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Review Article

Does phacoemulsification speed the progression of diabetic retinopathy? A meta-analysis

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Abstract: The objective of the present study is to evaluate the influence of phacoemulsification on postoperative progression of diabetic retinopathy and incidence of diabetic macular edema in patients with diabetes and cataract. To perform a meta-analysis for this study, the computerized databases including Medline, Embase and Cochrane library were searched to identify eligible studies, in which patients with diabetes and cataract received phacoemulsification in one eye and the non-operated contralateral eye was considered as the control group. The progression rate of diabetic retinopathy and incidence of diabetic macular edema in two study groups were extracted from the enrolled articles. Statistical analyses were performed using CMA-2 software, where dichotomous variables were expressed as odds ratio (OR) and 95% confidence intervals. As a result, a total of 7 articles were eventually included in this meta-analysis. Both the progression rate of diabetic retinopathy and incidence of diabetic macular edema in the operated eye after phacoemulsification (OR=1.53, 95% CI: 1.04-2.26, P=0.03) was higher than the non-operated contralateral control (OR=1.86, 95% CI: 1.03-3.37, P=0.04). Heterogeneity and publication bias was measured. The results showed that phacoemulsification tends to accelerate the progression of diabetic retinopathy and increase the incidence of diabetic macular edema in patients with cataract. These findings will need to be confirmed in a large sample and long follow-up studies.

Keywords: Phacoemulsification, diabetic retinopathy, diabetic macular edema, meta-analysis

Introduction

Studies suggest that cataracts are more likely to develop in diabetic patients at an earlier time compared with non-diabetic patients [1, 2]. Cataract surgery is required mainly for the therapy of patients with diabetes and cataract to improve their vision. It can be more convenient for timely screening and treatment of diabetic retinopathy (DR) after the surgery [3]. Some studies have reported that the DR progression tended to accelerate after cataract extraction, and the incidence of diabetic macular edema (DME) was increased [4-6]. However, there were other studies [7, 8] suggesting that DR progression was associated with poor glucose control, long course of diabetes as well as the outcomes of insulin therapy for diabetes, instead of cataract extraction [9, 10]. There is also controversy in the impact of extracapsular cataract extraction on DR progression and the incidence of DME. While some studies have found that the DR progression was accelerated and the incidence of DME was increased after extracapsular cataract extraction [11, 12], the influence of phacoemulsification, which tends to induce a relatively small incision, on DR progression and DME incidence was found different in other studies [10, 13-17]. Multiple factors have been identified to influence DR progression, including type, degree of control, course, and control pattern of diabetes, as well as hypertension and hyperlipidemia [18]. In order to control these potential confounding factors in studying the influence of phacoemulsification on postoperative DR progression in two groups of diabetes patients, well-designed studies selected patients with comparable DR in the two eyes, where one eye received the cataract extraction and the non-operated contralateral eye served as the control to ensure that the two groups were comparable. In this

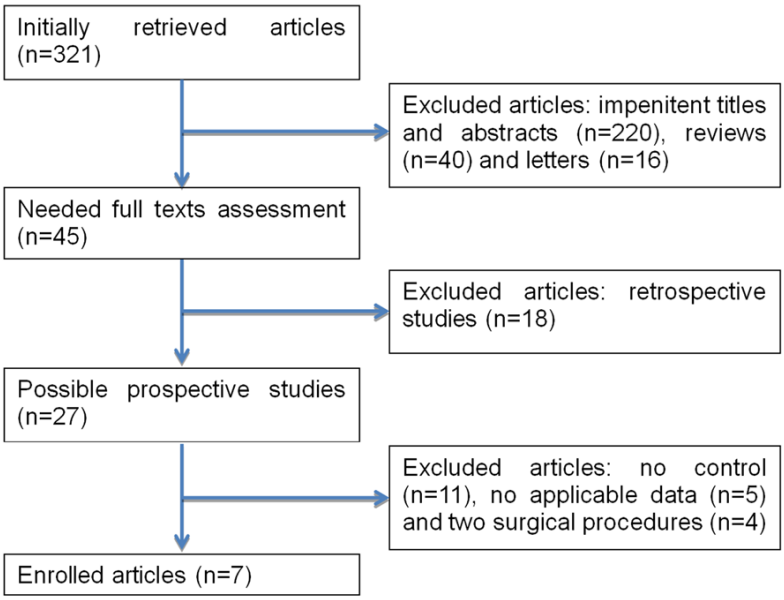

Figure 1. Flow chart describing the article selection process. Three hundred and twenty-one articles were initially retrieved from databases Medline, Embase, and Cochrane library, as well as the bibliographies of eligible studies. Studies that did not fulfill the inclusion criteria were excluded, and eventually 7 articles involving in total 579 diabetes patients with cataracts were included in our meta-analysis.

