Phacoemulsification cataract surgery with prophylactic intravitreal bevacizumab for patients with coexisting diabetic retinopathy: a meta-analysis

Short Title: Intravitreal Bevacizumab injection

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Tables and figures: 1 table and 6 figures

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Summary Statement

Cataract surgery combined with intravitreal bevacizumab for patients with diabetic retinopathy appears to be an effective and safe treatment in the short term at least. High-quality studies are still needed to evaluate the long-term effects of this combined surgery.

ABSTRACT

Purpose: To evaluate the clinical effectiveness of intravitreal bevacizumab injection (IVB) combined with cataract surgery in the treatment of patients with cataract and coexisting diabetic retinopathy (DR).

Methods: Pertinent comparative studies were identified through systemic searches of PubMed, EMBASE and the Cochrane Controlled Trials Register up to March 1, 2016. Outcome measures included corrected distance vision acuity (CDVA), central macular thickness (CMT) and progression of DR and maculopathy. A meta-analysis was performed by using RevMan (Cochrane Collaboration, Oxford, UK).

Results: Six studies describing a total of 283 eyes were identified. The meta-analysis results showed that CDVA measured at 1 and 3 months after cataract surgery was significantly better in the IVB groups than in the control groups ($P<0.00001$ and $P=0.01$), while the CDVA at 6 months did not vary significantly between the two groups ($P=0.24$). Similarly, the CMT at 1, 3 and 6 months after surgery was significantly thinner in the IVB groups than in the control groups ($P=0.01$, $P=0.0004$ and $P=0.01$, respectively). At 6 months, the progression of postoperative DR and maculopathy occurred more frequently in the control group than the IVB group ($P=0.0001$ and $P<0.0001$, respectively).

Conclusion: Our meta-analysis indicates that cataract surgery combined with IVB appears to be an effective treatment in patients with coexisting DR in the short-term (up to 6 months). More randomized, prospective and large sample sized trials are needed to evaluate the long-term effects of IVB at the time of cataract surgery in

patients with DR.

INTRODUCTION

Diabetic retinopathy (DR) is common eye disease secondary to structural changes at the capillary endothelium, leading to loss of integrity of the blood-retinal barrier. Hyperglycaemia directly impacts the endothelium causing increased vascular permeability, microaneurysms, capillary occlusions, haemorrhages, exudation, and the accumulation of extracellular fluid and proteins within the macula. Advanced proliferative DR can cause vitreous haemorrhaging and tractional retinal detachments resulting in severe visual loss.[1] Diabetic macular edema (DME) is a frequent manifestation of DR that causes central visual loss.[2-4]

Apart from the direct occlusive and DME changes to the retina in diabetes, an important cause of visual loss in patients with diabetes is the acceleration of cataracts.[5] Hence, patients with diabetes have a higher prevalence of cataract than the normal population[6] and patients with pre-existing DR have worse prognosis for surgical outcomes.[7-9] It remains controversial as to the optimal timing of cataract surgery in patients with DR due to reports of progression of DR and an exacerbation of DME following cataract surgery.

A study by Kim *et al*.[10] reported that approximately 22% of patients with diabetes develop increases in central retinal thickness (CMT) after uncomplicated phacoemulsification, and they suggested that the presence of clinically significant macular oedema (CSMO) is a strong risk factor for subsequent macular thickening after cataract surgery.

It has been well acknowledged that vascular endothelial growth factor (VEGF) plays a key role in promoting new vessel growth and increases vascular permeability in the eyes of patients with diabetes.[11] Patel *et al*.[12] reported that in patients with DR, the levels of $VEGF_{165}$ and other cytokines in the aqueous humour peaked at day 1 and normalised at 1 month following cataract surgery. Funatsu *et al*.[8] also suggested that high VEGF levels in the aqueous humour predicted a significant risk for a post-operative exacerbation of macular oedema following phacoemulsification in patients with non-proliferative DR. Therefore, anti-VEGF therapy performed at the time of cataract surgery appears to be a reasonable intervention for preventing complications related to the progression of DR.

