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Efficacy and Safety of Bevacizumab Combined with Mitomycin C or 5-Fluorouracil in Primary Trabeculectomy: A Meta-Analysis of Randomized Clinical Trials

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Glaucoma · Trabeculectomy · Bevacizumab · Mitomycin c · 5-Fluorouracil · Meta-analysis

Abstract
Aim: The objective of this study was to evaluate the efficacy and safety of bevacizumab combined with antimetabolite as an adjunctive therapy in primary trabeculectomy for glaucoma. ***Materials and Methods:*** PubMed, Cochrane Library, and EMBASE were searched for relevant randomized controlled trials. Efficacy was evaluated by the postoperative mean intraocular pressure (IOP), complete success, and qualified success rates. Safety was evaluated by postoperative complications and surgical interventions. ***Results:*** A total of 3 randomized controlled trials were included in the meta-analysis. The primary outcome was postoperative mean IOP at the 12-month follow-up. No significant difference in IOP was found between the bevacizumab + antimetabolite (mitomycin c or 5-fluorouracil) group and the antimetabolite alone group (weighted mean difference –0.27; 95% CI –1.38 to 0.83). There were no significant differences in complete success rates, qualified success rates, postoperative complications, and surgical interventions between the experimental treatment group and the conventional treatment group. ***Conclusions:*** Results of the meta-analysis demonstrated that the combination of bevacizumab (1.25 mg/mL) with a regular concentration of antimetabolite did not show more benefit or harm compared with using antimetabolite alone. Further randomized controlled trials are needed to evaluate the efficacy and safety of bevacizumab combined with lower concentrations and a shorter application time of antimetabolite.

Introduction

A reduction of intraocular pressure (IOP) is currently the only treatment option for glaucoma – the second leading cause of blindness worldwide [1, 2]. For patients who have undergone antiglaucoma medical therapy or laser treatment that has proven ineffective, trabeculectomy or various forms of nonpenetrating surgery can be considered, of which trabeculectomy is shown to be more effective for IOP control [3]. The major drawback of trabeculectomy is postoperative scarring, which may lead to failure of the filtering bleb, thus limiting its success rate

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[4, 5]. As such, antimetabolites such as mitomycin c (MMC) and 5-fluorouracil (5-FU) are the most common antifibrotic agents used in conjunction with trabeculectomy to increase its efficacy [6].

Recently, bevacizumab, an anti-vascular endothelial growth factor (VEGF) antibody, was identified as a potential adjunctive therapy for decreasing the failure rate of filtering blebs after trabeculectomy [7]. Recent studies have indicated that subconjunctival injections of bevacizumab posttrabeculectomy are more effective at prolonging bleb survival in rabbits compared with both 5-FU and control groups, exhibiting less postoperative scarring [8]. Several randomized clinical trials (RCTs) have been conducted to explore the efficacy and safety of bevacizumab compared with MMC, 5-FU, or placebo. Fakhraie et al. [9] reported that intracameral bevacizumab significantly increased the complete success rate of trabeculectomy compared with placebo. Kaushik et al. [10] reported that control of IOP was similar in the subconjunctival bevacizumab group and the MMC group. A lower degree of peripheral bleb and nonbleb vascularity was found in the bevacizumab treatment group [10]. However, a recently published Cochrane systematic review reported that anti-VEGF alone may not be as effective as MMC in controlling IOP over 12 months [11]. Therefore, several studies were performed to evaluate the outcomes of bevacizumab treatment combined with antimetabolites in trabeculectomy.

Currently, only 1 meta-analysis has been conducted to systematically assess combination adjunctive therapy in primary trabeculectomy [12]. The study examined the relevant literature available by August 2013, and identified 1 RCT (bevacizumab + 5-FU), 1 phase I/II RCT (ranibizumab + MMC), and 1 nonrandomized, retrospective, comparative study evaluating the percentage IOP reduction as the primary outcome. However, the gathered evidence was insufficient to reach a clear conclusion.

In the present study, only RCTs were included in this meta-analysis to ensure a greater relevance of the evidence. Moreover, RCTs not included in the previous study (i.e., published after 2013) were also included to evaluate the efficacy and safety of bevacizumab combined with antimetabolites in primary trabeculectomy for the treatment of glaucoma.

Materials and Methods

Literature Search

We conducted a systematic literature search using the PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE databases to identify relevant articles. The search was performed using a study design filter to identify RCTs, without a limitation in the language of the article. The last literature search was performed on March 20, 2017. A combination of the following terms was entered: (trabeculectomy or filtration surgery) and (bevacizumab, or Avastin®, or anti-VEGF). We also searched the EU Clinical Trials Register and ClinicalTrials.gov for ongoing trials.

