Phacoemulsification versus combined phacotrabeculectomy in the treatment of primary angle-closure glaucoma with cataract: a Meta-analysis

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Abstract

AIM: To compare the efficacy and safety of phacoemulsification (Phaco) against combined phacotrabeculectomy (Phacotrabe) in primary angle-closure glaucoma (PACG) with coexisting cataract.

METHODS: By searching electronically the PubMed, EMBASE, Scientific Citation Index and Cochrane Library published up from inception to January 2014, all randomized controlled trials that matched the predefined criteria were included. The quality of included trials was evaluated according to the guidelines developed by the cochrane collaboration. And the outcomes estimating efficacy and safety of two different surgical treatments were measured and synthesised by RevMan 5.0.

RESULTS: Five randomized controlled trials were selected and included in Meta-analysis with a total of 468 patients (468 eyes) with both PACG and cataract. We found that Phacotrabe had a greater intraocular pressure (IOP) lowering effect [preoperative IOP: weighted mean difference (WMD)=0.58, 95% confidence intervals (95% CI, −0.53 to 1.69), \( P=0.31 \); postoperative IOP: WMD =1.37, 95% CI (0.45 to 2.28), \( P=0.003 \)], a lower number of anti-glaucoma medications [risk ratio (RR)=0.05, 95% CI (0.02 to 0.18), \( P<0.00001 \)] needed postoperatively and less serious damage of optic nerve [RR=0.48, 95% CI (0.21 to 1.07), \( P=0.07 \)], but a higher risk of complications [odds ratio (OR)=0.04, 95% CI (0.01 to 0.16), \( P<0.00001 \)] compared with Phaco. The rest studies indicated that there had no significantly difference between the two surgical methods for postoperative best-corrected visual acuity (BCVA) [WMD=−0.05, 95% CI (−0.14 to 0.05), \( P=0.32 \)] and loss of visual field [RR=1.06, 95% CI (0.61 to 1.83), \( P=0.83 \)].

CONCLUSION: Phaco alone compared with Phacotrabe had a better effect in IOP reduction, whereas the security decline. Considering the number of sample size, our results remains to be further studied.

KEYWORDS: phacoemulsification; phacotrabeculectomy; primary angle-closure glaucoma; cataract; Meta-analysis
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INTRODUCTION

The World Health Organization ranks glaucoma as the second most common cause of blindness after cataract, and as the leading cause of irreversible blindness. According to estimates of the WHO, by 2020 primary angle-closure glaucoma (PACG) will affect 20 million people, and 5.3 million will be blind \(^1\). Previous studies considered the pupillary block caused by lens is the main pathogenesis of PACG.

PACG is characterised by narrow anterior segment structure with advancing age, the lens assumes greater thickness, a greater curve of its anterior surface, and the zonules loosen. These factors cause increasing shallowness of the anterior chamber and iridolenticular contact. The outflow pathway was blocked, and therefore intraocular pressure (IOP) continuously increases, if things go on like this, there will be damage to the optic nerve and loss of visual field \(^2\). In addition, because the prevalence increases with age, a considerable number of PACG patients associated with cataract are in need of treatment. A large number of studies\(^3-4\) have demonstrated that the lens extraction can relieve pupillary block, deepen the anterior chamber and make part of the adhesion of anterior chamber angle separated so that it increases the outflow of aqueous humor and obviously reduce IOP. The patient's vision can be improved at the same time. So phacoemulsification (Phaco) or phacotrabeculectomy (Phacotrabe) have usually been documented for the patients of PACG associated with cataract, aiming to reduce the IOP and improve visual acuity. However, what kind of operation is more effective and safe is lack of evidence.
In order to evaluate the efficacy and safety of the two different operation methods, numerous randomized controlled studies have been conducted at home and abroad. However, the sample size of these studies tend to be small, there is a certain difference between the results. So in the pursuit of a more objective evaluation, we use Meta-analysis to compare these two options in the clinical treatment of glaucoma and provide evidence-based scientific basis for the choice of surgical approach.

