• Meta-Analysis •

Internal limiting membrane peeling with different dyes in the surgery of idiopathic macular hole: a systematic review of literature and network Meta-analysis

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Abstract

• AIM: To evaluate the effect of internal limiting membrane (ILM) peeling with indocyanine green (ICG), brilliant blue G (BBG), triamcinolone acetonide (TA), trypan blue (TB), or without dye for the treatment of idiopathic macular hole (IMH).

• METHODS: A search was conducted using PubMed, EMBASE, and CENTRAL (Cochrane Central Register of Controlled Trials) for related studies published before October 2018.

• RESULTS: A total of 29 studies and 2514 eyes were included in this network Meta-analysis. For IMH closure, the rank from the best to the worse treatment was: BBG, TB, TA, ICG, and no dye. There was a significant difference in postoperative IMH closure rate between BBG and no dye. The rank of the best to the worse treatment to improve visual acuity was: BBG, TB, no dye, TA, and ICG. The improvement rate of visual acuity after using BBG was significantly higher than ICG. The improvement rate of visual acuity was more favorable with TB than ICG, TA, and no dye.

• CONCLUSION: BBG can contribute to better anatomical and functional outcomes compared to other dyes for ILM peeling in patients with IMH. The results show that the best treatment of ILM peeling with dyes is BBG.

• KEYWORDS: idiopathic macular hole; brilliant blue G; trypan blue; internal limiting membrane peeling; network Meta-analysis

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INTRODUCTION

Idiopathic macular hole (IMH) is an important condition that leads to blindness[1]. Patients with IMH have a prevalence of 8 cases per 100 000 people[2], and patients with visual impairment have an incidence of 0.2/1000 to 0.3/1000[3-4]. IMH has a serious impact on patients' quality of life, however, it can be repaired by the surgery of pars plana vitrectomy (PPV)[5].

In 1971, Machemer *et al*[6] firstly described a vitrectomy. With the development of medical technology, vitrectomy combined with inner limiting membrane (ILM) peeling shows better outcomes compared to no ILM peeling[7-9]. However, the ILM is thin and transparent which makes it a challenge for the surgeon, and it is difficult to distinguish the boundary and range of the peeling[10]. It is for this reason that indocyanine green (ICG) dye, which was initially used for fluorescein angiography, was firstly used for ILM staining in 2000 and improved the visualization of ILM during the surgery and promoted the development of ILM peeling[11]. Since then, ILM peeling with ICG has been widely reported to promote the surgery of MHs[12-13]. However, ICG could also cause damage to the retinal ganglion cells and retinal pigment epithelium (RPE) because of its toxicity, the mechanism might be related to the oxidative toxicity of ICG[14]. Brilliant blue G (BBG) is an alternative dye for staining ILM and has been frequently used throughout the world. However, *in vitro*, it has been shown that BBG is related to cellular toxicity[14-15], and other dyes applied to ILM peeling surgeries have also shown toxic effects on the retina[16-17], such as trypan blue (TB) and triamcinolone acetonide (TA)[2,18].

In summary, almost all kinds of biological dyes have potential side effects on the retina. At present, there are few comparative reports of postoperative results from ICG, BBG, TB, TA, and no dye assisted ILM peeling for patients with IMH. Therefore, this network Meta-analysis study is mainly for patients with

IMH, to analysis and summarize the anatomical outcome (rate of postoperative primary MH closure) and functional outcome [rate of vision improvement and best corrected visual acuity (BCVA)] for ILM peeling with ICG, BBG, TB, TA, and no dye.

MATERIALS AND METHODS

This systematic review and a Meta-analysis were conducted according to the recommendations from the Cochrane Handbook for Systematic Review of Interventions[19].

Search Strategy The PubMed, MEDLINE, EMBASE, and CENTRAL (Cochrane Central Register of Controlled Trials) were searched for related published studies, with no language restrictions before October 2018. The terms used for the systematic search were ("brilliant blue", OR "indocyanine green", OR "triamcinolone acetonide", OR "trypan blue", OR ICG, OR TB, OR TA, OR BBG) AND ("internal limiting membrane peeling", OR "primary macular hole", OR "idiopathic macular hole"). We also manually collected the reference lists for the original studies and review articles were examined by internet-based search for additional eligible articles.

Eligibility Criteria The articles taken from the internet-based search were established to screen the qualified trials. The eligible studies must have been met: 1) comparative studies; 2) contained at least two groups, with the ILM-peeling procedure and with application of ICG, or BBG, or TB, or TA, or peeling without staining; 3) included only IMH patients, and ILM peeling was conducted in case and control groups; 4) at least one of the outcomes of interest was included.

