocular surface infection, and lacrimal drainage system obstruction. Antibiotic eyedrops were not routinely employed prior to the cataract surgery. Just before surgery, periorbital disinfection was performed using gauze soaked with 10% povidone iodine solution. This was followed by a thorough cleaning of the periorbital region with 2 cotton swabs soaked with 10% povidone-iodine solution. Afterwards, irrigation of the conjunctival sac with 10 mL of 5% povidone-iodine solution was performed. On those days, no peri-operative antibiotic prophylaxis, including intracameral and subconjunctival injections, were used by any surgeons in our hospital.

Postoperatively, the decisions using topical antibiotics (levofloxacin or tobramycin) were based on surgeon preferences. Steroid eyedrops were prescribed for 1-2wk. The postoperative check-ups were usually performed at day 1, 1wk, 1, 3mo and then as needed afterwards. When endophthalmitis was diagnosed, the patient immediately underwent an aqueous and/or vitreous tap and/or vitrectomy to isolate any organisms followed by intravitreal injections of vancomycin and ceftazidime. A prescription of systemic antibiotics was dependent on surgeons' preferences. Both culture-positive and culture-negative cases were included, and after sampling the causative microorganisms, antibiotic treatment was initiated. A pars plana vitrectomy was conducted on the endophthalmitis patients who presented with light perception or worse[13].

Statistical Analysis Statistical analysis was performed using the SPSS statistical software version 16.0 (SPSS Inc, Chicago, IL, USA). Descriptive analyses were used to describe demographics, pre-operative characteristic, surgical settings and complications. The Mann-Whitney *U* test was used to compare data between two unrelated groups in which normal distributions were not verified. A univariate analysis by Chi-square test or Fisher's exact test was performed to demonstrate significance of associated factors with a P value <0.1. Variables that were significant in the univariate analysis were examined in a multivariate logistic regression model by which differences were considered statistically significant with a P value <0.05.

RESULTS

Demographic Data of the Case Group Of the 24 090 patients undergoing cataract surgery from 2007 to 2015, 1476 cases (6.1%) had diabetes prior to surgery. The incidence rate of PCE in diabetic patients was 1.0% (15/1476) which was greater than the incidence of PCE in non-diabetic patients 0.11% (25/22 614). Fifteen diabetic cases with PCE and 179 diabetic controls without PCE were included in the study. In the case group, 8 (53%) were females. The median age at time of cataract surgery was 68 (range, 36-80)y. Two patients

Table 1 Demographics and pre-operative characteristics comparison between diabetic patients with PCE (case) and without PCE (control) groups *n* (%)

Characteristics	Total (*n*=194)	Case (PCE, *n*=15)	Control (No PCE, *n*=179)	*P*
Female	125 (64)	8 (53)	117 (65)	0.35[a]
Age (y), median (range)	65 (36-97)	68 (36-80)	65 (36-97)	0.36[b]
Recent pre-operative FPG >190 mg/dL	24 (12)	0	30 (17)	0.07[c]
Insulin therapy	23 (12)	4 (27)	19 (11)	0.08[c]
Diabetic nephropathy	13 (7)	1 (7)	12 (7)	1.00[c]
Diabetic neuropathy	4 (2)	1 (7)	3 (2)	0.28[c]
DR				
No DR	97 (50)	11 (73)	86 (48)	0.06[a]
Mild to moderate NPDR	26 (13)	2 (13)	24 (13)	1.00[c]
Severe NPDR to PDR	71 (37)	2 (13)	69 (39)	0.05[c]
DME	19 (10)	2 (13)	17 (10)	0.65[c]

PCE: Post-cataract surgery endophthalmitis; FPG: Fasting plasma glucose; DR: Diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; DME: Diabetic macular edema. [a]Chi-square test; [b]Mann-Whitney *U* test; [c]Fisher's exact test.

