Title Page:

The Risk of Posterior Capsule Rupture during Phacoemulsification Cataract Surgery in Eyes with Previous Intravitreal Anti Vascular Endothelial Growth Factor Injections.

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Abstract:

Purpose: To investigate if previous intravitreal anti vascular endothelial growth factor (VEGF) injections are a predictor for posterior capsule rupture (PCR) during phacoemulsification cataract surgery.

Setting: National Health Service: Whipps Cross University Hospital Eye Treatment Centre. District General, London, United Kingdom

Design: Single centre, retrospective, electronic medical record (EMR) database study with univariate analysis.

Methods: EMR (Medisoft) was used to extract data for eyes undergoing phacoemulsification surgery between 01.08.16 to 01.01.18. Patient demographics, indication for intravitreal therapy, treatment type, number of previous intravitreal injections (IVI), diabetic status, surgeon grade and operative complications were included as variables for analysis.

Results: Data was available for 4047 cataract operations. Of these, 108 had undergone previous anti-VEGF IVI treatment. Three eyes were noted to have pre-operative PC trauma and were excluded from the final analysis. The logistic regression analysis after exclusion of the eyes with pre-existing damage to the PC confirmed that prior anti-VEGF IVI treatment was associated with an increased risk of PCR when compared to the non IVI group (9.26% vs 1.88%, $p<0.0001$). There is a dose dependent relationship between the number of anti-VEGF injections and the likelihood of PCR.

Conclusions: Previous intravitreal anti-VEGF injections are significantly correlated with an increased risk of surgical PCR despite the absence of visible structural damage to the PC pre-operatively.

Synopsis

Prior intravitreal anti-VEGF injections are a significant under reported risk factor for posterior capsule rupture during cataract surgery. There is a dose related risk which is statistically and clinically significant.

Introduction

Anti-vascular endothelial growth factor (VEGF) agents have transformed the clinical management of sight threatening retinal diseases such as age related macular degeneration, diabetic maculopathy[1,2], branch and central retinal vein occlusion (BRVO + CRVO)[3,4], and neovascular glaucoma[5,6]. Since their introduction as intravitreal therapies, anti-VEGF agents have become the gold standard treatment in these conditions. Whilst the safety profile of intravitreal injections is well established, there are only a handful of studies that focus on the possible impact of multiple prior intravitreal injection (IVI) procedures on cataract surgery outcomes. Patients often require multiple injections as a result of suggested loading regimens, partially due to the relatively short intravitreal half-life of these medications[7].

Current guidance on safe administration of intravitreal injections states that the site of the injection should be 4.0mm behind the limbus if phakic and 3.5mm if pseudophakic. It is also recommended that patients are supine to prevent lens touch[8]. The proximity of the needle to the lens may be associated with an increased risk of lenticular trauma either subclinical or through needle penetration thus increasing the risk of posterior capsular rupture (PCR) during phacoemulsification surgery[9]**.** Two landmark trials, ANCHOR[2] and MARINA[10], reported only 1 case of lens trauma as a complication but recent real-world studies have shown a higher proportion of PCR as a result of prior intravitreal injections[9,11,12]. Moreover, previous studies have reported increased risk of PCR in patients who received intravitreal

injections prior to cataract surgery, in the absence of obvious damage to the posterior capsule (lens touch)[9,13,14].

The focus of this study was to further analyse whether prior intravitreal anti-VEGF injections are a significant risk factor for PCR during cataract surgery despite the absence of signs of visible trauma, and whether there was a cumulative risk in eyes which received multiple injections.

Methods:

This was a retrospective, single centre, comparative, non-interventional, cohort study approved by the Barts Health NHS Trust Clinical Effectiveness Board (Project number 8565). The study was conducted in accordance with the declaration of Helsinki and the UK's Data Protection Act. Anonymised data was extracted using the electronic healthcare record system, Medisoft (Medisoft Limited, Leeds, UK) from Whipps Cross University Hospital over the period 01 August 2016 to 01 January 2018. Whipps Cross University Hospital is based in East London, UK, and is the sole NHS provider of eye care for a population 650,000 people. The study period was chosen to coincide with a period immediately following a department-wide recognition of a possible link between IVI and PCR. As such, all patients with a history of IVIs underwent careful slitlamp examination of the PC, with any adverse findings documented.