Inclusion Criteria

The inclusion of studies was based on the following criteria: (1) RCTs, (2) patients arranged for primary trabeculectomy, (3) comparison of the outcome between bevacizumab combined with antimetabolites (MMC or 5-FU) versus antimetabolite (MMC or 5-FU) alone in primary trabeculectomy, and (4) follow-up duration >6 months. The exclusion criteria were: (1) phase I/II clinical trials, (2) studies involving other types of glaucoma surgery such as failed glaucoma surgery, bleb revision, and phacotrabeculectomy, (3) observational studies or non-RCTs, (4) bevacizumab alone versus antimetabolite, and (5) pediatric glaucoma.

Data Extraction and Quality Assessment

Data were extracted from eligible clinical trials by 1 researcher and another researcher checked the accuracy of these data. For each study, a standard data extraction sheet was used to record information including the year of publication, first author, countries, number of patients, age, diagnosis, surgical technique, adjunctive therapy medication, follow-up period, postoperative IOP measurements, complete success, qualified success, failure, postoperative complications, and surgical intervention events.

The Cochrane Risk of Bias Tool was used to assess the quality of the studies. This assessment included 6 parts: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias. The risk of bias was determined according to the criteria described in the Cochrane Reviewer's Handbook 5.1.0 [13, 14].

Statistical Analysis

The meta-analysis was conducted using Review Manager 5.3. The postoperative mean IOP was analyzed as a continuous variable and the outcome measurement was reported as weighted mean difference (WMD) with 95% confidence interval (CI). Surgical success, postoperative complications, and surgical interventions were analyzed as dichotomous variables and the outcome measurements were analyzed as the risk ratio (RR) with 95% CI. A p value <0.05 was regarded as statistically significant. Heterogeneity was assessed by Q test and I^2, and $p < 0.10$ and $I^2 > 40\%$ were considered to indicate significant heterogeneity. A random-effects model was used in all situations, based on different clinical characteristics among all of the included trials.

Results

Literature Search

The literature search process is shown in Figure 1. The initial search yielded 60 relevant studies. Of those, 32 were excluded due to duplication. Additionally, 22 studies were excluded based on titles or abstracts not fulfilling

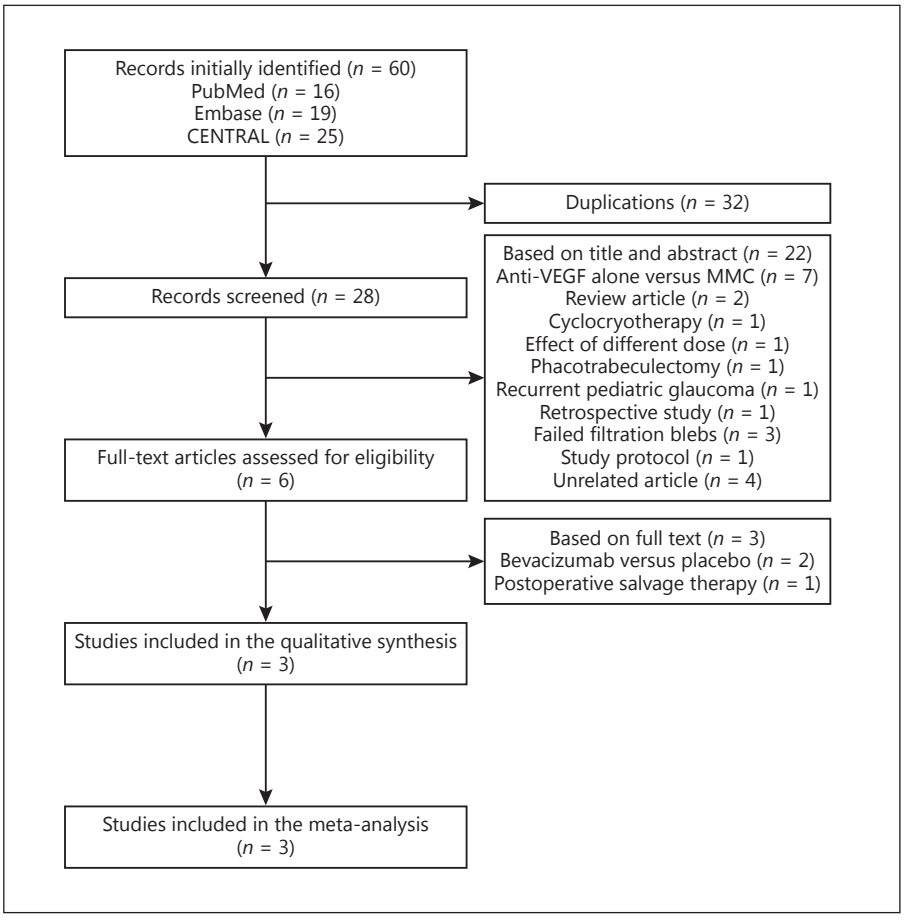


Fig. 1. Literature search process of eligible randomized controlled trials.

the inclusion criteria. Subsequently, the remaining 6 full-text articles were assessed for eligibility. Finally, 3 controlled RCTs were included in the meta-analysis.