Table 2 Comparison of surgical settings and complications between diabetic patients with PCE (case) and without PCE (control) groups *n* (%)

Characteristics	Total (*n*=194)	Case (PCE, *n*=15)	Control (No PCE, *n*=179)	*P*[a]
Phacoemulsification	185 (95)	14 (93)	171 (96)	0.52[b]
Extracapsular cataract extraction	9 (5)	1 (7)	8 (4)	
IOL type for implantation				
1-piece	105 (54)	10 (67)	95 (53)	0.31
3-piece	89 (46)	5 (33)	84 (47)	0.35
Acrylic IOL	126 (65)	8 (53)	118 (66)	0.33
Posterior capsule rupture	7 (4)	1 (7)	6 (3)	0.44[b]
Suturing wound	62 (32)	7 (47)	55 (31)	0.25
Staff surgeon	110 (57)	9 (60)	101 (56)	0.79
Operating room, floor 3	96 (49)	7 (47)	89 (50)	0.82

PCE: Post-cataract surgery endophthalmitis; IOL: Intraocular lens. [a]Chi-square test; [b]Fisher's exact test.

(14%) had non-ophthalmic complications including diabetic nephropathy and diabetic neuropathy. None of the patients were immunocompromised or under immunosuppressive treatments. At the time of surgery, 4 (27%) experienced any degree of diabetic retinopathy (DR) while 2 (13%) of these had severe non-proliferative or proliferative DR.

Demographic Comparison of Case and Control Group Regarding pre-operative fasting plasma glucose and HbA_{1c} levels, no patients with PCE had pre-operative fasting plasma glucose levels of more than 190 mg/dL. HbA_{1c} levels were recorded for 33% (5/15) of the case group and 21% (37/179) of the control group. Of these, the median HbA_{1c} level of case and control groups was 8.5% (range, 5.4%-9.6%) and 7.5% (range, 5.1%-12.4%) respectively. The comparison of median HbA_{1c} levels between case and control groups was not significantly different by Mann-Whitney *U* Test (*P*=0.57). Table 1 demonstrates demographics and pre-operative characteristic comparisons between case and control groups.

None of the cases and controls underwent immediate sequential bilateral cataract surgery. Most procedures performed in the case group were phacoemulsification (93%). The most common types of IOL used were 1-piece, acrylic and foldable IOL. Intraoperative complications included one case of posterior capsule rupture and vitreous loss. Most surgeons performing surgery were staff surgeons. All patients developed endophthalmitis within 4wk and the median onset of endophthalmitis after cataract surgery was 5d (range, 1-23d). Table 2 shows comparisons of surgical settings and complications between case and control groups.

Univariate and Multivariate Analysis To evaluate associated factors influencing the incidence of PCE in diabetic patients, relevant characteristics of the case and the control groups were initially analyzed using a univariate method. From univariate analysis, 4 factors including recent pre-operative fasting plasma glucose, insulin therapy, presence of DR, and severe non-proliferative or proliferative DR were significantly

Table 3 Characteristics of 15 cases with PCE *n* (%)

Characteristics	PCE (*n*=15)
Median recent pre-operative FPG (mg/dL)	110 (range, 75-181)
Median onset of endophthalmitis after cataract surgery (d)	5.0 (range, 1-23)
Hypopyon	10 (67)
Totally obscured fundus	9 (60)
Micro-organisms (*n*=9)	
Staphylococcus epidermidis	5 (32)
Staphylococcus aureus	1 (7)
Streptococcus viridans	1 (7)
Enterococcus faecalis	1 (7)
Eschericia coli	1 (7)
Systemic treatment (*n*=9)	
Oral ciprofloxacin	8 (53)
Systemic vancomycin + ceftazidime	1 (7)
Median visual acuity logMAR	
At day 1 after surgery	0.5 (range, 0.3-2.3)
Presenting acuity (at the diagnosis of endophthalmitis)	2.0 (range, 0.5-2.3)
At 1-month follow-up	0.7 (range, 0.1-2.9)
Complications (*n*=5)	
Secondary glaucoma	4 (27)
Neovascular glaucoma	1 (7)

PCE: Post-cataract surgery endophthalmitis; FPG: Fasting plasma glucose.

associated with PCE (Tables 1 and 2). Multivariate logistic regression analysis, adjusting for blood glucose level, revealed that insulin treatment was significantly associated with an increased risk of endophthalmitis (OR 3.9, 95%CI 1.0-15.0, *P*=0.04) compared to patients without insulin treatment.

