

Analysis of Conjunctival Bacterial Flora among Patients Undergoing Multiple Intravitreal Injections for Diabetic Macular Oedema: A Cohort Study

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ABSTRACT

Introduction: Intravitreal Injections (IVI) are frequently used for the treatment of Diabetic Macular Oedema (DME). Serial IVI in these patients along with topical antibiotics as prophylaxis for infection has raised concern about the probable detrimental effect on conjunctival flora. However, the risk of postoperative endophthalmitis is higher in diabetics, especially with poor glycaemic control or in the presence of Chronic Kidney Disease (CKD) owing to poor immunity. Hence, preoperative conjunctival microbial growth has been studied in these patients to understand the need for antibiotic prophylaxis.

Aim: To evaluate the preoperative conjunctival microbiological profile in diabetic patients treated with serial IVI (minimum of three) for DME and its association to their glycated Haemoglobin (HbA1c) levels and the presence of associated CKD.

Materials and Methods: This retrospective cohort study conducted in the Department of Ophthalmology at ESIC Medical College and Research Institute, Bengaluru, Karnataka, India, in May 2021. Total 92 eyes of 79 patients with type 2 diabetes mellitus who had received a minimum of three serial IVI of anti-Vascular Endothelial Growth Factor (anti-VEGF) injections for DME between May 2018 to January 2020 were included in the

study. Conjunctival swabs for culture were taken from each eye before the injection and were evaluated for microbial growth. The association between microbial growth and HbA1c levels and/or CKD was analysed statistically using the Chi-square test.

Results: The conjunctival cultures taken before IVI, were positive in 27 (29.3%) of 92 eyes. Among them, Coagulase Negative *Staphylococcus* (CoNS) bacteria were isolated in 15 (55.5%) of 27 eyes followed by Micrococci in 10 (37%) eyes and diphtheroids in 2 (7.4%) eyes. The average HbA1c among the eyes with positive growth was 7.23 ± 1.31 as compared to 6.64 ± 1.08 in eyes with no growth (p -value=0.1). There was a statistically significant association of culture positivity in patients with CKD and having HbA1c $\geq 7\%$ (p -value=0.01) with CONS being the most common organism.

Conclusion: A statistically significant association of conjunctival swab culture positivity in type 2 diabetics with DME requiring multiple IVI having uncontrolled diabetes HbA1c $\geq 7\%$ and the presence of CKD was observed in the present study. Hence, the routine use of topical antibiotics as infection prophylaxis may be recommended in these patients as an additional precaution against endophthalmitis.

Keywords: Chronic renal failure, Diabetic retinopathy, Glycated haemoglobin, Vascular endothelial growth factor

INTRODUCTION

Intravitreal Injection (IVI) of anti-Vascular Endothelial Growth Factor (anti-VEGF) has become the standard of care in the management of patients with Diabetic Macular Oedema (DME). Although, IVI is considered to be an effective and safe method, endophthalmitis is the most feared complication. The incidence of post-IVI endophthalmitis has been reported to be 0.131% [1].

Treatment of DME in many patients requires repeated intravitreal anti-VEGF injections owing to the chronicity of the disease. The recurrent monthly usage of perioperative topical antibiotics as infection prophylaxis in DME patients requiring multiple IVI has been reported to cause detrimental effects on their conjunctival flora, questioning their routine use [2]. However, diabetic patients also have a higher risk of postoperative endophthalmitis than non diabetic patients [3]. Also, patients with chronic renal failure have innate and adaptive immunity defects, thus predisposing them to infection [4,5]. The main source of bacteria isolated in cases of postinjection endophthalmitis is the patient's conjunctival bacterial flora. Therefore, evaluation of the conjunctival bacterial flora as a surrogate marker is of utmost importance to prevent postoperative endophthalmitis [6].

There is an ongoing confusion regarding the use or avoidance of perioperative topical antibiotics in patients with DME requiring serial IVI, especially those with poor glycaemic control and chronic renal

disease. For this purpose, retrospective cohort study was done to analyse the preoperative conjunctival flora of type 2 diabetic patients who have undergone three or more consecutive IVI of anti-VEGF for DME. The association of conjunctival cultures to their systemic glycaemic control (glycated haemoglobin, HbA1c) and the presence of Chronic Kidney Disease (CKD) in the study group was also analysed.

MATERIALS AND METHODS

This retrospective cohort study conducted in the Department of Ophthalmology at ESIC Medical College and Research Institute, Bengaluru, Karnataka, India, in May 2021. Informed consent was obtained from the study subjects and ethical clearance for the study was obtained from the review board (Ref No. 532/L/11/12/Ethics/ESICMC&PGIMSR/Estt.Vol.IV Dtd: 20/06/2021). The case records of all 79 patients over the age of 18 years and those who were treated with IVI of anti-VEGF for DME between May 2018 to Jan 2020 were collected.