Characteristics of the Trials

Table 1 summarizes the characteristics of the included trials. A total of 226 patients were enrolled in these 3 trials. In Vandewalle et al. [15], patients were randomized to the bevacizumab group (experimental group) and placebo group (control group; 72 patients per group). MMC was used in both groups when the target pressure was measured as <14 mm Hg. From the 4 subgroups (bevacizumab, bevacizumab + MMC, MMC + placebo, and placebo), the 2 groups in which patients received bevacizumab + MMC or MMC + placebo were included in the meta-analysis. At the 12-month follow-up, 39, 66, and 36 patients in Kiddee et al. [16], Vandewalle et al. [15], and Suh and Kee [17], respectively (i.e., a total of 141 eyes), had successfully completed the studies, and thus were included in our meta-analysis.

Quality of Trials

The quality of the included controlled RCTs was assessed using the Cochrane Risk of Bias tool. The outcomes of this assessment are summarized in Figure 2. The risks of random sequence generation, incomplete outcome data, selective reporting, and other bias were low in the 3 trials. Suh and Kee [17] did not report the methods used for allocation concealment and blinding, thus the associated risks were unclear.

Efficacy Analysis

A total of 141 eyes from 3 studies were pooled to evaluate the postoperative mean IOP (Fig. 3), as well as complete and qualified success rates (Fig. 4) at the 12-month follow-up. The combination treatment group showed numerically lower postoperative IOP compared with the antimetabolite group (WMD −0.27; 95% CI −1.38 to 0.83). In addition, the differences in complete (pooled RR 1.11; 95% CI 0.84–1.47) and qualified success rates (pooled RR 0.99; 95% CI 0.87–1.14) between the combination and an-

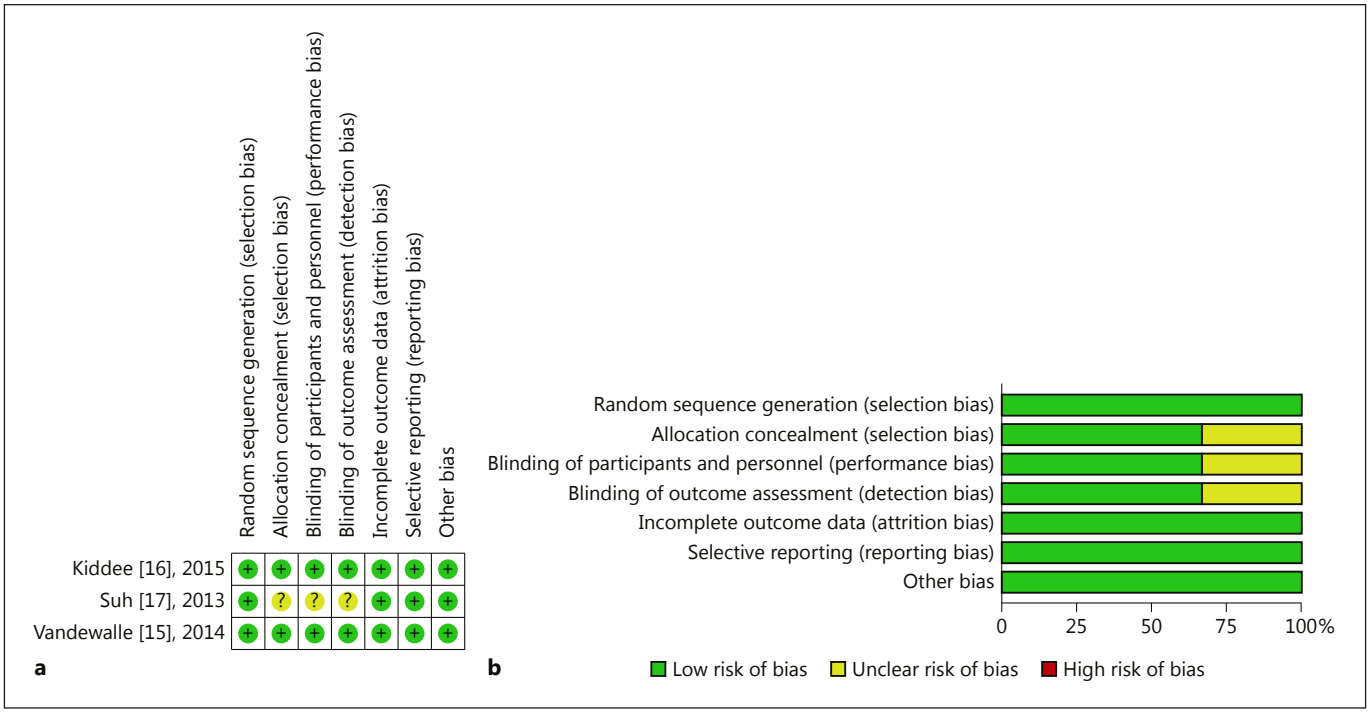


Fig. 2. Summary (**a**) and graph (**b**) of risk of bias.