Causative Pathogens and Visual Prognosis The organism causing PCE was identified by a positive culture from a vitreous specimen in 9 (60%) of the 15 patients (Table 3). Among the positive cultured specimens, the most common causative agents identified were gram-positive organisms (89%). *Staphylococcus* species represented the most common group, and was found in 6 (67%) patients. Fungus was not detected in any of the samples. All cases received intravitreal injections of vancomycin and ceftazidime. Seventy-three percent underwent immediate pars plana vitrectomy. None were eviscerated or enucleated. However, two cases (13%) experienced phthisis bulbi at a median follow-up period of 20 (range, 3-112)mo. At 1-month and 3-months follow-up, median best corrected visual acuity (BCVA) was equal at 0.7 logMAR (20/100) compared with 0.5 logMAR (20/60) at day 1 after surgery. Sixty-seven percent had BCVA of 20/200 or better. Table 4 shows the clinical summary of all cases in detail.

DISCUSSION

Previous studies reported various risk factors associated with PCE in the normal population, for example, pre-operative medical conditions, type of cataract surgery, intraoperative complications, no intracameral antibiotic usage[14-18]. Among these, diabetes has been the most common metabolic illness associated with PCE[2,9,14,19-21]. However, there have been no studies performed to specifically investigate PCE in diabetic patients. The present study pioneered investigation of the risk factors for endophthalmitis after cataract surgery in patients with diabetes and demonstrated insulin treatment as the only significant factor associated with PCE.

On the contrary to unanimously agreed upon perioperative glycemic control, insulin treatment, though rarely reported, has been controversial as an associated risk factor with non-surgical[4] and surgically related infection[22-23]. Contradictory results regarding wound infection after caesarean section in insulin-dependent diabetic women were reported by the two previous studies. Though insulin was not included in an analysis of the research, given that it was the designated treatment of the study population, it could be a confounding variable influencing the occurrence of infection[22-23].

The only available literature related to insulin treatment and the eye is accelerating corneal epithelial healing by insulin treatment which may represent a preventive effect of insulin on PCE[24-25]. However, there has been no evidence proving the efficacy of insulin treatment in corneal wound healing after cataract surgery. Recently, Donnelly *et al*[4] performed a large prospective cohort study examining the association of diabetes

Table 4 Clinical summary of diabetic patients developing PCE

Case	Sex/Age	Pre-operative FPG level (mg/dL)	Causative organisms	Antibiotic treatment (local, systemic)	Pars plana vitrectomy	Complications	Initial BCVA	Final BCVA
1	F/36	75	-	IVC	ND	NVG	2.3	2.3
2	F/44	150	*Escherichia Coli*	IVC, ciprofloxacin	Y	-	0.8	0.3
3	M/64	103	-	IVC	Y	Secondary glaucoma	0.5	0.5
4	F/64	96	-	IVC, ciprofloxacin	Y	Secondary glaucoma	0.4	2.3
5	M/80	158	*Staphylococcus epidermidis*	IVC, ciprofloxacin	Y	-	0.5	0.3
6	F/73	110	-	IVC, ciprofloxacin	ND	-	0.6	0.3
7	M/55	132	*Streptococcus viridans*	IVC, ciprofloxacin	Y	Secondary glaucoma	2.0	2.9
8	F/68	174	*Enterococcus fecalis*	IVC, vancomycin, ceftazidime	Y	-	0.5	0.4
9	M/76	87	*Staphylococcus epidermidis*	IVC, ciprofloxacin	Y	-	0.8	0.3
10	M/37	109	*Staphylococcus aureus*	IVC	Y	Secondary glaucoma	2.0	1.4
11	M/69	100	*Staphylococcus epidermidis*	IVC	Y	-	1.0	1.0
12	F/74	145	-	IVC	Y	-	2.0	0.3
13	F/80	171	*Staphylococcus epidermidis*	IVC	Y	Epiretinal membrane	0.5	2.9
14	F/76	181	*Staphylococcus epidermidis*	IVC, ciprofloxacin	ND	-	0.7	0.3
15	M/67	110	-	IVC, ciprofloxacin	ND	-	2.0	0.3