**MATERIALS AND METHODS**

**Search Strategy** We combined uncontrolled terms and mesh terms with "primary angle-closure glaucoma, phacoemulsification, cataract extraction, lens extraction, phacotrabeculectomy" to search the relevant literature electronically from the PubMed, EMBASE, Scientific Citation Index and Cochrane Library published up to January 2014, the manually searching of relevant conference proceedings was used as the supplement (Table 1). The articles of randomized controlled trial comparing the clinical effectiveness of Phaco versus Phacotrabe for PACG with cataract were included. And all the studies included must be approved by an appropriate institutional review board or ethics committee, at least follow the principles outlined in the Declaration of Helsinki.

**Inclusion and Exclusion Criteria** Studies eligible for inclusion in this Meta-analysis should meet the following criteria: 1) types of studies: all randomized controlled clinical trials comparing the effectiveness of Phacotrabe and Phaco are included; duplicate publications and the researches with small sample size (<30) or without complete original data are excluded; 2) types of participants: participants in the trials were people with a diagnosis of angle-closure glaucoma. The trials with patients who had conducted ophthalmic operation and combined other ocular and systemic disease were not included; 3) types of interventions: anti-metabolites could be used intraoperatively in Phacotrabe group, follow-up time must be more than one year; 4) types of outcome measures: reported outcomes had to include either the primary outcome or one of the secondary outcomes.

To assess efficacy, we used the reduction in IOP from baseline as the primary measurement. Secondary efficacy measures were postoperative best-corrected visual acuity (BCVA), progression of visual field damage, reduction for topical glaucoma drugs, or complete success rate (defined as the proportion of patients who achieved the target IOP with or without anti-glaucoma medication at the study end point). To assess safety, we used the proportion of patients experiencing an adverse event, including hypotony, malignant glaucoma, hyphema, choroidal detachment and endophthalmitis.

**Studies Selection and Data Collection** Two authors (Wang F and Wu ZH) independently confirmed the quality of the included studies based on the criteria recommended by the Cochrane Back Review Group[5]. The following criteria were scored yes and no, or unsure by two independent reviewers. If studies met at least 5 of the 12 items, it was considered low risk of bias. The quality assessment of the included studies is presented in Table 2.

**Qualitative Assessment** Bias risk of the trials was assessed with the criteria list recommended by the Cochrane Back Review Group[5]. The following criteria were scored yes and no, or unsure by two independent reviewers. If studies met at least 5 of the 12 items, it was considered low risk of bias. The quality assessment of the included studies is presented in Table 2.

**Table 1**: Demographic characteristics of studies

<table>
<thead>
<tr>
<th>Publications</th>
<th>Location</th>
<th>Sample size (P/T)</th>
<th>Mean age (P/T) $\bar{X} \pm s$</th>
<th>Follow up (mo)</th>
<th>Study type</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tham et al[10] 2008</td>
<td>China</td>
<td>72 (35/37)</td>
<td>71.9±6.7/71.4±6.6</td>
<td>24</td>
<td>RCT</td>
<td>IOP, BCVA, glaucomatous drugs, complications, C/D, visual field</td>
</tr>
<tr>
<td>Tham et al[10] 2009</td>
<td>China</td>
<td>51 (27/24)</td>
<td>70.3±7.4/70.4±9.0</td>
<td>24</td>
<td>RCT</td>
<td>IOP, BCVA, glaucomatous drugs, C/D, visual filed</td>
</tr>
<tr>
<td>Tham et al[10] 2010</td>
<td>China</td>
<td>72 (38/34)</td>
<td>70.2±8.1/69.9±7.9</td>
<td>12</td>
<td>RCT</td>
<td>IOP, BCVA, glaucomatous drugs, C/D, UBPM</td>
</tr>
<tr>
<td>Rhiu et al[9] 2010</td>
<td>Korea</td>
<td>41 (20/21)</td>
<td>69.4±9.8/72.1±8.0</td>
<td>25.8±16.8</td>
<td>CCT or RCT</td>
<td>IOP, glaucomatous drugs, complications</td>
</tr>
</tbody>
</table>

P: Phaco; T: Phacotrabe; BCVA: Best-corrected visual acuity; logMAR: Logarithm of the minimum angle of resolution; IOP: Intraocular pressure; GON: Glaucomatous optic neuropathy; GVFL: Glaucomatous visual field loss; RCT: Randomized clinical trial; SD: Standard deviation.

