• Meta-Analysis •

Outcomes of 4 surgical adjuvants used for internal limiting membrane peeling in macular hole surgery: a systematic review and network Meta-analysis

Xia-Wei Wang, Yan Long, Yang-Shun Gu, Dong-Yu Guo

Department of Ophthalmology, the First Affiliated Hospital of Zhejiang University, Hangzhou 310003, Zhejiang Province, China

Correspondence to: Dong-Yu Guo. Department of Ophthalmology, the First Affiliated Hospital of Zhejiang University, 79 Qingchun Road, Hangzhou 310003, Zhejiang Province, China. 1317058@zju.edu.cn

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Abstract

● **AIM:** To compare the outcomes of four adjuvants used for internal limiting membrane (ILM) peeling in macular hole surgery, including indocyanine green (ICG), brilliant blue G (BBG), triamcinolone (TA) and trypan blue (TB), through systematic review and random-effects Bayesian network Meta-analysis.

● **METHODS:** PubMed, Cochrane library databases and Web of Science were searched until August 2018 for clinical trials comparing the above four adjuvants. ORs for postoperative best corrected visual acuity (BCVA) improvement and primary macular hole closure rates were compared between the different adjuvants.

● **RESULTS:** Twenty-seven eligible articles were included. For postoperative BCVA improvement, results of BBG-assisted peeling were significantly more favorable than those of ICG (WMD 0.08, 95% credible interval 0.01-0.16) and TA ranked highest. No significant differences were found between any other two groups in postoperative BCVA improvement. For postoperative primary macular hole closure rates, BBG ranked highest. However, no significant differences were shown between any two groups.

● **CONCLUSION:** TA and BBG are the optimum adjuvants for achieving postoperative BCVA improvement macular hole surgery with adjuvant-assisted ILM peeling. Among all adjuvants, the use of BBG is associated with the highest postoperative macular hole closure rate.

● **KEYWORDS:** internal limiting membrane; surgical adjuvants; best corrected visual acuity improvement; primary macular hole closure rate; network Meta-analysis

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INTRODUCTION

The tangential traction of the vitrous cortex and epiretinal membrane is considered to be highly associated with macular holes (MH), and vitrectomy combined with internal limiting membrane (ILM) peeling is a widely accepted surgical procedure for treating MH. The procedure is noted for increasing the likelihood of primary anatomical closure and improving visual function[1].

Because the ILM is thin and transparent, several adjuvants have been used as vital stains to enhance ILM visibility. The first and most frequently used adjuvant is indocyanine green (ICG). However, ICG is known to damage the retinal ganglion cells and retinal pigment epithelial (RPE) cells, as well as to decrease retinal function during vitrectomy[2]. Therefore, many other alternative dyes, including brilliant blue G (BBG), triamcinolone (TA) and trypan blue (TB) are attracting more attention[3-4]. Recently, many studies of these major adjuvants have compared postoperative best corrected visual acuity (BCVA) improvement and primary closure rates[5-7]. Shukla *et al*[6] showed better optimization of visual and functional outcomes using BBG and TB, compared with those of ICG. While in the another study[5], the use of ICG or TB appeared to yield similar improvements in terms of postoperative BCVA. However, these studies were non-systematic and limited to only two or three adjuvants used for ILM peeling; more protocols or more systematic reviews and Meta-analyses are needed to clarify differences. Recently, Azuma *et al*[7] conducted a traditional Meta-analysis with a limited number of studies. In order to compare more than two adjuvants at the same time, we selected Bayesian network Meta-analysis, a unique method described previously[8-9]. The purpose of this study was to conduct a random-effects Bayesian network Meta-analysis to compare the major adjuvants (ICG, BBG,

TA, TB) used in MH surgery in terms of postoperative BCVA improvement and postoperative primary MH closure rate in order to establish the optimum adjuvant for use in ILM peeling for MH.