study, a systematic meta-analysis was performed to evaluate whether phacoemulsification accelerates DR progression and increases the DME incidence by identifying and polling prospective studies using the non-operated contralateral eye as control. Random effects models were used following MOOSE guidelines [19] for observational studies and the QUORUM guidelines for randomized controlled trials [20].

Methods

Search strategy for the identification of studies

The computerized databases Medline, Embase, and Cochrane library were searched to identify eligible studies in English-language journals published before July 2015. An in-depth literature search was performed using keywords "cataract extraction", "extracapsular cataract extraction", "phacoemulsification", "diabetes", "cataract", "diabetic retinopathy", "diabetic macular edema", "progression" and "incidence". Additionally, the bibliographies of retrieved studies were manually searched.

Articles that fulfilled the following criteria were included: (1) prospective studies involving diabetes patients with cataracts with one eye being performed cataract extraction and the non-operated contralateral eye as the control; (2) a follow-up duration of no less than 6 months; (3) phacoemulsification was applied in cataract extraction; (4) available data on DR progression rate and/or DME incidence. Conference abstracts, duplicate publications, case reports, reviews and letters were excluded.

Quality assessment

The quality of included studies was assessed according to the following criteria: (1) appropriateness of the inclusion criteria and grouping of subjects; (2) rationality of the experimental design; (3) accuracy of the statistical analysis method; (4) presence of discussion in terms of the potential bias. Each item was scored from 0 to 4: 0= no or poor, 1= moderate, 2= good or excellent. The assessments were independently conducted by two investigators. Any discrepancies were resolved by discussion until a consensus was reached. If consensus was not able to be reached, experts were invited to make the final decision.

Data extraction

All retrieved studies were first de-identified (blinded title, author list, journal name, and year of publication) before selection. Titles and abstracts were independently reviewed by two investigators, and then the full texts were assessed to decide the eligibility of the article. All the data were independently extracted by two investigators using a standard table for data extraction. The extracted data included authors, research location, date of publication, follow-up duration, sample size, subject characteristics, interventions and endpoint data, etc. During this process, consensus was obtained through consultation in case of divergent opinions.

Table 1. Basic information of the enrolled articles

Author	Country	Published time (year)	Follow-up duration (month)	Diabetes type	Gender (number of cases: M/F)	Age (year: range/SD)	Diabetes course (year: range/SD)	Preoperative HbAlc (%) (range/SD)	Number of cases with hypertension (%)	Number of cases received insulin therapy (%)	Quality score
Hong	Australia	2009	12	1, 2	-	-	-	-	-	-	8
Romero-Aroca	Spanish	2006	12	2	60/72	70.72 (62)	16.2 (5~35)	-	89 (67.42)	48 (35.4)	8
Flesner	Denmark	2002	6	1, 2	20/19	70 (8.5)	14.8 (13.8)	8.3 (1.8)	28 (72)	16 (41)	7
Krepler	Austria	2002	12	2	13/29	72.1 (9.7)	16 (11)	7.3 (1.7)	26 (61)	21 (50)	8
Squirrell	British	2002	12	2	27/23	73 (59~88)	13 (2~38)	8.5 (5.8~11.1)	29 (58)	20 (40)	6
Kato	Japan	1999	12	-	26/40	62.8 (9.7)	15.4 (8.0)	-	-	37 (50.1)	6
Wagner	German	1996	6	-	-	-	-	-	-	-	7