Table 1. Preoperative baseline characteristics of included RCTs

	Kiddee [13], 2015	Vandewalle [14], 2014[a]	Suh [15], 2013
Study design	RCT	RCT	RCT
Sample size, *n*			
Experimental group	20	72	12
Control group	19	72	24
Mean age (± SD), years			
Experimental group	67.2 (8.8)	69.0 (10.0)	64.1 (10.1)
Control group	65.3 (8.5)	69.0 (10.0)	60.5 (7.9)
Follow-up, months	12	12	24
Conjunctiva flap type	Fornix-based	Fornix-based	Fornix-based
Intervention			
Experimental	Bevacizumab + MMC	Bevacizumab + MMC (*n* = 35) or bevacizumab (*n* = 37)	Bevacizumab + 5-FU
Controlled	MMC + placebo	MMC + placebo (*n* = 37) or placebo (*n* = 35)	5-FU
Bevacizumab injection site	Subconjunctival	Intracameral	Intracameral and subconjunctival
Mean OP (± SD), mm Hg			
Experimental group	25.9 (4.2)	24.8 (8.1)	31.1 (7.8)
Control group	26.2 (4.0)	25.6 (9.9)	35.6 (12.7)
Country	Thailand	Belgium	Korea
Outcome analysis	Per-protocol	Per-protocol	Per-protocol

OP, ocular pressure. MMC was used when the target pressure was <14 mm Hg. We included only the patients who received bevacizumab + MMC or placebo + MMC into our meta-analysis.

[a] After randomization, the experimental group (bevacizumab) and control group (placebo) were each split into 2 subgroups.

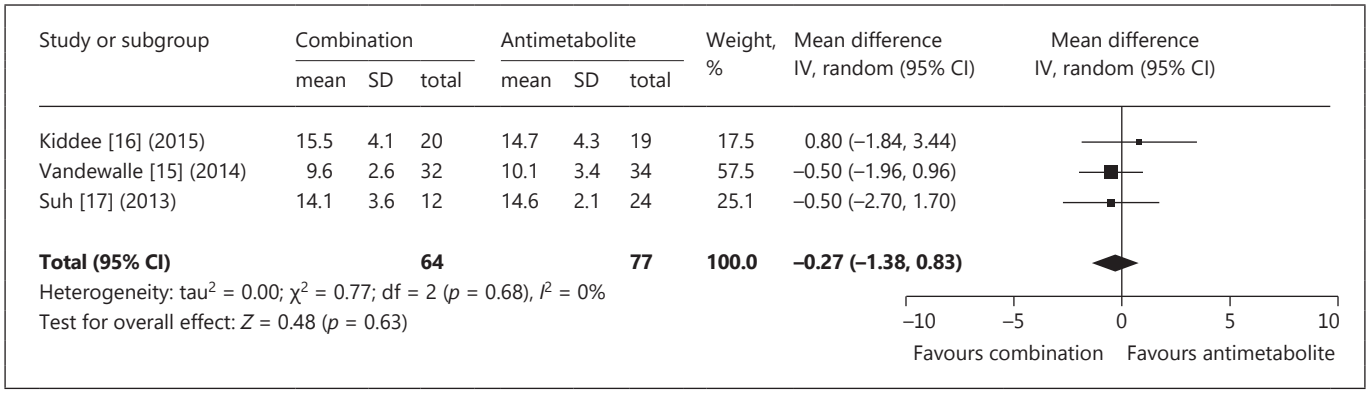


Fig. 3. Postoperative mean IOP at the 12-month follow-up.