MATERIALS AND METHODS

Search Strategy The protocol for the systematic review was based on PRISMA guidelines[10]. We conducted a search for all available published studies of associations between different adjuvants for ILM peeling in MH surgery and functional outcomes using the index terms "macular hole", "indocyanine green OR brilliant blue OR triamcinolone OR trypan blue" to search databases including PubMed, Cochrane library databases and Web of Science until the end of August 2018 without language or date restrictions. A manual search was also performed of reference lists of published articles and literature searches were complemented by perusing the reference lists of previous Meta-analyses.

Selection Criteria Inclusion criteria were: 1) randomized controlled trials or cohort studies published as peer-reviewed articles with full manuscripts available; 2) patients with MH who had undergone MH surgery with ILM peeling using ICG or BBG or TA or TB, or peeling without staining; 3) use of BCVA or primary MH closure rate as clinical end-points; 4) follow-up time for postoperative BCVA no less than six months; 5) for studies having the same content, the latest one was applied. Exclusion criteria: 1) noncomparative, single-arm study; 2) lack of primary data, the materials in four tables required for study or the improved BCVA (mean±SD, logMAR) after surgery were not available, or the relevant materials could not be obtained through calculation; 3) studies with duplicate reports, poor quality or obscure description of data used for study.

Data Extraction and Assessment for Risk of Bias Two investigators (Guo DY, Wang XW) independently reviewed the full manuscripts of eligible studies and extracted information into an electronic database, including patient characteristics, inclusion and exclusion criteria, treatment protocols, and outcomes. Risk of bias of individual studies was assessed by the same reviewer (Guo DY) with Cochrane Collaboration's risk of bias assessment tool in RevMan 5.2 software for RCTs[11] and Newcastle-Ottawa scale for non-randomized trials[12].

Data Analysis Primary closure rate and BCVA data recorded after MH surgery with ILM were analyzed. First, node-splitting analyses were provided to initially detect the consistency between studies (data not shown). To account for the absence of significant inconsistency and heterogeneity between studies, the relative effects of the interventions were analyzed using a consistency model based on a random-effects Bayesian model. Results of the analysis are presented as weighted mean difference (WMD) and odds ratios (ORs) with associated 95% credible intervals (CrIs). To assess whether inconsistencies were shown between direct and indirect comparisons, the pooled WMD and ORs from the network Meta-analysis were compared with corresponding WMD and ORs from traditional pair-wise random-effects Meta-analysis of direct comparisons. In addition, by using the pair-wise Meta-analysis, a statistical evaluation of the heterogeneity of the included studies was carried out using the I^2 parameter. Treatments were ranked for each outcome in each simulation on the basis of their posterior probabilities. By calculating the hazard ratio (HR) for each treatment compared with an arbitrary common group and counting the proportion of iterations of the Markov chain, we assessed the probability that each adjuvant treatment was the most efficacious regimen, the second most efficacious, the third most efficacious and so on.

Traditional pair-wise Meta-analysis was performed using Stata 12.0. Bayesian network Meta-analysis was done with ADDIS version 1.16.6. According to the ADDIS software, the NMA was conducted using a Bayesian random-effects model, using the Markov chain Monte Carlo simulation. For each model, 50 000 simulations were generated for each of the four chains and the first 20 000 simulations were discarded as the burn-in period. Convergence was assessed using the Brooks-Gelman-Rubin method[13].

RESULTS

Study Characteristics After the retrieval and eliminating steps taken in accordance with retrieval strategy and inclusion & exclusion criteria, 27 applicable studies were included (Table 1)[6,14-39]. The flow diagram that allowed for identification of eligible studies is illustrated in Figure 1. All included studies were published as full manuscripts and have low risk of bias (data not shown). Figure 2 shows the characteristics of the included studies. In total, 1849 eyes were included in the Meta-analysis; the ILMs of 891, 321, 200, 100, 337 eyes were peeled using ICG, BBG, TA, TB and no dye (ND).