Inclusion and Exclusion criteria: The patients who had received a minimum of three serial IVI of anti-VEGF (Ranibizumab or Aflibercept) were included in the study. The patients treated with triamcinolone acetonide injection, who had any prior ocular surgery within the past six months, chronic use of any topical antibiotics or topical

steroids, or usage of contact lenses six months before the study were excluded from the study.

All patients had undergone IVI after routine investigations (including HbA1c) and physician clearance for the procedure. Among them, those with CKD underwent IVI after nephrologist clearance.

Study Procedure

Swab collection method: A thorough ocular examination was done to look for any abnormalities in the eyelids and conjunctiva. Two days before the planned injection, conjunctival swabs were taken from the eye to be treated. Samples were obtained after anaesthetising the conjunctival sac with sterile 0.5% proparacaine ophthalmic solution and gently rubbing the lower fornix with a sterile cotton swab (no antibiotics or antiseptics were used). Care was taken to minimise contact with the eyelids and eyelid margin. The swabs were transported to the microbiology laboratory within 30 minutes and were inoculated on culture plates with 5% sheep blood agar, chocolate agar and MacConkey's agar; later incubated at 37°C in ambient air. Any growth was identified by various tests like gram's stain, catalase test, modified oxidase test and coagulase test [7]. After 48 hours, the culture plates were reviewed and listed the number of positive and negative cultures.

The patients with positive microbial growth were deferred IVI and started on topical moxifloxacin eye drops four times a day for five days. The conjunctival culture was repeated a week later and IVI was done after the swab showed no growth. The eyes with no culture growth were started on topical moxifloxacin eye drops, a day before IVI as prophylaxis. All the study patients had followed the same protocol in the previous injections done before the study period.

Intravitreal injection technique: All the intravitreal injections were done in the operating room by a single surgeon. Each patient received an injection from a new single use vial of ranibizumab or aflibercept. Topical anaesthesia with proparacaine was applied in the conjunctival sac. The periorbital area was cleansed with 10% Povidone Iodine (PVI), and 5% PVI drops were applied in the conjunctival sac for two minutes. A self-adhesive sterile drape large enough to mask the patient's face was placed. After applying the lid speculum, using a 30 gauge needle, 0.05 mL of anti-VEGF agent (ranibizumab or aflibercept) was injected through the pars plana route 3.5-4 mm from the limbus. Postinjection the culdesac was again flushed with PVI eyedrops. The eye was patched for two hours after injection and topical moxifloxacin (0.5%) eye drops were continued four times a day for five days for infection prophylaxis. Patients were reviewed on the next day, one week and a one month postinjection to look for endophthalmitis or any complications.

In the present study, the association between the conjunctival swab bacterial growth with preoperative HbA1c level and the renal status (presence or absence of CKD) in the study patients was assessed. Patients with HbA1c $\geq 7\%$ were considered as having poor glycaemic control (American Diabetes Association) [8]. Chronic kidney disease was defined as GFR < 60 mL/min/1.73 m² for ≥ 3 months, with or without kidney damage and on regular treatment at our hospital nephrology clinic (National Kidney foundation KFDOQI guidelines) [9].

STATISTICAL ANALYSIS

The data collected was entered on Microsoft excel and was analysed using IBM, Statistical Package for Social Sciences (SPSS) statistical software version 18.0. Descriptive statistics were analysed as proportions for frequencies and mean with standard deviation for continuous measures. The Chi-square test was used to find the association between the categorical variables. A p-value < 0.05 was considered as statistically significant.

RESULTS

Among the 146 patient records collected during the study period, 92 eyes of 79 patients fulfilling the inclusion and exclusion criteria

were included in the study. Out of total, 66 patients had IVI in one eye, while 13 patients had been treated in both eyes during the study period. Among the patients, 54 (68.35%) were males and 25 (31.64%) were females. The mean age of participants was 58.21 ± 9.13 years. The majority of the study participants were in the age group over 50 years. These patients had received an average of 4.3 (range 3-8) intravitreal injections in the past for DME. During the study period, 78 (84.8%) eyes received ranibizumab and 14 (15.2%) eyes received aflibercept. Conjunctival bacterial growth was seen in 27 (29.34%) of 92 eyes while 65 (70.6%) eyes had no growth. There was no significant association between age and positive conjunctival growth (p-value=0.185) nor association between sex and positive conjunctival growth (p-value=0.171). The bacteria isolated from the positive cultures were Coagulase Negative *Staphylococcus* (CoNS) being the most common in 15 (55.5%) of 27 eyes, Micrococci in 10 (37%) eyes and diphtheroids in 2 (7.4%) eyes [Table/Fig-1].