PCE: Post-cataract surgery endophthalmitis; FPG: Fasting plasma glucose; BCVA: Best corrected visual acuity; F: Female; M: Male; IVC: Intravitreal injection of vancomycin and ceftazidime; Y: Yes; ND: Not done; NVG: Neovascular glaucoma.

and insulin therapy with hospitalization for infection and found that participants receiving insulin therapy experienced a more pronounced infection risk. They hypothesized that insulin use may function as a marker for advanced diabetic disease and could affect risk of infection. In addition, an unexplained mechanism directly related to insulin and inoculation of pathogenic organisms into soft-tissue by regular insulin injections could pose a higher risk of infection to diabetic participants receiving insulin therapy compared to those not receiving insulin[4,26].

Poor peri-operative control of glycemic markers can influence surgical site infection as presented in various subspecialties[27-33]. This includes optimizing control of fasting plasma glucose and HbA_{1c} level. HbA_{1c} is vital and has been thought to represent average glycemia roughly over the last 6-8wk. It is also associated with microvascular complications and macrovascular diseases[34-35]. Unfortunately, our HbA_{1c} data gathered was insufficient to rule out HbA_{1c} as a significant factor associated with endophthalmitis after cataract surgery in type 2 diabetic patients, because it was not routinely performed in pre-operative screening for diabetic patients. Further study has been established including HbA_{1c} profile within pre-operative screening for diabetic patients in our setting.

Regarding pre-operative fasting plasma glucose level, most ophthalmologists in Thailand have followed guidelines of other specialties indicating that fasting plasma glucose levels before intraocular surgery should be kept less than 200 mg/dL in order to prevent the risk of post-operative infection[31-32]. Interestingly, none of the endophthalmitis cases in our series had fasting plasma glucose levels greater than 190 mg/dL. Though this may suggest that strict glycemic control may not be mandatory prior to cataract surgery, caution should be exercised in the interpretation of the results. Besides, surgery can cause patients metabolic stress and create a state of functional insulin insufficiency, resulting in transient hyperglycemia during and after an operation[36]. Post-operative glucose level was also reported as a risk of surgical site infection[32-33].

The present study is the first reporting an incidence of PCE in diabetic patients, which is significantly greater than one in non-diabetic patients. This is not surprising given that patients with diabetes have been known to have an impaired immune response which poses a higher risk for developing postoperative infection[37-38]. However, the incidence of PCE could have been reduced by using intracameral antibiotic prophylaxis which is a standard practice of the present day[39].

Regarding isolated micro-organisms, the most common organism isolated from diabetic patients with PCE in our study was coagulase-negative which is also consistent with the results of previous works reported on PCE in diabetic patients and the general population[1,40-41].

Every case received immediate intravitreal antibiotic injections as standard treatment. Though we agreed and followed the recommendation by EVS for early vitrectomy in PCE developing in diabetic patients, improvement of vision at 1-month follow-up compared with pre-operative vision was demonstrated in only 47% (7/15) of cases. The cases experiencing postoperative BCVA of better or equal than 20/40 in our study was only 6% (1/15) compared with previous studies reporting 32%-39% in diabetic patients developing PCE[8,41]. Besides impaired immune function and microvascular

complications in diabetic patients as aforementioned, the difference could be due to previous studies' potential bias of using final BCVA with variable follow-up instead of BCVA at the same follow-up[42].

This study is limited by its retrospective fashion and by the fact that results are from a single hospital database. In addition, the profile of HbA_{1c} and duration of diabetes was lacking for analysis. Ideally to achieve a more updated and precise glycemic level, pre-operative and post-operative fasting plasma glucose monitoring is necessary. Pre-operative fasting plasma glucose should be more recent, for example, within one month prior to surgery. The reproducibility of the study is also limited since, nowadays, intracameral antibiotic prophylaxis is routinely used in cataract surgery. In conclusion, this retrospective case-control study reports associated risk factors of PCE in a cohort of diabetic patients to include only insulin treatment. We believe that insulin treatment is a proxy marker for advanced diabetic disease and could affect risk of infection. Further studies investigating the impact of HbA_{1c} and other diabetes-related factors should be performed to elucidate profiles in pre-operative diabetic status as risk factors for PCE in diabetic patients.

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