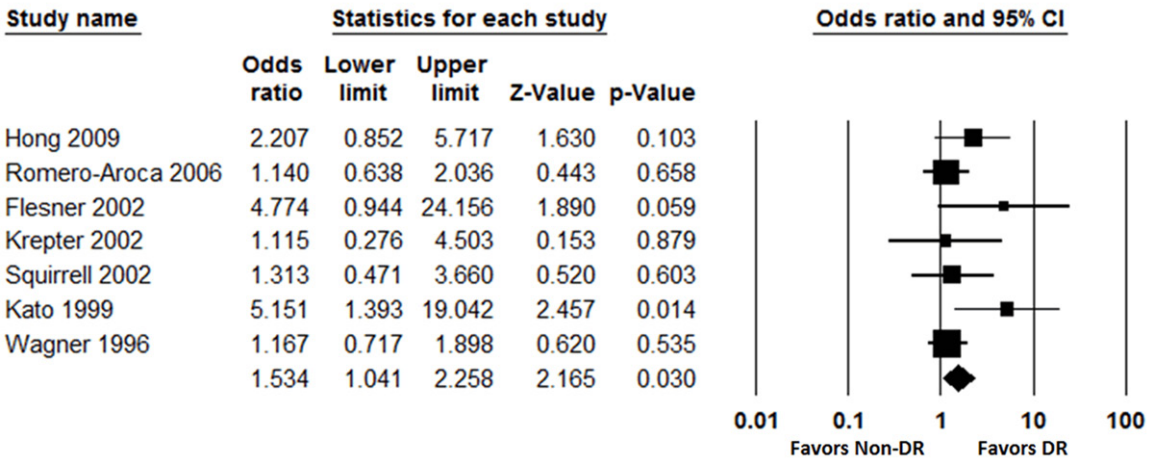

Figure 2. Forest plot for the aggregate progression of diabetic retinopathy. The progression rate of diabetic retinopathy was extracted from the enrolled articles and pooled for a random effect meta-analysis. The effect size was expressed as odds ratio (OR) and 95% confidence intervals. Results showed that the progression rate of diabetic retinopathy in the operated eye after phacoemulsification was higher than the non-operated contralateral control, with OR=1.53, 95% CI: 1.04-2.26, P=0.03.

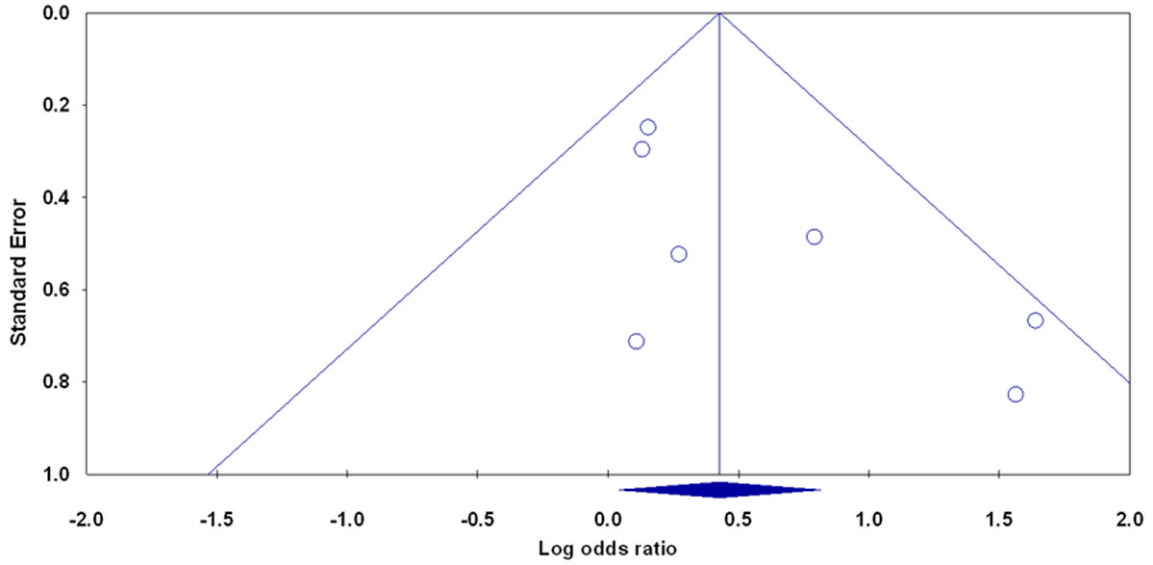

Figure 3. Funnel plot for the progression of diabetic retinopathy. The publication bias was evaluated using funnel plots. A difference of P<0.05 was considered statistically significant. No significant publication bias was revealed in the inverted-funnel plot, excluding the result bias of the progression of diabetic retinopathy due to failure of including positive studies.