To assess efficacy, we used the reduction in IOP from baseline as the primary measurement. Secondary efficacy measures were postoperative best-corrected visual acuity (BCVA), progression of visual field damage, reduction for topical glaucoma drugs, or complete success rate (defined as the proportion of patients who achieved the target IOP with or without anti-glaucoma medication at the study end point). To assess safety, we used the proportion of patients experiencing an adverse event, including hypotony, malignant glaucoma, hyphema, choroidal detachment and endophthalmitis.

### Statistical Analysis

Overall Meta-analysis of all the studies included was carried out to compare the postoperative IOP reduction between Phaco and Phacotrabe. In addition, five analyses were conducted: analysis to compare postoperative BCVA, reduction in glaucoma medications, incidence of postoperative complications, progression in optic nerve
morphology and visual field. Continuous outcomes are reported as a weighted mean difference (WMD), dichotomous outcomes are reported as a risk ratio (RR). All outcomes are reported with 95% confidence intervals (95% CI). We considered \( P<0.05 \) to be statistically significant in the test for overall effect. To assess heterogeneity in results of individual studies, we used the \( I^2 \)-based \( I^2 \) index (significant heterogeneity was set at \( I^2>50\% \) level). If the \( I^2 \) index is greater than 50\%, we will consider it as statistical heterogeneity, if there is no substantial heterogeneity, we combine the study results in a Meta-analysis using a random-effects model. If there is no substantial heterogeneity and statistical heterogeneity as per the \( I^2 \) index we will combine the results of the included studies in a Meta-analysis using a fix-effects model. If there is substantial heterogeneity and statistical heterogeneity, instead we will take subgroup analysis or present the studies in a tabulated or narrative summary. We will also examine funnel plot for evidence of other sources of heterogeneity, such as publication bias. And all the statistical analysis was performed using Revman 5.0.

**RESULTS**

**Article Selection Process** Our search strategy identified a total of 2930 articles involving those key words, and the number was cut down to 525 after we set the qualifier of randomized controlled trials (RCTs), human studies, last 10y and full text articles (Figure 1). Then we screened the titles and abstracts, 512 publications were further excluded. Finally only five articles\(^8-^{10}\) with complete original data were retrieved including 468 patients (468 eyes). Table 1 shows the flow chart of how we arrived at the final articles. There are a total of five studies brought into the Meta-analysis, all of them are RCTs with specific inclusion and exclusion criteria. All of them reported follow-up and baseline. And none of them described whether blinding methods and allocation concealment were adopted. Three of the studies explicitly pointed out the methods they used to randomization while the others didn't. Overall, the quality of all the trials were classified as low risk of bias.

**Outcome Assessment**

**Intraocular pressure** The comparison of preoperative and postoperative IOP was reported in 5 studies of all ones. The data extracted from the 4 studies were combined to make a Meta-analysis. 1) Preoperative IOP (Figure 2): the test for heterogeneity was not significant (\( I^2=0\% \), \( P=0.39 \)). The outcome of Meta-analysis shows the difference between the two groups is not significant (WMD=0.58; 95% CI, -0.53 to 1.69; \( P=0.31 \)); 2) Postoperative IOP (Figure 3): the test for heterogeneity was not significant (\( I^2=0\% \), \( P=0.57 \)). The outcome of Meta-analysis shows the difference between the two groups is statistically significant (WMD=1.37; 95% CI, 0.45 to 2.28; \( P=0.003 \)), indicating that the effect of IOP-reduction is better for Phacotrabe than Phaco. The remaining one studies only reported the mean value of postoperative IOP, and both of them show the same results; 3) IOP changes were not described in the articles, but