Data Extraction and Quality Assessment The data were extracted independently by two reviewers and were rechecked after the first extraction. Any disagreement of eligibility during the extraction was discussed by the two reviewers and resolved. The extracted information from each study included the first author, year, study type, number of subjects, age, stages of MHs, preoperative BCVAs (logarithm of the minimal angle of resolution, logMAR), follow-up time, and dyes. The outcomes of interest were extracted and included the following: the primary closure rate (MH closure after the initial surgery) and the number of people with improved visual acuity. We contacted the authors for any missing data.

The quality of the retrospective studies was assessed using the Newcastle-Ottawa Scale (NOS)[20]. The NOS was used to evaluate the selection, comparability, and outcome or exposure for cohort or case-control studies. The maximum for selection was 4 stars, for comparability was 2 stars, and for outcome or exposure was 3 stars. The maximum NOS score was 9 stars, and the studies with 6 stars were considered to have a relatively high quality.

The quality of the randomized clinical trial (RCT) studies, using the methods of the Cochrane Handbook for Systematic Reviews of Interventions[21], were assesed according to the following parameters: bias in sequence generation; bias in allocation concealment; bias in masking of participants and personnel; bias due to incomplete outcome data; bias due to selection of outcome reporting; and other bias.

Statistical Analysis

Methods for direct treatment comparisons Odds ratios (ORs) and 95% confidence intervals (CI) were calculated as effect measures. We pooled summary estimate using the random-effects method, which recognized and anchored studies as a sample of all potential studies[22]. The I^2 statistic was calculated as a measure of the proportion of overall variation that was attributable to between-study heterogeneity.

Methods for indirect and mixed comparisons To evaluate the relative efficacy of postoperative IMH closure rate and the rate of vision improvement and BCVA for ILM peeling with ICG, BBG, TB, TA, and no dye for the patients with IMH, we used a random-effects network Meta-analysis, within a frequentist frame-work taken into account simultaneously[23]. Besides, the surface under the cumulative ranking curve (SUCRA) was used to assess the ranking probabilities for all treatments on anatomical and functional outcomes in order to obtain a treatment hierarchy[24]. A loop specific approach was used to assess the presence of inconsistencies locally in network Meta-analysis models, that is, whether the information of both sources of evidence was similar enough to be combined[25]. ORs and 95%CI were also calculated as effect measures.

Funnel plot and publication bias The difference between the observed effect size and comparison specific summary effect for each study was calculated. Then, this variable was regressed on standard error (SE) and thus, a simple linear regression line was added in the funnel plot, which could help us explore visually if there was a publication bias in the results among the original studies. All of the analyses were conducted using STATA 15.1 software (pairwise Meta-analysis, network Meta-analysis, I^2 calculations, SUCRA graphs, and funnel plot). $P<0.05$ was considered statistically significant.

RESULTS

Selection of Studies A total of 1425 articles were initially identified. Then, we excluded 1341 unrelated articles by screening the titles and abstracts and 55 duplicate articles were also excluded. A total of 34 articles with full text that met the inclusion criteria were assessed. Subsequently, 3 articles were from the same trial and 2 articles did not contain interest data. Finally, a total of 29 studies with full text, published between 2004 and 2014 were selected for the network Meta-analysis (Figure 1).

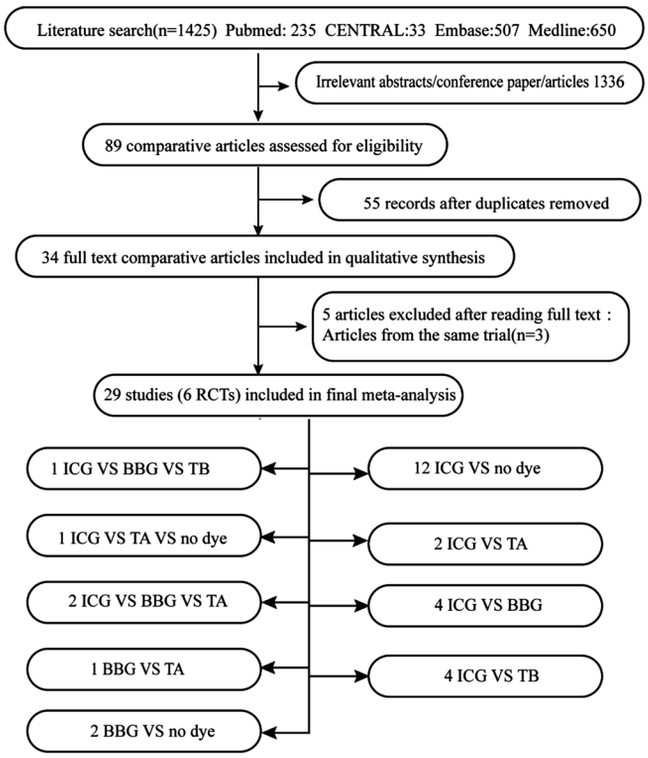

Figure 1 Study selection.