Postoperative BCVA Improvement Nineteen studies were included in this Meta-analysis with a total of 1227 patients who received the surgery performed with one of the five adjuvants used to assist ILM peeling (Figure 2). Results of the random-effects network Meta-analysis are summarized in Figure 3. Compared with ICG, BBG showed remarkably more efficacious postoperative BCVA improvement (WMD 0.08, 95%CrIs 0.01-0.16). Although not significant, TA was noticeably more efficacious than ICG (WMD 0.09, 95%CrIs -0.00-0.19). No significant differences were shown between any other two groups in postoperative BCVA improvement. A direct comparison of results from traditional pair-wise Meta-analysis and network Meta-analysis did not suggest inconsistencies between direct and indirect evidence (data not shown).

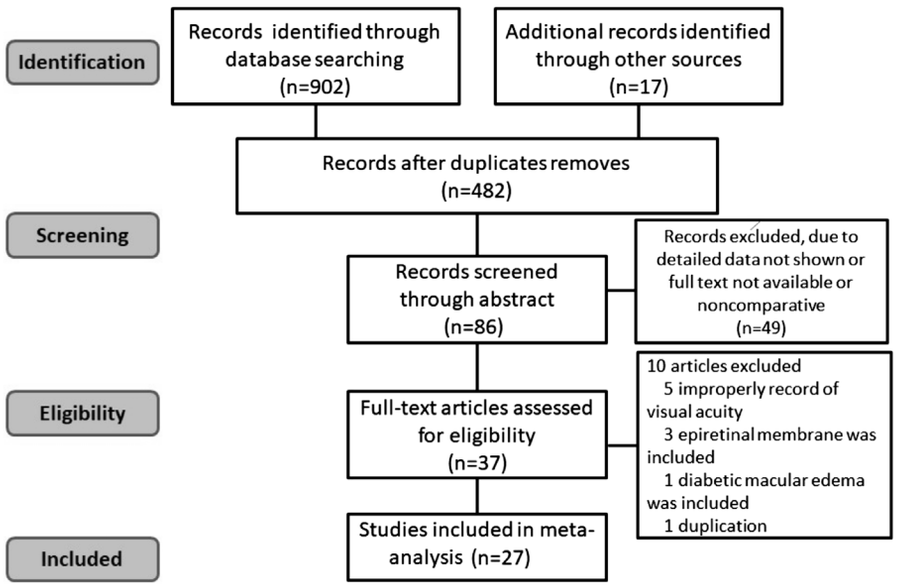

Figure 1 Literature search and selection.

Table 1 Characteristics of the included studies[6,14-39]