Bevacizumab (Avastin, Genetech, Inc., San Francisco, CA) is a humanised monoclonal antibody that inhibits all isoforms of VEGF-A. To date, several comparative studies[13-19] have been performed to assess the efficacy of intravitreal bevacizumab at the time of cataract surgery in order to prevent the postoperative progression of DR. However, the results from these studies were inconsistent. Furthermore, the scientific evidence of a single study can be limited by a small sample size, different populations, follow-up period, and surgical technique. Therefore, the aim of this study was to undertake a meta-analysis to evaluate the clinical effectiveness of intravitreal bevacizumab, injected at the time of cataract surgery in patients with cataract and coexisting DR.

METHODS

Databases and Search Strategy

Reports of clinical trials comparing cataract surgery with and without simultaneous IVB therapy in patients with DME were identified through a systematic search of PubMed, EMBASE and the Cochrane Controlled Trials Register up to March 1, 2016. A comprehensive search was conducted using the following terms: diabetic macular oedema, DMO, diabetic macular edema, DME, anti-VEGF therapy, bevacizumab, avastin, diabetic maculopathy and cataract. No language restriction was used. Citations initially selected by a systematic search were first retrieved as title and/or abstract and screened independently by two reviewers. Potentially relevant reports were retrieved as complete manuscripts and assessed for compliance to the inclusion and exclusion criteria. The reference lists of original reports and review articles retrieved by the search were reviewed for additional studies not included in the initial search.

Inclusion and Exclusion Criteria

The following selection criteria were used to identify published studies for inclusion in this meta-analysis: (i) randomised controlled studies (RCTs) or cohort studies; (ii) patients aged more than 18 years, with cataract and pre-existing DR, who were scheduled for cataract surgery alone (control group) or combined with an intravitreal injection of bevacizumab at the end of surgery (IVB group); (iii) all patients received similar routine medication pre- and post-operatively, and no further IBV were performed for patients of both groups during the follow-up times and (iv) pre- and post-operative corrected distance visual acuity (CDVA) or central macular thickness

(CMT) being measured, and a follow-up period of at least 3 months. Exclusion criteria were studies including patients with a history of ocular surgery, ocular inflammation, the presence of other ocular diseases, and intraoperative complications such as posterior capsule rupture and severe iris damage. Abstracts from conferences, full texts without raw data available for retrieval, letters, and review articles were excluded. Where multiple publications based on the same cohort were identified, the report with the largest number of patients was used.

Data Extraction

Two reviewers independently extracted data and assessed the methodological quality of the trials. Results were compared and any discrepancies resolved by discussion involving a third reviewer when necessary. The recorded characteristics of the studies included: name of first author, year of publication, geographical location of the study, major inclusion and exclusion criteria, number of eyes, mean age and gender of patients in each group, follow-up periods and the proportion of withdrawals.

Assessment of Bias Risk

Two authors independently assessed the studies using the Cochrane Collaboration's "Risk of Bias" tool from the Cochrane Handbook for Systematic Reviews of Intervention.[20] The criteria used for this were random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessments (detection bias);

incomplete outcome data (attrition bias); selective reporting (reporting bias); and other sources of bias.

Outcome Measures

The main outcome measures were the mean change in CDVA from baseline and the mean change in CMT from baseline at 1, 3 and 6 months. Progression of post-operative DR and diabetic maculopathy after surgery were also assessed as secondary outcome parameters. DR was considered to have progressed when (i) a patient with pre-existing DR developed a higher grade of retinopathy, with or without progression within the macula (e.g., mild non-proliferative DR progressed to moderate non-proliferative DR or more), or (ii) a patient with or without maculopathy developed CSMO or an increase in retinal thickening or hard exudation associated with retinal thickening from baseline levels.[17]

Statistical Analysis

Original data were obtained from the articles as far as possible; data that could not be obtained were calculated if possible (e.g., when standard deviations (SD) were not available, they were calculated using the sample sizes and standard error [SE]). When neither the SD nor SE of end point measurements were available, the baseline SD was used as an estimate of the SD of any time point post-operatively. When only the *P*-value for the difference between the two groups was reported, the SD was calculated according to the *P*-value and the sample sizes.[20]