Demographic data, including age, sex, ethnicity and diabetic status were collected as well as the indication for treatment, drug name and number of previous intravitreal anti-VEGF injections. Surgeon grade and intra-operative complications were included for univariate

analysis. The main inclusion criterion was phacoemulsification cataract surgery during the study period. Exclusion criteria included patients below the age of 18, non-phacoemulsification cataract extraction techniques, and cataract surgery combined with any other intraocular procedures including intravitreal injections at the time of cataract surgery or combined minimally invasive glaucoma surgery. For patients undergoing cataract surgery to both eyes only one eye was included in the study cohort. The study cohort was further sub-divided into two groups; those that had received at least one IVI prior to cataract surgery and those which had not.

The primary outcome measure was PCR during phacoemulsification cataract surgery as defined by the Royal College of Ophthalmologists' (RCO) National Ophthalmology Database (NOD) audit of cataract surgery[15]**.** This included events such as zonular rupture, loss of nucleus into the vitreous, intraocular lens (IOL) into the vitreous, and non-specified vitreous loss.

All datasets collected were entered into a database created using Microsoft Excel 2010 (Microsoft Corp, Redmond, Washington). Statistical analysis was conducted using IBM SPSS software version 25 (IBM Corp., Armonk, NY). Any eyes with pre-operative documentation of a visible breach of the posterior capsule, were excluded from the final analysis. For continuous variables, normality of data distribution was determined using the Shapiro-Wilk test, where normality was defined as $p \geq 0.05$. For normally distributed data, comparison between subgroups was carried out using Student's t-test; for data which were not normality distributed, the Wilcoxon matched-pair signed-rank and Mann-Whitney U tests were used for matched and unmatched data respectively. Categorical variables were compared using the Chi-squared test. Univariate logistic regression was performed to assess

the association between the number of previous intravitreal anti-VEGF injections and the occurrence of PCR.

Results:

During the study period, 4047 eyes from 4047 patients were included for analysis. The background demographic information is included in table 1**.** Intravitreal injections were provided by 15 trained clinicians including 3 retinal consultants, 4 post-residency retinal fellows and 8 residents. Surgery was performed by 10 consultants and 12 junior surgeons of differing grades. The overall rate of PCR was 2.08% (84/4047), and visual acuity was significantly improved from 0.64 ± 0.57 to 0.25 ± 0.32 logMAR ($P < 0.0001$). One third of the surgery was carried out on eyes of Black or Asian ethnicity and over a third had a history of Diabetes Mellitus.

One hundred and eight eyes (2.7%) had received previous anti-VEGF injections. Within this group, the mean number of injections received was 10.4 ± 8.1. (Figure 1)

Three eyes in the IVI subgroup were noted to have visible pre-operative lenticular damage to the posterior capsule. The rate of PCR in the IVI group including the three cases was 9.26% (10/108). The PCR rate in the IVI group excluding these 3 cases was 6.67% (7/105). In both groups, the rates of PCR were significantly higher than the non-IVI group (1.88%; OR: 4.93, $p < 0.0001$ and OR: 3.55, $p = 0.0047$ respectively) (Table 2).

The intraoperative stage at which PCR occurred in the 7 cases is included in table 3, dropped nucleus occurred in 2 cases. Immediate anterior vitrectomy was performed in all cases; in the 2 cases of dropped nucleus, a same-day referral to a vitreoretinal specialist was made and subsequent pars plana vitrectomy was performed.

The univariate logistic analysis of the number of previous injections as a risk factor for PCR showed a dose dependent increase of 8.6% relative risk per injection (OR 1.086, 95% CI: 1.040-1.135, p=0.0002,). The PCR rate was higher in those who received more than 10 injections compared to those who received 10 or less (6.1% vs 14.3%, p=0.18).

Within this cohort, patients' ethnicity and diabetic status were not found to be statistically significant risk factors for PCR. Similarly, the grade of the operating surgeon also did not have a statistically significant effect. Further subgroup analysis based on the type of anti-VEGF agent was not performed due to a large proportion of our cohort having received multiple agents during their treatment.