Baseline Characteristics of the Included Studies Table 1 shows the baseline characteristics of the included studies. Among 29 of the included studies, 6 articles were RCTs, 4 articles were three-arm trials, and 23 articles were retrospective trials. A total of 2514 eyes were included, with 1132 in the ICG group, 340 in the BBG group, 89 in the TB group, 236 in the TA group, and 717 in the no dye group. The follow-up duration was between 6 and 19mo. MH was stage 2-4. The concentration of ICG was 0.05-2.5mg/mL. TB was 0.025-0.25 mg/mL, and BBG was 0.25-0.5 mg/mL (Table 1). The different dyes were assessed by studies that compared ICG *vs* BBG *vs* TB (*n*=1), ICG *vs* TA *vs* no dye (*n*=1), ICG *vs* BBG *vs* TA (*n*=2), BBG *vs* TA (*n*=1), BBG *vs* no dye (*n*=2), ICG *vs* no dye (*n*=12), ICG *vs* TA (*n*=2), ICG *vs* BBG (*n*=4), and ICG *vs* TB (*n*=4; Figure 1).

Quality Assessment of the Included Studies For the Newcastle-Ottawa Scale, 18 retrospective studies had scores ≥6 and 4 retrospective studies had 5 (Table 2). For RCT studies, bias could be considered low in six RCTs (Figure 2).

Network Plots Figure 3 presents the corresponding structure of network, where 5 treatments formed 10 different pairs of comparisons. The network plots whose nodes were weighted corresponding to the sample size that showed direct comparison of different dyes, such as BBG, ICG, TB, TA, and no dye. The number of included trials for specific direct comparison decides the thickness of straight lines. The line between the two treatments indicates evidence of direct comparison. Figure 3A shows the network relationship of the IMH closure rate. The line indicates that there were 8 direct comparisons and the remaining 2 lines had no direct comparison. Figure 3B shows the improvement rate of visual acuity after ILM peeling. The connection indicates that there were 6 direct comparisons and the remaining 4 had no direct comparison evidence. Figure 3C shows the result of BCVA in postoperative patients. The connection indicates that there were 5 direct comparisons, and the remaining 4 had no direct comparison evidence.

Forest Plots of the Pairwise and Network Meta-Analysis Forest plot of the pairwise Meta-analyses shows the result of the MH closure of dyes had no significant difference. The result of improved visual acuity shows that ILM peeling BBG was better than ICG (OR 0.12, 95%CI 0.02-0.66, heterogeneity I^2=0). The results of BCVA after ILM peeling with TA and BBG were better than ICG (OR 0.08, 95%CI 0.02-0.14, heterogeneity I^2=0, P=0.536; OR 0.10, 95%CI 0.02-0.17, heterogeneity I^2=53.5%, P=0.072; Figure 4).

Figure 5 presents the results of network Meta-analysis. It shows the result of MH closure rate after ILM peeling. For no dye *vs* BBG, the rate of BBG assisted IMH closure was higher than no dye, significantly (OR: 0.36, 95%CI: 0.14-0.92). Other comparisons was no statistical significance. Figure 5 B shows the result of the rate of improved visual acuity after ILM peeling. For ICG *vs* BBG, TB *vs* ICG, TB *vs* TA, and no dye *vs* TB, the difference was statistically significant (OR 0.19, 95%CI 0.04-0.9; OR 4.57, 95%CI 1.46-14.32; OR 3.53, 95%CI 1.03-12.13; OR 0.29, 95%CI 0.09-0.96, respectively). It shows that the improvement rate of visual acuity after using BBG was higher than ILM peeling with ICG. The improvement rate of visual acuity of TB was higher than ILM peeling with ICG, TA, and no dye (Figure 5B, Table 3). The difference of BCVA after surgery was not statistically significant (Figure 5C, Table 3).