All statistical analyses were performed using RevMan software (version 5.2; Cochrane

Collaboration, Oxford, UK). A pooled risk ratio (RR) with the 95% confidence interval (CI) was calculated for dichotomous outcomes. For the continuous outcomes, the weighted mean difference (WMD) and their 95% confidence interval (CI) were calculated. Statistical heterogeneity was tested using the chi-square and I^2 statistic. Heterogeneity was tentatively graded as low, moderate and high with an I^2 statistic of <25%, approximately 50% and >75% respectively.[21] Considering the different clinical characteristics among study groups (e.g. severity of DMO; difference of pre-operative CDVA, etc) and the variation in sample sizes, the random effects model was used to pool the data. A sensitivity analysis was performed by excluding non-randomised control trials or studies including patients without DME. A *P*-value less than 0.05 was considered statistically significant. Potential publication bias was examined using a funnel plot.[22]

RESULTS

Identification and Selection Studies

The selection of studies is summarised in Figure 1. A total of 55 articles were identified, out of which 48 articles were excluded. Of the seven publications that initially were considered potentially relevant, one was excluded due to a lack of suitable data for performing the meta-analysis.[15] Thus, a total of six studies (five RCTs and one cohort study) were included in the final meta-analysis.[13, 14, 16-19]

Study Characteristics and Risk of Bias

The characteristics and quality assessment of the six studies are summarised in Tables 1. Overall, 283 eyes (142 assigned to the IVB group and 141 assigned to the control group) were pooled from the six studies, with sample sizes varying from 26 to 68 across studies. The mean patient age ranged from 60 to 69 years, and 53% were men. The duration of follow-up ranged from 3 to 6 months. There was no significant difference between groups in duration of disease and degree of retinopathy before surgery. All five RCTs[13, 14, 15-19] employed appropriate methods of randomisation, and four RCTs[13, 14, 15, 19] reported using more than one blinding method (surgeon, examiner or patient masked). The risk of bias for all studies is shown in Figure 2.

Central Macular Thickness

The values of CMT at baseline were obtained from all studies except for cheema et al.[17] The combined results showed that there was no significant difference in the pre-operative CMT between the two groups [five studies (215 eyes)[13, 14, 16, 18, 19]; WMD = -1.62; 95% CI -13.29 to 10.05; *P*=0.79; Figure 3A]. After surgery, the mean CMT was significantly thinner in the IVB group than the control group at 1 month [five studies (257 eyes)[13, 14, 16, 17, 19] ; WMD = -59.23; 95% CI -104.13 to –14.32; *P*=0.01; Fig. 3B], 3 months [six studies (283 eyes)[13, 14, 16-19]; WMD = -45.83; 95% CI -71.2 to -20.46; *P*=0.0004; Fig. 3C] and 6 months [four studies (260 eyes)[13, 14, 17, 18]; WMD = -42.7; 95% CI -76.37 to -20.46; *P*=0.01; Fig. 3D], respectively. A sensitivity analysis was performed to examine the effect of excluding the cohort study by Chen *et al*.,[19] but this did not alter the results at 1 month (WMD = -46.14; 95% CI -96.17 to 3.90; *P*=0.04) and 3 months (WMD = -42.02; 95% CI -69.63 to -14.41; *P*=0.003). Also, the

results showed the same trend after excluding the study by Fard et al.[14] which included the patients without DME at 3 months (WMD = -38.71; 95% CI -72.51 to -4.92; *P*=0.02) and 6 months (WMD = -60.50; 95% CI -110.72 to -10.29; *P*=0.02), except for 1 month (WMD = -47.69; 95% CI -101.02 to 5.46; *P*=0.08).