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**Table 2 Qualitative assessment**

<table>
<thead>
<tr>
<th>Criteria list</th>
<th>Tham et al(^8) 2008</th>
<th>Tham et al(^7) 2009</th>
<th>Tham et al(^8) 2010</th>
<th>Rhiu et al(^9) 2010</th>
<th>Paul et al(^10) 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>U</td>
<td>U</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
</tr>
<tr>
<td>Patient blinding</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
</tr>
<tr>
<td>Surgeon blinding</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
</tr>
<tr>
<td>Outcome timing</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Cointerventions</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Compliance</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Risk of bias</td>
<td>8/12 (low)</td>
<td>8/12 (low)</td>
<td>8/12 (low)</td>
<td>7/12 (low)</td>
<td>7/12 (low)</td>
</tr>
</tbody>
</table>

Y: Yes; U: Unsure.
according to the results above, we thought there also existed difference of IOP changes that consistent to postoperative IOP.

**Visual acuity** The comparison of postoperative visual acuity was reported in 4 studies of all ones (Figure 4). The data extracted from the studies were combined to make a Meta-analysis. The test for heterogeneity was not significant ($I^2=0\%$, $P=0.51$). The outcome of Meta-analysis shows the difference between the two groups is statistically not significant (WMD=-0.05; 95% CI, -0.14 to 0.05; $P=0.32$).

**Glaucomatous drugs** The comparison of postoperative glaucomatous drugs was reported in 3 studies of all ones (Figure 5). The data extracted from the studies were combined to make a Meta-analysis. The test for heterogeneity was not significant ($I^2=0\%$, $P=0.81$). The outcome of Meta-analysis shows the difference between the two groups is statistically significant (RR=0.05; 95% CI, 0.02 to 0.18; $P<0.00001$), indicating that the effect of IOP-control is better for Phacotrabe than Phaco.
Figure 6 Forest plot of postoperative complications.

Figure 7 Forest plot of loss of visual filed.

Figure 8 Forest plot of damage of optic nerve.

extracted from the studies were combined to make a Meta-analysis. The test for heterogeneity was not significant ($I^2=0\%, P=0.94$). The outcome of Meta-analysis shows the difference between the two groups is statistically not significant (OR, 1.06; 95% CI, 0.61 to 1.83; $P=0.83$).

**Damage of optic nerve**

The comparison of damage of optic nerve was reported in 3 studies of all ones (Figure 8). The data extracted from the studies were combined to make a Meta-analysis. The test for heterogeneity was not significant ($I^2=19\%, P=0.29$). The outcome of Meta-analysis shows the difference between the two groups is not significant (OR, 0.48; 95% CI, 0.21 to 1.07; $P=0.07$).

**DISCUSSION**

Chronic angle-closure glaucoma is one of the leading causes of blindness globally increasing with age, therefore frequently coexists with cataract. Pupillary block is the most common pathogenic mechanism of PACG, and the lens play a vital role in the pupillary block. So, in theory, removing the lens causes a greater deepening of the chamber and reopening of the angle, then the pupillary block can be eliminated and the progression of angle-closure glaucoma can be prevented. What's more, ultrasonic energy and rinsing of perfusing solution can also be helpful to reduce the range of goniosynechia [11]. With the improvement of facilities and technology, performing Phaco combined with intraocular lens implantation in the treatment of cataract coincurred with glaucoma has become possible. So it is common practice to perform combined cataract and trabeculectomy (Phacotrabe) or Phaco alone to solve these two problems simultaneously. To patients suffering from both PACG and cataract, the curative effect of lens extraction depends on the reopening degree of functional anterior chamber, outflow of aqueous humor and target IOP patients needed to achieve clinical cure. Performing Phaco only might be beneficial in some cases, it can reduce the IOP and improve the visual acuity. But for some others, the effect is less than ideal. Perhaps it is because goniosynechia has existed for a long time or function of trabecular meshwork has already been damaged. They need further treatment such as medication or filtering techniques to control the progression of glaucoma. It is generally considered that Phaco treats better for PACG patients than primary open angle glaucoma (POAG) patients[12]. And among PACG patients, curative effect is better in acute primary angle-closure glaucoma (aPACG) than in chronic primary angle closure glaucoma (cPACG)[13-14]. Moreover, in terms of the IOP control, pure pupillary block angle-closure glaucoma ranks first, followed by pure non-pupillary block angle-closure glaucoma and multiple mechanism