Ranking Probability of Therapeutic Effects Figure 6 shows the ranking probability of each treatment. The larger the area under the curve was the better treatment effect. Figure 6A shows the rate of MH closure after ILM peeling. The area under the BBG group was the largest, the effect of TB group was the second, and the TA group was the third. The rate of MH closure after ILM peeling with no dye was the worst. Figure 6B shows the rate of improvement of visual acuity. The effect of ILM peeling with BBG group was the first and the effect of TB group was the second. The effect was similar between TA and the no dye group which were the third, and the effect of the ICG group was the worst. Figure 6C shows the result of postoperative BCVA, which was different from A and B. Therefore, Figure 6C shows the larger area under the curve, the larger logMAR value was the worse treatment effect. The result of treatment effect after ILM peeling with no dye was similar to the BBG and TA groups, which were better than the ICG group.

Table 1 Baseline characteristics of the included studies

Study	Trial type	No. of eyes	Age (y)	Gender (M/F)	Treatment group	Preoperative BCVA	Follow-up months	MH stage
Shukla, 2011[26]	Retrospective	50 (15:20:15)	59.5±7.3; 58.8±7.7; 58.7±7.9	24/26	BBG 0.5 mg/mL TB 0.15%; ICG 1.25 mg/mL	0.2±0.13; 0.19±0.09; 0.18±0.08	6	s3-s4
Christensen, 2009[27]	Randomized	77 (34:18)	66.9/66.6	8:27/9:9	ICG 0.05%; TB 0.15%	50.5±5.9; 49.9±6.5	12	s2-s3
Bellerive, 2013[28]	Randomized	25 (11:14)	64.5±9.4; 65.4±4.9	5:6/3:11	ICG 2.5 mg/mL; TB 0.06%	38.9±8.5; 39.8±5	12	s2-s4
Lee, 2005[29]	Retrospective	37 (19:18)	70.7/68.6	NA	ICG 0.05%-0.5%; TB 0.15%	0.91/0.85	>6	s2-s4
Beutel, 2007[30]	Randomized	40 (19:19)	67.2±4.7; 69.3±5.9	7:13/9:11	ICG 0.05%; TB 0.15%	20/40; 20/50	6	s2-s4
Baba, 2012[31]	Retrospective	73 (28:35)	65.7±7.3; 67.1±4.8	9:19/17:18	ICG 1.25 mg/mL; BBG 0.25 mg/mL	0.8±0.3; 0.8±0.3	6	s2-s4
Williamson, 2014[32]	Retrospective	318 (209:109)	68.9	107/211	ICG 0.5 mg/mL; BBG; NA	0.97±0.45	6	s2-s4
Fukuda, 2011[33]	Retrospective	53 (22:31)	68/67	12:10/14:17	ICG 1.25 mg/mL; BBG 0.25 mg/mL	0.59±0.27; 0.61±0.29	6	s2-s4
Horio, 2004[34]	Randomized	40 (20:20)	64.7±6.9; 63.5±6.9	7:12/5:15	ICG 0.125%; no dye	0.92±0.25; 0.92±0.24	>12	s2-s4
Ando, 2004[35]	Retrospective	97 (28:21)	64.5/65.3	8:20/7:14	ICG 0.5%; no dye	0.77±0.53; 0.98±0.43	>12	s2-s4
Nakamura, 2009[36]	Retrospective	75 (16:38)	64.5±1.4; 64.5±0.8	6:10/12:26	ICG 0.25%; no dye	0.81±0.07; 0.82±0.05	>12	s2-s4
Shiono, 2013[37]	Retrospective	34 (19:15)	66.3±9.3; 66.3±9.3	NA	ICG 2.5 mg/mL; no dye	0.77±0.34; 0.65±0.4	6	s2-s4
Ferencz, 2006[38]	Retrospective	30 (21:9)	65.7±5.8; 70.0±4.9	7:14/2:7	ICG 0.125%; no dye	0.83±0.27; 0.89±0.23	>6	s2-s4
Kumagai, 2006[39]	Retrospective	190 (96/94)	65.3±7.3; 65.3±6.7	33:63/28:66	ICG 0.1%; no dye	0.7±0.34; 0.78±0.33	>12	s2-s4
Schaal, 2009[40]	Retrospective	240 (90:66)	69/63	NA	ICG 0.5%; no dye	20/60-20/150	>12	s2-s4
Lochhead, 2004[41]	Retrospective	68 (34:34)	69.9/67.5	10:24/10:24	ICG 0.5%; no dye	1.00/0.99	<12	s3-s4
Nagai, 2007[42]	Retrospective	53 (35:18)	65.3±6.6; 64.3±5.5	8:27/6:12	ICG NA; no dye	0.83±0.27; 0.89±0.23	>12	s2-s4
Mochizuki, 2014[43]	Retrospective	97 (61:15:21)	65.9±8.6; 68.6±7.4; 63.2±7.6	16/32	ICG 2.5 mg/mL; BBG 0.025% TA	NA	12	s2-s4
Karacorlu, 2005[44]	Retrospective	30 (15:15)	64.6/64.5	8:7/9:6	ICG 0.05%; TA	NA	>6	s3-s4
Nomoto, 2008[45]	Retrospective	67 (27:40)	65.8±7.7; 61.7±9.3	5:22/14:26	ICG 0.25%; TA	0.81±0.4; 0.78±0.3	12	s2-s4
Tsipursky, 2013[46]	Retrospective	430 (119:97:209)	68.7±8.0; 67.5±8.0; 67.4±8.1	NA	ICG 0.125%; TA 40 mg/mL; no dye	0.86±0.38; 0.78±0.31 0.86±0.63	12	NA
Machida, 2014[47]	Randomized	48 (16:16:16)	64.6 ±7.62	16/32	ICG 2.5 mg/mL; BBG 0.25mg/mL; TA	NA	12	NA
Caramoy, 2012[48]	Randomized	56 (15:11)	NA	NA	ICG 0.5 mg/mL; BBG 0.25 mg/mL	0.5±0.08; 0.55±0.1	12	NA
Fu, 2014[49]	Retrospective	83 (41:42)	56.74±3.62	9:33/7:34	BBG 0.25 mg/mL; no dye	0.10±0.052; 0.13±0.046	6	s2-s4
Kumar, 2011[50]	Retrospective	94 (47:47)	60.8±3.71; 60.3±3.92	NA	BBG 0.05%; TA	1.15±0.38	>12	s2-s4
Selton, 2012[51]	Retrospective	40 (20:20)	69.2±7.8; 66.4±7.0	NA	BBG NA; no dye	NA	6	s2-s4
Rüfer, 2007[52]	Retrospective	61 (36:25)	NA	15:46	ICG NA; no dye	0.71±0.30	12	s2-s4
Meyer, 2008[53]	Retrospective	91 (46:45)	NA	NA	ICG NA; no dye	NA	19	s2-s4
Brasil, 2006[54]	Retrospective	142 (81:61)	64.46±8.45; 65.04±7.26	17/64; 17/44	ICG 2.5mg/mL; no dye	0.12±0.15; 0.18±0.18	NA	s2-s4