Statistical analyses

Meta-analyses were performed using Comprehensive Meta-analysis (CMA-2) software (Biostat, Englewood, NJ, USA). The outcomes were pooled statistically using the odds ratio (OR) and 95% confidence intervals (CI) calculated for the progression rate of diabetic retinopathy and incidence of diabetic macular edema, and articles with P<0.05 and 95% CI unequal to 1 were considered statistically significant difference in OR point estimate. A random effect meta-analysis was conducted to investigate the outcomes in the operated eye after phacoemulsification compared with the non-operated contralateral control, because random effects models assume that true effects are different across studies owing to heterogeneity

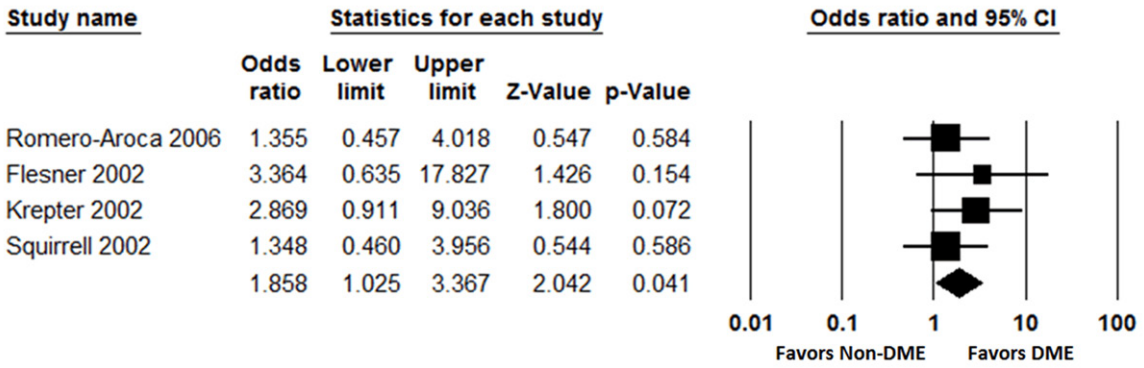

Figure 4. Forest plot for the aggregate diabetic macular edema. The figure shows that the incidence of diabetic macular edema was significantly accelerated by phacoemulsification in diabetes patients combined with cataract (OR=1.86, 95% CI: 1.03-3.37, P=0.04).