Corrected Distance Visual Acuity

The combined results showed that there was no significant difference in the pre-operative CDVA between the two groups [six studies (283 eyes)[13, 14, 16-19]; WMD = -0.01; 95% CI -0.04 to 0.02; *P*=0.45; Fig. 4A]. After surgery, the mean CDVA was better in the IVB group than the control group at 1 month [five studies (257 eyes)[13, 14, 16, 17, 19]; WMD = -0.18; 95% CI -0.25 to -0.12; *P*<0.00001; Fig. 4B] and 3 months [six studies (283 eyes)[13, 14, 16-19]; WMD = -0.08; 95% CI -0.15 to -0.02; *P*=0.01; Fig. 4C]. However, no difference was found between the two groups at 6 months [four studies (260 eyes)[13, 14, 17, 18]; WMD = -0.05; 95% CI -0.15 to 0.04; *P*=0.24; Fig. 4D]. A sensitivity analysis was performed to examine the effect of excluding the cohort study by Chen *et al*.,[19] but this did not alter the results at 1 month (WMD = -0.18; 95 % CI -0.25 to -0.11; *P*<0.0001) and 3 months (WMD = -0.08; 95 % CI -0.14 to -0.01; *P*=0.02). Also, the results showed the same trend after excluding the study by Fard et al.[14] at 1 month (WMD = -0.14; 95% CI -0.22 to -0.05; *P*=0.002), 3 months (WMD = -0.12; 95% CI -0.20 to -0.03; *P*=0.008) and 6 months (WMD = -0.09; 95% CI -0.25 to 0.06; *P*=0.24).

Secondary Outcomes

At 6 months after surgery, the rate of progression of DR and maculopathy in the IVB group was 9.7% (14/144 eyes) and 6.5% (4/62 eyes), and in the control group was 39.5% (45/114 eyes) and 50.8% (32/63 eyes), respectively. The pooled RRs comparing the proportion of patients with progression of DR and diabetic maculopathy at 6 months after surgery were in favour of the IVB group. Examination of the forest plot revealed that progression of post-operative DR [four studies (228 eyes)[13, 14, 16, 17]; RR = 0.33; 95% CI 0.19 to 0.58] and maculopathy [two studies (125 eyes)[13, 17]; RR = 0.18; 95% CI 0.09 to 0.37] occurred more frequently in the control group compared to the IVB group. The difference between groups was statistically significant (P=0.0001 and P<0.0001; respectively), with no heterogeneity identified (Figures 5A and 5B).

Adverse Effects

No severe ocular or systemic adverse events related to IVB during the follow-up periods were reported in all six studies.

Publication Bias

Publication bias was assessed for all pooled WMDs with confidence intervals and is shown as funnel plots in Figure 6. No evidence of publication bias was found.

DISCUSSION

Our meta-analysis, which included 6 studies revealed that the CDVA measured at 1 and 3 months following cataract surgery was significantly better in the IVB group compared with the control group. However the difference at 6 months was not

statistically significant. The CMT at 1, 3 and 6 months after surgery was significantly lower in the IVB group than in the control group and the progression of DR and maculopathy occurred less frequently in the IVB group compared to the control group.

The rate of progression of DR following cataract surgery in the general diabetes population ranges from 20% to 40%.[23-26] Mittra *et al*.[25] found that in 150 eyes undergoing phacoemulsification cataract surgery, DR progression was observed in 37 eyes (25%) with 6 to 10 months of follow-up. They also reported that non-proliferative and proliferative DR and surgical inexperience resulted in an increased rate of retinopathy progression.

The presence of DR before surgery is also an important risk factor for an increase in macular thickness after cataract surgery which can lead to a suboptimal visual outcome.[27] In the present study, four of the six included studies[13, 14, 16, 17] have reported the rate of progression of post-operative DR and maculopathy, and the results of meta-analysis showed that these progressions occurred more frequently in the control group than IVB group.

However, the rate of DR progression after cataract surgery is influenced by multiple variables and in particular worse outcomes are related to more advanced diabetic eye disease and poor glycaemic control.[28, 29] Moreover, the trauma related to surgery may play an important pro-inflammatory role, as for instance, it has been documented that the longer the duration of surgery and the less experienced the

surgeon, the greater the risk of progression of DR.[30] Therefore a large randomised controlled trial with strict baseline matching is recommended to evaluate the full effect of IVB therapy in a diabetic population undergoing cataract surgery.