| Variables | n (%) |
|--|-------------|
| Sex distribution | |
| Males | 54 (68.35%) |
| Females | 25 (31.64%) |
| Age groups (years) | |
| >50 | 60 (75.9%) |
| ≤ 50 | 19 (24.1%) |
| Conjunctival culture growth (in eyes) | |
| Negative | 65 (70.6%) |
| Positive | 27 (29.3%) |
| -Coagulase Negative <i>Staphylococcus</i> | 15 (55.5%) |
| -Diphtheroid | 2 (7.4%) |
| -Micrococci | 10 (37%) |

[Table/Fig-1]: Study group characteristics.

The average HbA1c level at the time of injection among the study patients was $6.81 \pm 1.17\%$ (range 5.1-9.3). The average HbA1c among the patients with positive bacterial growth was 7.23 ± 1.31 as compared to 6.64 ± 1.08 in patients with no growth [Table/Fig-2]. There was no statistically significant difference between the HbA1c of patients with and without the presence of culture growth (p-value=0.1). Chronic kidney disease patients who had positive growth had significantly higher HbA1c (mean HbA1c=8.09%) compared to those with no growth (mean HbA1c was 6.30%) (p-value < 0.001).

| Parameters | Swab growth present (n=27) | No growth (n=65) | p-value (Statistical association to positive culture growth) |
|------------------------------------|----------------------------|------------------|--|
| Average HbA1c | 7.23 ± 1.31 | 6.64 ± 1.08 | 0.1* |
| No of eyes with CKD (n=30) | 14 | 16 | 0.01# |
| Average HbA1c in patients with CKD | 8.09 | 6.30 | $< 0.001^*$ |

[Table/Fig-2]: Average HbA1c levels and CKD status compared to culture growth (N=92).

*Student's t- test, #Chi-square test

The CKD was present in 30 (32.60%) eyes, among them four patients were on dialysis and the remaining were on medical management. CKD was statistically associated with positive bacterial growth (p-value=0.01) [Table/Fig-3]. Among the 30 eyes with CKD, 14 (46.6%) eyes had positive microbial growth with CoNS being the most common bacteria isolated in 9 (30%) eyes. There was also a statistically significant association between positive growth found in CKD patients and their HbA1c levels (p-value=0.01).

No cases of endophthalmitis or worsening of nephropathy or other complications were reported in these patients at one month follow-up.

| Number of eyes studied | Growth present (27/92) (29.3%) | No growth (65/92) (70.6%) | p-value Statistical association to positive culture growth (Chi-square test) |
|------------------------------------|--------------------------------|---------------------------|---|
| With CKD (n=30) | 14 (46.6%) | 16 | 0.01 |
| Without CKD (n=62) | 13 (20.9%) | 49 | |
| With HbA1c \geq 7 (n=36) | 14 (38.8%) | 22 | 0.1 |
| With HbA1c<7 (n=56) | 13 (23.2%) | 43 | |
| With CKD and HbA1c \geq 7 (n=25) | 12 (48%) | 13 | 0.01 |
| Without CKD and HbA1c<7 (n=67) | 15 (22.3%) | 52 | |

[Table/Fig-3]: Conjunctival swab culture results.

DISCUSSION

The practice pattern of IVI of anti-VEGFs and infection prophylaxis varies from practice to practice and from country to country [10]. The use of topical PVI on the ocular surface, eyelids, and eyelashes; the use of an eyelid speculum; and the avoidance of needle contact with surfaces other than the injection site have all been recommended by expert reviewers universally. In contrast, the application of topical antibiotics, either before or after the injection procedure, has remained a topic of debate [2,11,12]. Recent survey noted the use of peri-IVI antibiotic practice among ophthalmologists across continents and reported antibiotic usage by 67% in Europe, 34% (pre-IVI) and 81% (post-IVI) in the USA, and 39% in the Asia-pacific region [13-15]. In contrast, among the Indian retina specialists 60% used topical antibiotics in the pre-IVI period and 89.3% used them in the post IVI period [10].