Author	Year	Race	Design	Dye, concentration	*n*	Stage 2,3,4 (*n*)	Follow-up (mo)
Mochizuki *et al*	2014	Japan	Retrospective	ICG 0.125%; TA 8 mg/mL; BBG 0.25 mg/mL	97	21, 35, 41	24
Machida *et al*	2014	Japan	Randomized	ICG 0.25%; TA; BBG 0.025%	48	NA	12
Meng *et al*	2014	China	Retrospective	ICG; TA	82	NA	3
Kumar *et al*	2011	India	Retrospective	TA 40 mg/mL; BBG 0.05%	94	14, 45, 35	16
Nomoto *et al*	2008	Japan	Retrospective	TA 40 mg/mL; ICG 0.25%	67	26, 26, 15	12
Kadonosono *et al*	2013	Japan	Prospective	ICG 0.5 mg/dL; BBG 0.5 mg/mL	40	NA	6
Baba *et al*	2012	Japan	Retrospective	BBG 0.25 mg/mL; ICG 0.125%	63	12, 31, 20	6
Zeng *et al*	2012	China	Retrospective	BBG 0.25%; ICG 0.25%	46	0, 25, 21	3
Shukla *et al*	2011	India	Retrospective	ICG 5 mg/mL; BBG 0.05%; TB 0.15%	50	NA	6
Williamson *et al*	2014	England	Retrospective	ICG 0.5 mg/mL; BBG	318	NA	6
Bellerive *et al*	2013	Canada	Randomized	ICG 2.5 mg/mL; TB 0.06%	25	NA	12
Shiono *et al*	2013	Japan	Retrospective	ICG 2.5 mg/mL	34	9, 18, 7	6
Schaal *et al*	2009	Japan	Retrospective	ICG 0.5%	156	64, 104, 31	12
Christensen *et al*	2009	Denmark	Randomized	TB 0.15%; ICG 25 mg/mL	52	12, 40 ,0	12
Nakamura *et al*	2009	Japan	Retrospective	ICG 0.25%	54	10, 32, 12	36
Nagai *et al*	2007	Japan	Retrospective	ICG 5 mg/mL	53	12, 29, 12	24
Husson-Danan *et al*	2006	France	Retrospective	ICG 0.5 or 0.8 mg/mL	38	1, 29, 8	12
Lai *et al*	2006	China	Retrospective	ICG 0.5%; TB 0.1%	92	16, 42, 34	18
Karacorlu *et al*	2005	Turkey	Retrospective	ICG 0.5 mL/mL; TA 40 mg/mL	30	0, 21, 9	6
Lee *et al*	2005	New Zealand	Retrospective	ICG 0.05% or 0.5%; TB 0.15% or 0.3%	37	10, 20, 7	10
Choi *et al*	2005	Korea	Retrospective	ICG	30	0, 8, 22	12
Hahm *et al*	2005	Korea	Retrospective	ICG 0.5%	67	0, 26, 51	12
Lochhead *et al*	2004	England	Retrospective	ICG 5 mg/mL	68	0, 54, 14	6
Slaughter *et al*	2004	Australia	Retrospective	NA	68	NA	6
Wei *et al*	2013	China	Prospective	TA 4 mg/mL	47	NA	12
Fukuda *et al*	2011	Japan	Retrospective	ICG 0.125%; BBG 0.25 mg/mL	53	24, 21, 8	6
Selton *et al*	2012	France	Retrospective	BBG	40	NA	6

NA: Not available; Stage 2-4: MH stage was classified according to the system of Gass.

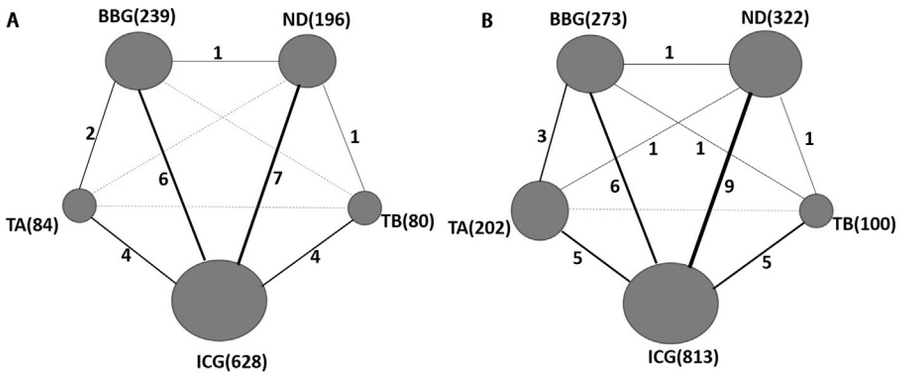

Figure 2 Network of the comparisons for the Bayesian network Meta-analysis Comparisons for postoperative visual acuity (A) and primary closure rate (B). The size of the nodes is proportional to the number of patients (in parentheses) to receive the treatment. The width of the lines is proportional to the number of trials (beside the line) comparing the connected treatments.

A

ND				
-0.05(-0.15,0.05)	BBG			
0.04(-0.04,0.11)	0.08(0.01,0.16)	ICG		
-0.06(-0.18,0.06)	-0.01(-0.13,0.10)	-0.09(-0.19,0.00)	TA	
0.00(-0.12,0.11)	0.05(-0.08,0.17)	-0.03(-0.13,0.06)	0.06(-0.08,0.20)	TB

B

ND				
0.33(0.08,1.17)	BBG			
0.84(0.38,2.06)	2.61(0.88,10.18)	ICG		
0.61(0.15,2.55)	1.89(0.46,8.92)	0.74(0.17,2.78)	TA	
0.96(0.17,5.22)	2.97(0.46,22.26)	1.11(0.22,5.18)	1.56(0.19,12.14)	TB

Figure 3 Results of the random-effects network Meta-analysis Pooled WMD for postoperative BCVA improvement (A) and ORs for primary closure Rate (B). The column adjuvant is compared with the row adjuvant. Numbers in parentheses are the 95%CrIs.