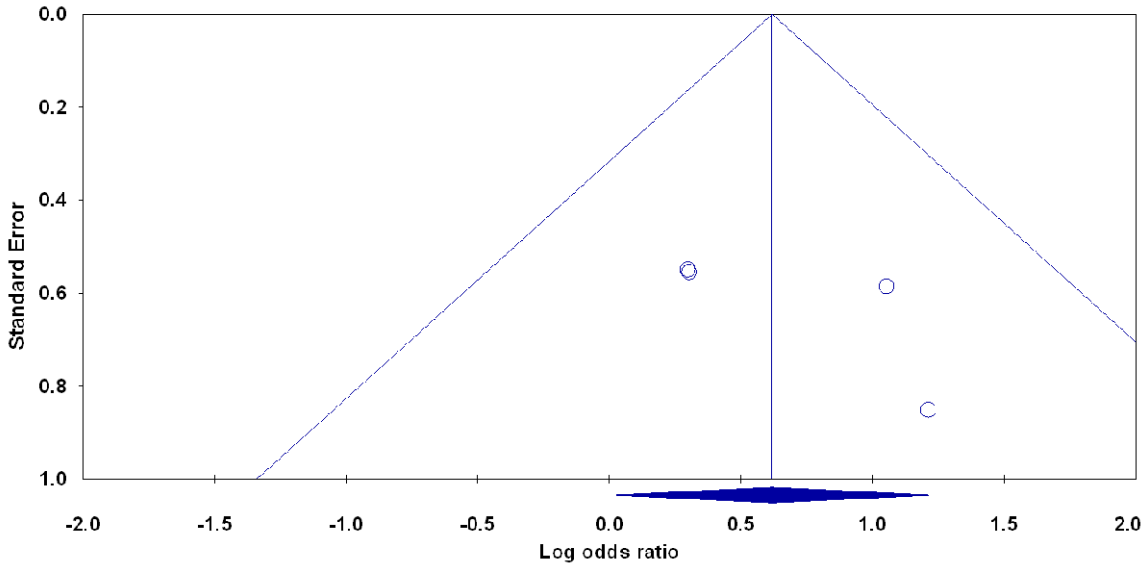

Figure 5. Funnel plot for diabetic macular edema. No publication bias was revealed in the inverted-funnel plot for the aggregate diabetic macular edema.

of patients, treatments or other factors, and thus, create wider confidence intervals and minimize the risk of Type I error.

Heterogeneity between the studies was tested using Q statistic method, and its size was quantitatively assessed using I^2 method. I^2 values of 25% may be considered low, 50% moderate, and 75% high. Factors with suspicious heterogeneity, such as diabetes course and diabetes control, were assessed using subgroup or sensitivity analysis. The publication bias was evaluated using funnel plots, where a good integrity and symmetry indicated a small publication bias. A difference of $P<0.05$ was considered statistically significant.

Results

Literature search results and characteristics of enrolled articles

A totally of 321 articles were retrieved using the previously described search strategy, and these lection process is shown in **Figure 1**. Nine articles accorded with the inclusion criteria. Among these studies two articles involved patients who received extracapsular cataract extraction for cataract surgery and these studies were therefore excluded. Eventually 7 articles [8, 10, 14-17, 21] were included in our meta-analyses, which were from 7 countries and published between 1996 and 2009, as

illustrated in **Table 1**. A total of 579 patients with diabetes and cataract were enrolled in these 7 articles, including 579 eyes undergoing phacoemulsification and 579contralateral eyes serving as control group. Among the 7 articles, the follow-up duration was 6 months in 2 articles and 1 year in the rest articles. Surgical procedures, DR diagnostic grading criteria (Internal Diabetic Retinopathy Grading), and DR progression identification were comparable among the 7 articles.

DR progression after phacoemulsification

According to all the 7 articles reviewed, DR progression was observed in the operated and non-operated contralateral eyes after phacoemulsification, and the OR value and 95% CI of each article were shown in **Figure 2**. The progression rate of diabetic retinopathy in the operated eye after phacoemulsification was higher than that of the non-operated contralateral control eye, with OR=1.53, 95% CI: 1.04-2.26, P=0.03. Sincethe heterogeneity test did not show a statistically significant difference (I^2=25%, P=0.24) among the articles, after excluding two articles with longest diabetes course and largest Glycated hemoglobin (HbAlc) due to the fact that the diabetes course and preoperative diabetes control were factors affecting DR progression, the results were comparable to those of the whole, and the difference was still statistically significant (OR= 1.65 (1.15-2.37), P=0.007, I^2=43%, P=0.13; and 1.40 (1.02-1.93), P=0.04, I^2=31%, P=0.21, respectively). As shown in **Figure 3**, there was no significant publication bias.

DME progression after phacoemulsification

Five out of seven articles reported the incidence of postoperative macular edema. However, the article by Wagner and his colleagues [16] did not distinguish the genuine DME and Irvine-Gass syndrome. Thus only 4 articles were included in the analysis of DME incidence, heterogeneity test of which did not show a statistically significant difference (I^2 =0%, P=0.63). Data were merged using random effects model, and the results showed that the DME incidence in the operated eye was significantly higher than that of the contralateral control eye (OR=1.86, 95% CI: 1.03-3.37, P=0.04) (**Figure 4**). It is shown in **Figure 5** that there was no significant publication bias for the incidence of postoperative macular edema.