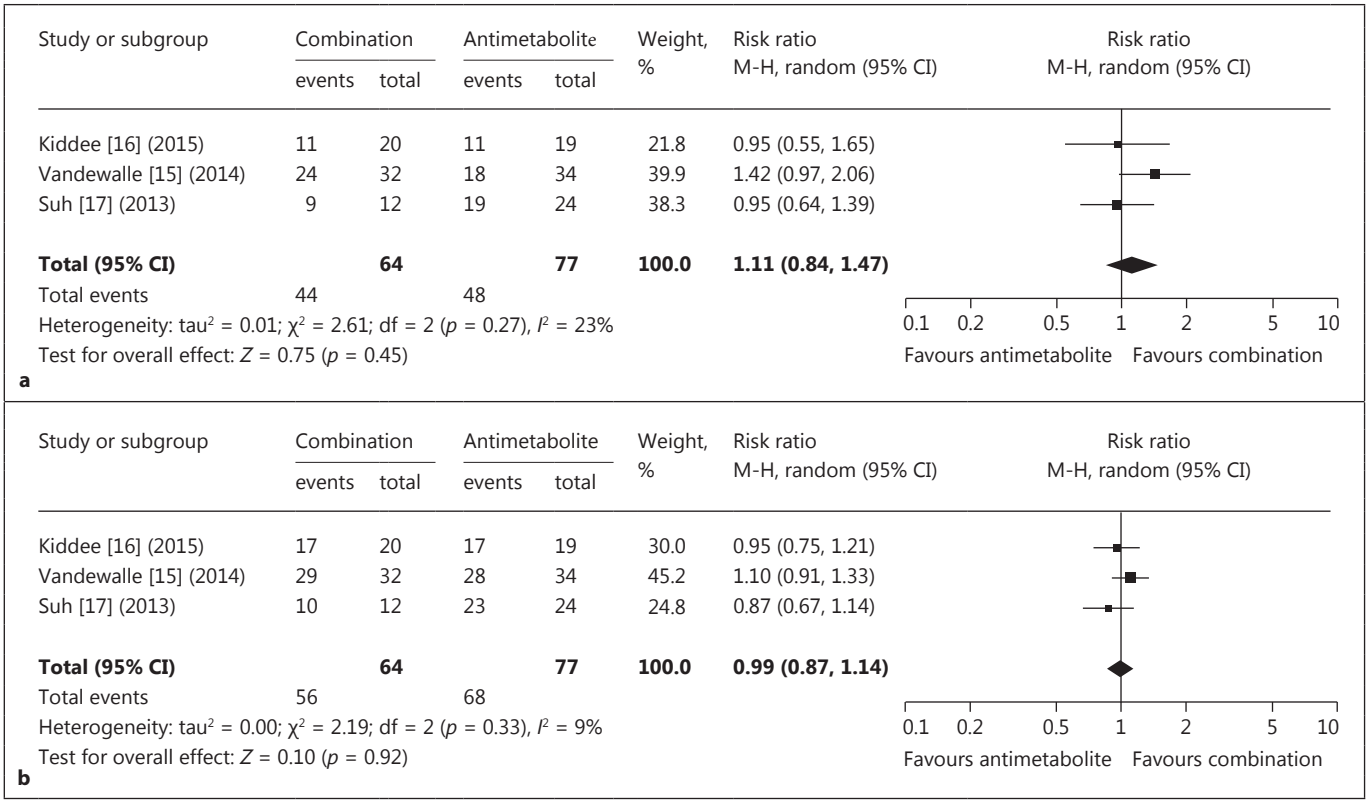


Fig. 4. Surgical success rate of primary trabeculectomy at the 12-month follow-up: complete success (**a**) and qualified success (**b**).

timetabolite alone treatment groups were not statistically significant.

Postoperative Complications and Surgery

The postoperative complications and surgical interventions are shown in Figure 5. No significant differences were identified between the bevacizumab + antimetabolite and the antimetabolite alone treatment groups in the incidence of encapsulated bleb (pooled RR 0.94; 95% CI 0.35–2.52), hypotony (pooled RR 1.10; 95% CI 0.43–2.80), bleb leakage (pooled RR 1.57; 95% CI 0.61–4.03), laser suture lysis (pooled RR 1.19; 95% CI 0.79–1.79), and needling (pooled RR 0.48; 95% CI 0.07–3.27).