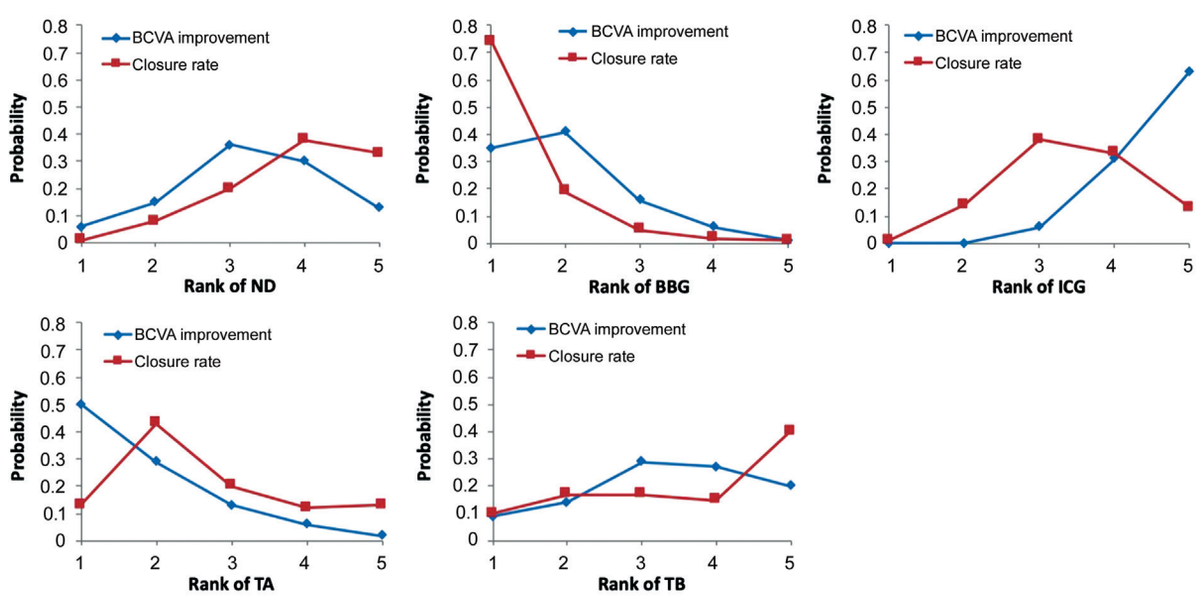

Figure 4 Ranking for postoperative BCVA improvement and primary closure rate of 5 adjuvants used for ILM peeling Ranking indicates the probability of being the most efficacious treatment.

The probabilities of most appropriate choice for each adjuvant were ranked at each of the possible five positions (Figure 4). TA was the most likely to achieve the most favorable prognosis for BCVA improvement, followed by BBG, TB and ND. ICG vision prognosis was the least favorable.

Primary Closure Rate Twenty-four studies were included

in this Meta-analysis with a total enrollment of 1710 patients (Figure 2). Results of the random-effects network Meta-analysis are summarized in Figure 3. According to the results of network Meta-analysis, no significant differences were found between any two of the different adjuvants in primary postoperative MH closure rates. Traditional pair-wise Meta-analysis also reached the same results.

Using ranked probability results, BBG was found to be the most favorable choice for achieving primary postoperative closure with significantly greater probability of MH closure than using TA, TB, ICG or ND (Figure 4).