601
angle-closure glaucoma (19). Other factors which can predict IOP control after Phaco in PACG are also under exploration. According to research (46), preoperative IOP and preoperative anterior chamber depth (ACD) have been found positively associated with postoperative IOP.

Combined surgery can also improve visual acuity while reducing IOP. It relieves different pathogenic factors of glaucoma at a time, for example, pupillary block, angle closure and ciliary block. It also built a new aqueous outflow drainage pathway, increasing the outflow of aqueous humor, thus reduce the IOP. Besides, it reduces the probability of occurrence of flat or absence of anterior chamber usually happens after trabeculectomy alone. And as we know, trabeculectomy can accelerate progression of cataract (17), so a second operation is avoided by performing Phacotrace. But Phacotrace is usually associated with a significant risk of complications and overtreatment. This is because Phacotrace is more complicated with long-duration operation and large surgical trauma.

What kind of criteria should be depended on to choose the surgical approach and when the operation should be done? Currently there is no evidence-based conclusion, surgeon often make a choice according to their experience and technology.

The scheme (10–19) most of Chinese physicians refer to: 1) Phacemulsification: goniosynechia <180°, number of anti-glaucoma drugs <3, meet the indications for cataract surgery, visual acuity <0.5; 2) Trabeculectomy: goniosynechia ≥180°, number of anti-glaucoma drugs ≥3, with slight lens opacity or without cataract, visual acuity ≥0.5; 3) Phacotrace: goniosynechia ≥180°, anti-glaucoma drugs ≥3, meet the indications for cataract surgery, visual acuity <0.5.

Our study found that Phacotrace had a consistently greater IOP lowering effect and a lower number of antiglaucomatous medications needed postoperatively compared with Phaco, but we also found that Phacotrace was associated with a high risk of complications such as hyphema, hypotony, choroidal detachment and shallow anterior chamber. The rest studies indicated that there had no significantly difference between the two surgical methods for postoperative BCVA, loss of visual field and progression on damage of optic nerve. But, the progression on damage of optic nerve and visual field weren't consistent with the results of IOP reduction. It may be explained that the postoperative IOP has not reached the target IOP and someone proposed that intraocular hypertension and large fluctuation of the IOP during surgery may lead to ocular hypoperfusion, resulting in the damage of optic nerve (20–21). The effect may be insignificant for normal person, but can be dangerous for glaucoma patients. This phenomenon still needed to be further discussed.

Some limitations of this Meta-analysis should be acknowledged and discussed. Firstly, the included studies were all observational studies, so it's difficult to avoid the bias coming from the experimental procedures and outcomes. Secondly, the sample size of the studies included ranged from 51 to 232, which were relatively small to reach a persuasive conclusion. Thirdly, among the 5 studies included, 4 were carried out by the same person, so we had to think about that there might be bias coming from it.

In view of the limitations mentioned above, our results still require large sample randomized controlled studies with multiply-center to verify. In addition, other factors including operation cost and needs of patients and other outcome measures including success rate of operation should also be considered.

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Conflicts of Interest: Wang F, None; Wu ZH, None.

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12 Hayashi K, Hayashi H, Nakao F, Hayashi F. Effect of cataract surgery on intraocular pressure control in glaucoma patients. J Cataract Refract
Declaration

Authors Zhe Zhang et al. have published an article titled as "Cornel biomechanical properties changes after coaxial 2.2-mm microincision and standard 3.0-mm phacoemulsification" in No.2 issue of IJO (2016;9:230-234).

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