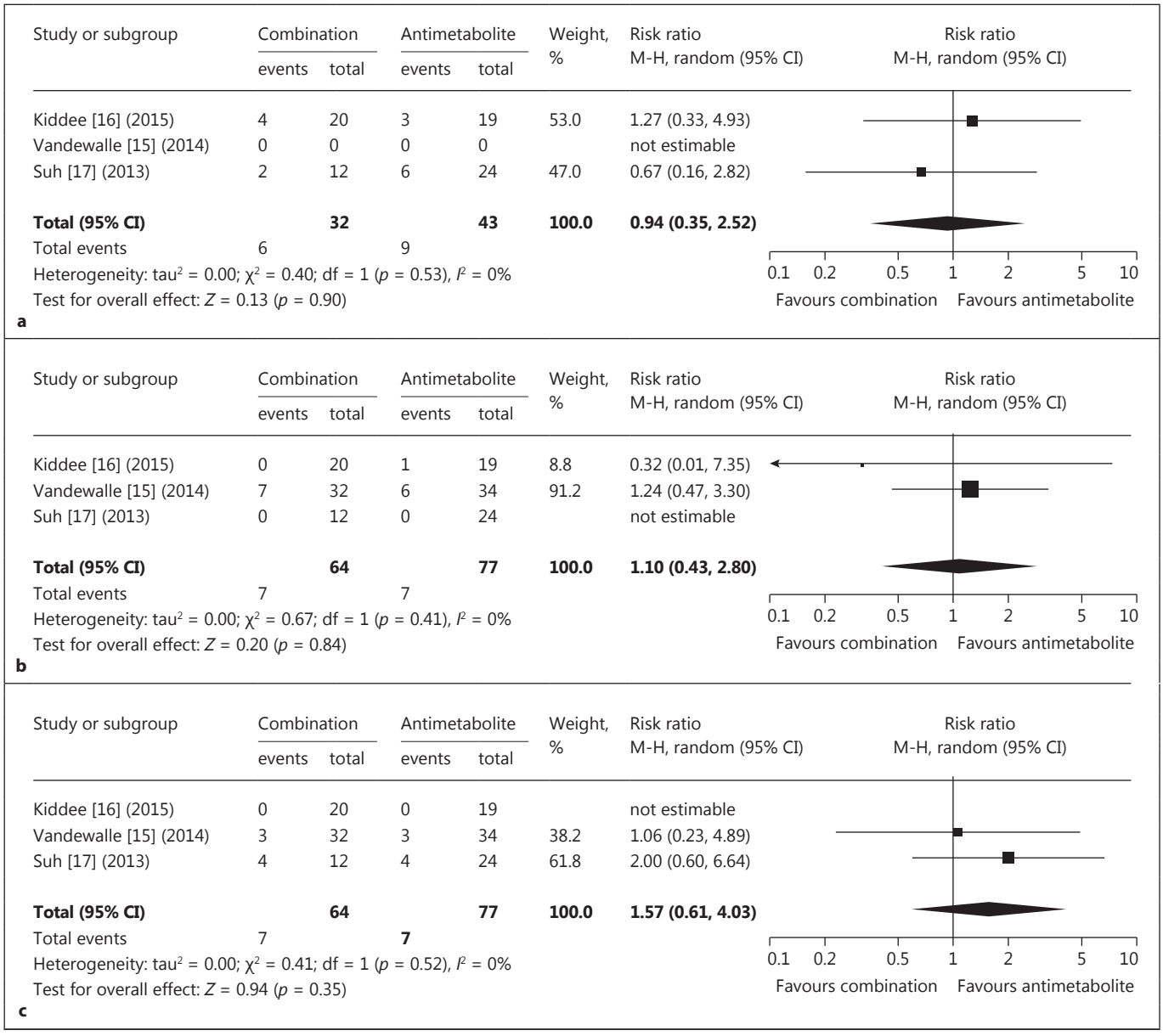
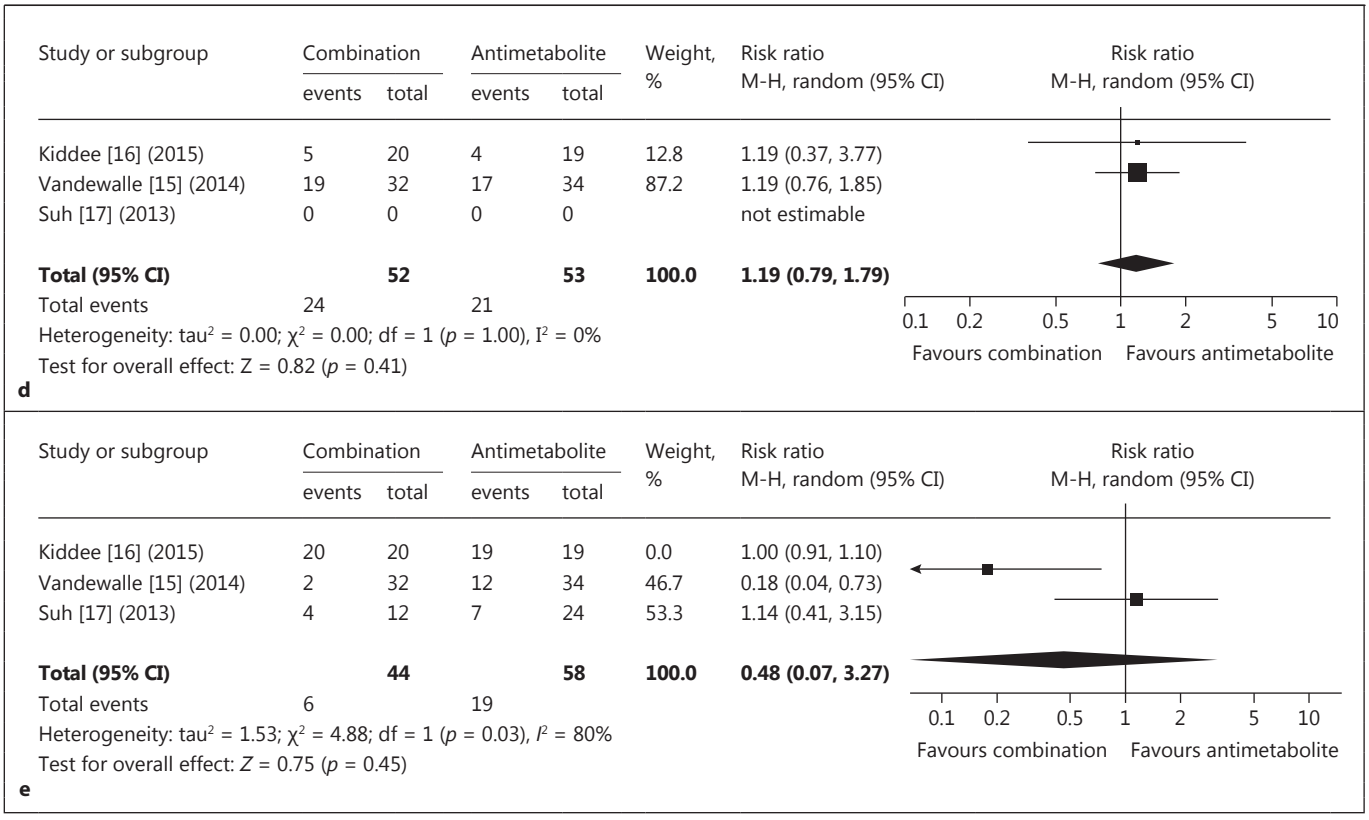