DISCUSSION

ICG, BBG, TB and TA are the four effective major adjuvants described so far for ILM peeling in MH surgery. To the best of our knowledge, this is the first network Meta-analysis that compares all major adjuvants and also includes both anatomical and functional outcomes in the comparison of those stains. BCVA improvement and primary postoperative MH closure rate are the two most important clues by which to assess operative outcomes since they may be associated with reduced metamorphosis and better visual quality. Results of the present study showed no significant differences between any two of the different adjuvants in primary postoperative MH closure rate, and TA and BBG were the optimum adjuvants for postoperative BCVA improvement when used in MH surgery with ILM peeling.

Previous studies have shown that ICG and BBG can improve ILM contrast of MH surgery significantly, and help the surgeons performing the surgery to strip the ILM effectively. BBG is a relatively new stain and its selective ILM staining properties and low adverse effects has made it widely adopted by surgeons. The scanning electron microscope images showing ILM specificity may be related to the predominant type IV collagen in ILM. In fact, TA and TB are not stains for ILM in the traditional sense because they have a poor dying effect for ILM and instead are used mainly for dying epiretinal membrane. After using TA and TB, however, the postoperative MH closure rate still shows no significant statistical differences compared with ICG and BBG, and TA has even ranked second (43% probability) according to the ranking data (Figure 4). In fact, in the present study, the ranking of stains showed that postoperative MH closure rates by skill oculists were not affected by the stains used for ILM, which is a similar result to those of Tsipursky *et al*[40]. Previous research has also shown that proper doses of TA remain an effective and low-cost treatment modality for macular edema and macular degeneration[8-9], and may also reduce inflammatory reaction after surgery and even have neuroprotective effects, leading to greater BCVA improvement[41]. Studies have found that ICG injured the retina both histologically and functionally, while BBG and TA did not[22,25,42], which is consistent with the ranking of adjuvants for BCVA improvement in the present study (Figure 4). However, one study also estimated the focal macular electroretinograms to evaluate RGC function after ICG-, BBG- or TA-assisted MH surgery, and no significant differences were noted[43]. Results of that study indicated that the three agents would not be toxic to the macula. Therefore, further studies may be necessary to determine whether the stains damage RCGs or not. In the present study, we found that BBG had a 74% possibility of becoming the optimum stain for postoperative MH closure as evidenced through the ranked results (Figure 4). Our result also matched the traditional findings of Azuma *et al*[7], but with further expansion. BBG obtains relatively better color contrast to help the oculist relieve the traction from ILM and also has few side effects affecting the retina, which makes it remarkably effective in both MH closure rate and BCVA improvement.

Strengths and Limitations The present study has several strengths. First, this Meta-analysis compared all major stains in MH surgery simultaneously and assessed every stain individually. The methods we employed overcame the difficulty of different measures of postoperative BCVA across studies and synthesized all available studies within a single Meta-analysis, avoiding potential selection bias[44]. The Bayesian network Meta-analysis also allowed us to compare adjuvants indirectly when no head-to-head trial existed and obtain more precise effect estimates by assessing direct and indirect comparisons[9-10]. In addition, we assessed every adjuvant both anatomically and functionally. This updated synthesis of existing evidence provided new insights into controversies on this issue and revealed important implications for clinical care and future research.

Our findings also have a few limitations. First, because of the limitations of time and word count restrictions for the paper, our study did not conduct subgroup analysis and regression analysis considering data of race/ethnicity or follow-up times, which may have resulted in loss of potential positive results. And we did not conduct subgroup analysis of dyes with different concentration, although the evaluation of the heterogeneity showed no significant difference, which would not great influence our results. Second, we used secondary data obtained from the articles included in the paper, basically conducting a retrospective study. Even though we made strict assessment of the included studies through the Cochrane risk of bias tool or Newcastle-Ottawa scale, some heterogeneity and publication bias could not be ruled out. Thus, multi-center, large sample randomized controlled trials are still needed to improve the level of evidence.

In conclusion, this network Meta-analysis shows that TA and BBG are the optimum adjuvants for achieving postoperative

BCVA improvement after MH surgery with ILM peeling. BBG appears to be the best choice for obtaining favorable postoperative MH closure rates.

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