Discussion

This study investigated whether phacoemulsification accelerates DR progression and increases the DME incidence using meta-analysis. Results showed that the DR progression and DME incidence elevated in the operated eyes after phacoemulsification compared with the non-operated contralateral controls. It has basically become a consensus that the intracapsular or extracapsular cataract extraction tends to accelerate DR progression and increase the DME incidence [11, 12, 22, 23], which is associated with a larger harassment of these two procedures to the ocular structure that lead to severe damage of blood-ocular barrier. However, there are inconsistent results of the DR progression rate and DME incidence after phacoemulsification. Among the enrolled 7 articles, 5 articles revealed that the DR progression and DME incidence did not show a statistically significant difference between the operated eyes and contralateral controls, while only 2 articles reported that there was significant difference [10, 15]. However, our meta-analysis showed that the phacoemulsification was likely to aggravate the DR progression and increase the DME incidence. These findings might be better explained by potential aggregated meta-analysis information which would include a larger sample size, higher statistical power, and would consider heterogeneity among the studies. In the articles with insignificant difference, absolute numbers of the DR progression and DME incidence in the operated eyes were both greater than those of the contralateral controls, and were close to the critical value of statistically significance, which tended to become significant after integration. Secondly, although the phacoemulsification had smaller harassment to the ocular structure compared with the intracapsular or extracapsular cataract extraction, it still induced different degrees of inflammation and damaged the blood-ocular barrier and the natural defense “lens diaphragm”, leading to diffusion and redistribution of the intraocular cytokines, accelerating the retinal microvascular disease, and thereby, accelerating the DR progression. Results in this study were consistent with the population-based epidemiological findings [24],

which indicated that the cataract extraction was an independent risk factor of DR progression.

The macular edema in diabetes patients after cataract extraction can be divided as genuine DME and pseudophakic macular edema, or Irvine-Gass syndrome [25]. Differential diagnosis of two kinds of macular edema is not very easy, and it is generally believed that fluorescein fundus angiography is conducive to their differentiation. Angiography showing typical petal-like fluorescein leakage in macular region combined with hyperfluorescence in disc while unaccompanied by microaneurysm or hard exudates in macular region are generally believed to be Irvine-Gass syndrome. The enrolled 4 studies [7, 10, 15, 17] revealed that phacoemulsification had no significant influence on the DEM incidence, while our meta-analysis showed that the DME incidence was higher in the operated eye, the reason of which might be similar to that of the DR progression. No significant publication bias of the 4 studies was revealed in the inverted-funnel chart, excluding the potential result bias due to failure of including positive studies. Because of low incidence and diagnostic difficulty of DME, as well as enrollment of only 4 studies involving DME incidence, the conclusion of this study requires further confirmation in future studies.

Optimally, controlled clinical trials are pooled into this analysis to evaluate the influence of phacoemulsification on postoperative progression of diabetic retinopathy and incidence of diabetic macular edema in patients with diabetes and cataract. However, due to the specialty of the issue, it is very difficult to select two groups of diabetes patients combined with cataract with comparable systematic control of diabetes, hypertension and degree of DR progression. Furthermore, if patients are randomly assigned to a group, the patients assigned to the non-operated group may result in aggravated cataract after 1-year follow-up, which fails to comply with the ethical principle. Realistically, the best research approach is to conduct prospective studies by enrolling patients with diabetes, with one eye receiving phacoemulsification and the non-operated contralateral eye as the control. Although this is a relatively ideal type of research, there are still several shortcomings. Firstly, the operated eye cannot be randomly selected, and researchers can only choose the one with more severe cataract opacity. The “internal environment” of the eye with more severe cataract may be worse than that of the contralateral eye, and its DR natural progression may be faster than that of the contralateral eye. This may confound the effects of cataract surgery. In addition, the blinding is not likely to be achieved. Despite these shortcomings, the contribution of our study to the existing literature could not be dismissed.

Conclusions

In summary, phacoemulsification may accelerate DR progression and increase DME incidence in diabetes patients with cataracts. Postoperative follow-up of these types of patients should be strengthened, especially within 6-12 months after the surgery, and appropriate interventions should be applied, if necessary, to avoid missing the optical treatment time. The conclusions of the enrolled studies require replication with a larger sample size and longer follow-up to further elucidate the influence of phacoemulsification on DR progression and DME incidence.

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Disclosure of conflict of interest

None.

Authors’ contribution

WS carried out the study, analyzed the data and drafted the manuscript. XQ and DY participated in the design of the study and performed the statistical analysis. WX conceived of the study, participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

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