Diabetic patients with preexisting DME are also at increased risk of worsening edema (i.e., macular edema increase and vision loss) following cataract surgery.[4] Our subgroup analyses confirmed the usefulness of prophylactic IBV for improving surgical visual outcomes and diminishing CMT in patients with or without DME before cataract surgery. Although the results are positive, a series of questions such as edema recurrence rate or the most appropriate subsequent therapies are worth further investigating.

It is often difficult to distinguish between DME and pseudophakic cystoid macular edema (PCME) after cataract surgery in diabetic patients.[31] However, the PCME is usually associated with complicated cataract extractions and resolves spontaneously in the majority of cases. All cataract surgeries included in the current meta-analysis were uncomplicated. In addition, optical coherence tomography (OCT) as a suitable tool to differentiate ME attributed to diabetes and PCME, was used in all including studies.[32]

Intravitreal triamcinolone[33] or dexamethasone intravitreal implant[34] has been shown to be effective for macular edema at the time of cataract surgery but has been associated with complications such as increased intraocular pressure. Although the exact pathogenesis of macular edema and its progression after cataract surgery is

not well understood, an imbalance between endothelial growth factors, cytokines, and inhibitory factors is likely to be involved. VEGF is an important factor in the development of macular oedema because it leads to a breakdown of the inner blood-retinal barrier and leakage of intravascular fluid from abnormal retinal capillaries, within the intra-retinal layers of the macula.[35, 36] Further, studies have reported a correlation between increased pre-operative levels of VEGF and interleukin-6 in the aqueous and a deterioration in macular edema.[8, 12, 37] It is hypothesised that anti-VEGF therapy, would help to prevent the development of macular edema following cataract surgery in patients with diabetes. The results of our meta-analysis suggest that patients with DR who undergo combined cataract surgery and IVB have better visual acuity (albeit in the short term), lower CMT and reduced progression of DR and maculopathy post-operatively compared to controls.

Normal physiological function requires low levels of systemic VEGF activity. Suppression of this baseline activity can cause hypertension, thromboembolic events, bowel perforation, and delayed wound healing.[38, 39] Thus, there is a theoretical risk with the application of intravitreal anti-VEGF drugs that it may influence normal physiological functions resulting in systemic complications. However, no systemic or ocular adverse events that could be related to the injection itself or the medication used was observed in all studies included in this meta-analysis.

This work has some limitations. First, we did not search for unpublished studies or conference abstracts. Second, the follow-up period was short in this meta-analysis (6

months). Third, the dose of bevacizumab (1.25mg) used in all studies is the dose most commonly used in clinical practice. Because no dose-ranging study has been done, the ideal intravitreal concentration remains to be determined.

As far as the authors are aware, this is the first systematic review to consolidate the current knowledge of published data regarding the use of bevacizumab in patients with DR who are undergoing cataract surgery. Our data suggests that cataract surgery combined with IVB for patients with DR appears to be an effective and safe treatment in the short term at least. Therefore, more randomised, prospective and large sample sized studies are needed to evaluate the long-term effects of intravitreal anti-VEGF therapy at the time of cataract surgery in patients with DR.

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Figure legends

Figure 1. Flowchart of literature search and study selection.

Figure 2. Assessment of risk of bias in included studies. (A) Risk of bias summary: review authors' judgments about each risk of bias item for each included study; (B) Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies. +: low risk of bias. ?: unclear risk of bias.

Figure 3. Forest plot comparison of central macular thickness after cataract surgery with and without intravitreal bevacizumab injection: (A) baseline, (B) 1 month, (B) 3 months, and (D) 6 months.

Figure 4. Forest plot comparison of best-corrected visual acuity after cataract surgery with and without intravitreal bevacizumab injection: (A) baseline, (B) 1 month, (C) 3 months, and (D) 6 months.

Figure 5. Forest plot comparison of the proportion of patients in (A) diabetic retinopathy progression and (B) maculopathy progression at 6 months after cataract surgery with and without intravitreal bevacizumab injection.

Figure 6. Funnel plot with respect to best-corrected visual acuity after surgery. No publication bias was observed.