Fig. 5. Postoperative complications and surgical interventions at the 12-month follow-up: encapsulated bleb (**a**), Hypotony (**b**), bleb leakage (**c**), laser suture lysis (**d**), and needling (**e**).

(Figure continued on next page.)

Discussion

Although MMC and 5-FU have been widely utilized in conjunction with trabeculectomy, their use is associated with cellular toxicity leading to serious complications such as hypotony, bleb leakage, and bleb-related endophthalmitis [18–21]. Bevacizumab was identified as a potential agent in conjunction with trabeculectomy [7, 22, 23]. However, bevacizumab alone may not be as effective as MMC in the long-term control of IOP [11, 22, 23]. Several clinical trials of bevacizumab combined with antimetabolites versus antimetabolite alone were conducted to validate this finding. However, the efficacy and safety of combination adjunctive therapy remains uncertain. In the present study, we included 3 RCTs in a meta-analysis. The efficacy of combination adjunctive therapy was eval-



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uated by the postoperative mean IOP, complete success, and qualified success at the 12-month follow-up. Safety was evaluated by the RR of postoperative encapsulated bleb, hypotony, bleb leakage, and surgical interventions, such as laser suture lysis and needling. The results showed that there was no significant difference in efficacy and safety between the combination and conventional treatment groups.

At the 12-month follow-up, control of IOP was similar in the combination versus the conventional group (WMD −0.27; 95% CI −1.38 to 0.83). In the study by Vandewalle et al. [15], the postoperative IOP of both treatment groups was significantly lower compared with the other 2 studies [16, 17], which may be due to the criteria of success in the 3 studies being different. The stricter criteria of success in the Vandewalle et al. [15] study may have contributed to more office-based interventions, such as early postoperative bleb massage and suture lysis, to fulfill their criteria of success. A previous meta-analysis [11], which included trials by Akkan and Cilsim [22] and Pro et al. [23], showed that MMC usage resulted in significantly better control of IOP than anti-VEGF antibodies at the 12-month follow-up [11, 22, 23]. Of note, Nilforushan et al. [24] reported that MMC offered better control of IOP than bevacizumab alone at the 1-month ($p < 0.001$) and 6-month ($p = 0.003$) follow-ups. According to our pooled results, adding MMC to bevacizumab may overcome the limitations of bevacizumab alone in IOP control. Comparing the complete success and qualified success rates at 12 months of follow-up, we found that bevacizumab combined with an antimetabolite was not inferior to conventional treatment in primary trabeculectomy among these 3 studies. As shown by Suh and Kee [17], no significant differences in the complete success ($p = 0.69$) and qualified success rates ($p = 1.00$) were observed in patients receiving bevacizumab combined with 5-FU, or 5-FU alone, at the 24-month follow-up (data not shown). Additional studies with longer follow-up periods are warranted to confirm the impact of combined bevacizumab with antimetabolites on the success rate of trabeculectomy.