In this study, the microbiological profile of conjunctival flora of diabetic patients who had received multiple IVI (minimum of three) was noted. The present study had a 29.3% conjunctival culture positivity rate and the most common bacterium isolated was Coagulase-negative *Staphylococcus* (CoNS) (55.5%). The results are consistent with published reports that showed that CoNS is the most common isolate from the conjunctiva [16-18]. Hsu J et al., reported a 77% culture positivity rate in cultures taken from the conjunctiva in patients receiving annual IVI [17], Kaldirim H et al., found CoNS (*Staphylococcus epidermidis*) as the bacterium with the highest culture positivity done after six serial IVI for DME, 50% culture positives noted one month after 3rd IVI (p-value <0.001) and 65.5% culture positives one month after the 6th IVI [2]. Yin VT et al., in a larger prospective study noted an increase in the percentage of isolates from 0% at baseline to 50% at three months after serial IVI, the most common isolate found being CoNS. Their study patients were treated with a three days course of topical moxifloxacin following each injection [19].

Studies have shown that the frequency of positive conjunctival cultures is found to be significantly higher in diabetics thereby increasing their risk of postoperative endophthalmitis compared to non diabetics [20-22]. Isenberg SJ et al., noted a definite synergy between the use of the combination of preop topical antibiotics-PVI before cataract surgery or IVI (83% sterile cultures) against the use of either of them (31% in antibiotic prophylaxis alone, 40% in PVI alone) in terms of positive bacterial cultures [23]. However, the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) study group showed no statistically significant difference in endophthalmitis rates between groups with and without antibiotic use, although there was a trend towards lower rates in the antibiotic-treated groups [24].

The relationship between HbA1c values and culture positivity rates was also analysed. Patients with higher HbA1c (mean 7.23) had a slight, non statistically significant trend for positive cultures, but in eyes, with CoNS growth, the mean HbA1c was even higher (mean 7.62). Similar results of higher mean HbA1c (8.2 \pm 1.0%, p-value=0.14) were noted by Einan-Lifshitz A et al., after the third IVI and and

Kaldirim H et al. (mean HbA1c 8.1%) in culture positive patients [2,25]. Patients with chronic renal, failure have innate and adaptive have innate and adaptive immunity defects, thus predisposing them to infectious disease [4,5]. In the present study, authors found a statistically significant association between the conjunctival growth of CoNS in CKD patients to higher HbA1c (mean 8.45). Kuo G et al., found seven dialysis patients having exogenous endophthalmitis after surgery. Of them, 57.1% had a positive vitreous culture with CoNS, and *Enterococcus faecalis* is the most common pathogen causing exogenous endophthalmitis in them [26].

The combination of periprocedural topical moxifloxacin 0.5% and antiseptic with 5% PVI has been proven to cause a greater decrease in positive cultures than the use of 5% PVI alone. It is known that after repeated exposure to PVI, there is no alteration in the conjunctival flora [27]. But the concern is about repeated short-term exposure to topical antibiotics during intravitreal injections and thereby the significant increase in the antibiotic resistance of ocular surface flora. However, in a recent study, Zhu X et al., noted that the diversity and distribution of the conjunctival microbiome can be restored in seven days after ceasing all postoperative medications regardless of type 2 diabetes mellitus presence, indicating that the influence of surgical procedures and perioperative topical antibiotics might be eliminated within a short period [28].

This study confirms a statistically significant increase in culture positivity in CKD patients with high HbA1c and a high positive growth rate in patients with HbA1c \geq 7%. All culture positives responded to five days course of topical moxifloxacin eye drops where repeat conjunctival swab had no growth. No cases of endophthalmitis were reported in the study patients.

Pretreatment with topical antibiotics is based on the rationale that such application may have a synergistic effect with PVI in reducing the number of bacteria on the ocular surface and at the injection site, hence preventing their intraocular entry during or after the IVI, thereby resulting in a decrease in the risk of postinjection endophthalmitis. Since, the visual outcomes of endophthalmitis are poor in patients with poor glycaemic status (HbA1c \geq 7%) and chronic renal disease or dialysis than in the general population, routine preop conjunctival growth evaluation, periprocedural topical antibiotic prophylaxis and PVI use can be beneficial in these patients [29].

Limitation(s)

In the present study, the antibiotic sensitivity pattern of the isolated microorganism which would have helped in determining antibiotic resistance patterns in patients with repeated injections. There is a need for a prospective study in large number of subjects to look for conjunctival flora in the diabetics after having received serial IVI and the antibiotic susceptibility patterns in the Indian population. Randomised controlled studies are needed to suggest for or against the use of topical antibiotics in these patients.

CONCLUSION(S)

A statistically significant association of conjunctival swab culture positivity in type 2 diabetics with DME requiring multiple IVI having uncontrolled diabetes (HbA1c \geq 7%) and the presence of CKD was observed in the present study. Hence, routine use of topical antibiotics as infection prophylaxis may be recommended in these patients as an additional precaution against endophthalmitis.

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