Discussion

The results from 4047 eyes undergoing phacoemulsification cataract surgery showed that previous intravitreal therapy is associated with a clinically and statistically significant increased risk of PCR even in the absence of visible posterior capsule trauma. Whilst the exact mechanism is unclear, it has been speculated that there may be local scleral deformation during administration of the anti-VEGF agent[16] causing inadvertent zonular trauma, but there may also be biochemical factors of which we are not aware. Previous studies have shown that administration of certain classes of intravitreal agents have been associated with cataract formation and zonular dehiscence but once again the mechanism is unclear[17,18].

Cases of unidentified PC trauma have the potential to cause significant complications during surgery hence the importance of pre-operative identification. Of note, in our study cohort PCR did occur in eyes where 'no evidence of posterior capsule trauma' was specifically recorded in the notes. Studies have shown that ocular coherence tomography (OCT) lens

reconstruction can provide accurate and quantitative estimates of lens volume, size and plane[19]. There may be room to use this technology in higher risk groups (>10 IVI injections) to aid pre-operative identification of PC trauma.

The patient demographics for the anti-VEGF cohort showed a higher proportion of white, British, female patients with a higher incidence of diabetes (including diabetic retinopathy) and AMD. However, these underlying factors did not account for the large difference in PCR rates in between the two groups.

The likelihood of PCR was approximately 5 times higher (9.26% vs 1.88%) in eyes with previous anti- VEGF IVI treatments. Even after excluding three eyes with pre-operatively identified posterior capsule trauma, the likelihood of PCR remained over 3 times higher (6.67% vs 1.81%). The results were statistically significant in both analyses.

This study also found a dose dependent increase of 8.6% relative risk per injection (OR 1.086) in patients which was similar to a study by Lee et al (OR 1.039)[11]. In addition to this, they reported 10 or more previous injections were associated with a 2.59 times higher likelihood of PCR. Our sub group analysis showed patients who had more than 10 injections had a comparable PCR rate of 14.3% ($p = 0.18$), which was 2.36 times higher patients who had received 10 or fewer injections.

The recent Royal College of Ophthalmologists NOD audit of cataract surgery found the PCR rate to be 1.92%[15]. The risk of PCR following prior intravitreal injections (OR 4.93), is comparable to no fundal view/vitreous opacities (OR 4.67) or brunescent cataract (OR 4.19) and is an important consideration when discussing surgery with patients. Informed consent should include a discussion of the much higher risk of PCR with prior anti-VEGF injections. Surgical teams can be alerted to higher risk situations and this allows for pre-operative

planning to employ risk reduction strategies and risk avoidance by junior trainees. It may be prudent to list these patients, especially those with over 10 injections, on a day with vitreoretinal cover.

We acknowledge that this study was conducted in a single centre and was limited by its retrospective nature. Furthermore, despite a cohort of over 4000 patients, the IVI group consisted of 108 patients and therefore formed a relatively small proportion of the overall dataset. As such, subgroups analyses were not possible as they would be of insufficient statistical power. It would be very informative to expand this study to a pooled, multicentre database to further our understanding of this issue.

In summary, the results of this study have shown that prior IVI anti-VEGF administration is a significant risk factor for PCR during phacoemulsification surgery and that this risk is dose dependent and higher for eyes which have received more than 10 injections. PCR occurred during different surgical steps with no obvious cause.

What was known:

- There is some evidence of risk of posterior capsule rupture following prior intravitreal anti-VEGF treatment. It is not recognised as a significant risk factor in the NOD audit.

What this paper adds:

- There is a significant risk of posterior capsule rupture with prior intravitreal anti-VEGF injections.

- There is a cumulative risk with a clinically significant increase in risk with patients who have had more than 10 injections prior to surgery. The risk is comparable to high risk factors such as poor fundal view or brunescent cataracts.
- It is worth considering listing patients with high numbers of prior injections with suitable VR cover.

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Conflict of Interest

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Tables and Figures

Table 1: Demographics of patients, there is a significant difference in the distribution of ethnicity between the two groups, as well as higher proportion of patients with diabetes or AMD.

Table 2: The rate of Posterior Capsule Rupture is higher in the IVI group, particularly in those receiving more than 10 injections.

Table 3: Table to show the nature of PC rupture in the 7 cases where there was no preoperative lenticular trauma identified.

Figure 1: Graph showing the distribution of number of intravitreal injections received by patients in the IVI group.