Postoperative complications and interventions such as encapsulated bleb, hypotony, bleb leakage, laser suture lysis, and needling were included in the meta-analysis. The pooled RR of these postoperative complications and interventions showed no significant difference between the combination and conventional treatment groups. These findings suggest that adding bevacizumab to anti-

metabolite treatment was as safe as using antimetabolite alone. Vandewalle et al. [16] reported a lower risk of postoperative needling in the bevacizumab + MMC group compared with the MMC alone group. Combining MMC with an anti-VEGF agent showed lower vascularity around the bleb and nonbleb areas of conjunctiva compared with antimetabolite alone [10, 25]. VEGFs and their receptors play an important role in angiogenesis during wound healing [26]. Therefore, adding bevacizumab – an inhibitor of angiogenesis – to MMC treatment may decrease the need for postoperative needling by attenuating the wound-healing process. However, Chua et al. [27] reported that there was no significant difference between the bevacizumab + 5-FU and 5-FU alone groups in terms of bleb and nonbleb vascularity. Suh and Kee [17] also reported no significant difference between bevacizumab + 5-FU and 5-FU alone in postoperative needling. Further investigation is needed to determine the effects of bevacizumab + MMC and bevacizumab + 5-FU in bleb vascularity, which may subsequently affect the need for postoperative needling through inhibiting vascularity around the surgical and bleb-associated sites. This may explain the heterogeneity of postoperative needling in our meta-analysis (Fig. 5e).

The shortcomings of our analysis must also be stated. The sample size (141 eyes from 3 trials) was not sufficiently large to reach a concrete conclusion. The inclusion of the only 2 treatment groups that fulfilled our inclusion criteria from the Vandewalle et al. [16] study may have increased the risk of bias. In addition, we evaluated the efficacy and safety for a 12-month follow-up period, which may not be sufficiently long to illustrate postoperative IOP changes. Also, complications have been reported to occur in longer follow-up periods [28]. Finally, in the study by Suh and Kee [17], information about allocation concealment, blinding of patients and investigators/raters, and blinding of outcome assessment was not adequate to appropriately assess the risk of bias. However, the overall quality of the included trials was of low risk of bias.

A Cochrane systematic review reported that there was no significant difference in IOP control between fornix-based and limbal-based trabeculectomy [29]. However, the authors reported a higher risk of shallow anterior chamber in the limbal-based trabeculectomy group [30]. EI-Sayyad et al. [31] also reported that efficacy, measured by IOP control and surgical success, was not significantly different. However, a cystic leaking bleb only occurred in the limbal-based group [31]. According to previous studies, the surgical method affects the occurrence of postoperative complications. In the present meta-analysis, all patients underwent fornix-based primary trabeculectomy, which is linked to fewer complications. However, there is a need for further studies investigating the effect of different flap types in combination conjunctive therapy. Among the included trials, 1 study [16] used subconjunctival bevacizumab injection, another study [15] used intracameral injection, and the third study [17] injected bevacizumab in both the subconjunctival and intracameral sites. The efficacy of bevacizumab injected in different sites, as well as the impact of subconjunctival and intracameral injections on the outcomes of combination adjunctive therapy, remains to be explored.

Although the optimum dose and duration of MMC administration remains controversial [32–35], Sihota et al. [36] reported that low-dose MMC (0.1 mg/mL) was probably safer and as effective as 0.2 mg/mL of MMC in a 1-min administration. Kim et al. [37] reported that shorter administration of MMC (0.5–1 min), at a dose of 0.5 mg/ mL, resulted in improved efficacy and safety compared with longer administrations. The RCTs included in this meta-analysis used 0.4 mg/mL MMC for 3 min [16] and 0.2 mg/mL MMC for 2 min [15]. Currently, there are no studies evaluating the efficacy and safety of bevacizumab (1.25 mg/mL) in combination with different concentrations of MMC (0.1–0.4 mg/mL) and different exposure durations. Further controlled RCTs are needed to assess the efficacy and safety of bevacizumab combined with lower concentrations of antimetabolite and shorter administration times, which is suggested to reduce the incidence of adverse events, while maintaining good IOP control.

In conclusion, the present study demonstrated that the combination of bevacizumab (1.25 mg/mL) with regular concentrations of antimetabolites showed similar efficacy and safety profiles compared with antimetabolite monotherapy. Further controlled RCTs with larger sample sizes are warranted to determine the efficacy and safety of bevacizumab combined with lower concentrations and a shorter administration time of antimetabolites.

Disclosure Statement

The authors have no conflicts of interest to declare.

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