BCVA: Best corrected visual acuity; NA: Not available; ICG: Indocyanine green; BBG: Brilliant blue G; TB: Trypan blue; TA: Triamcinolone acetonide.

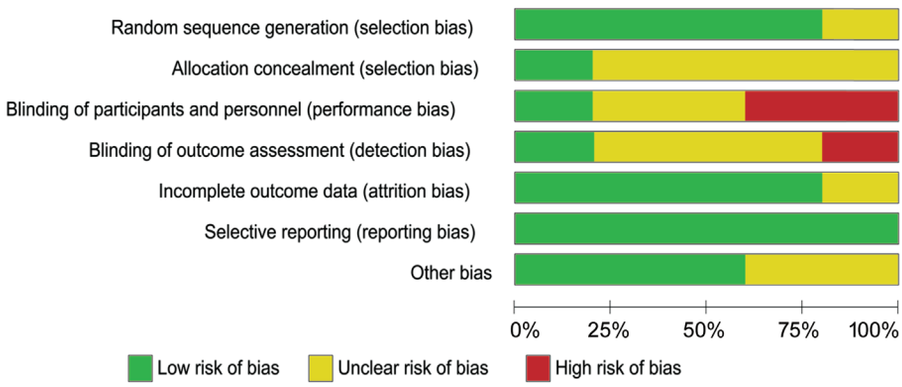

Figure 2 Bias assessment of the six randomized clinical trial studies were performed by "Cochrane Collaboration's tool for assessing the risk of bias".

Table 2 Quality assessment of the retrospective studies

Study	Country	Study quality (NOS Scale)			
		Selection	Comparability	Expose	Total score
Shukla, 2011[26]	India	4	2	1	7
Lee, 2005[29]	New Zealand	3	2	1	6
Baba, 2012[31]	Japan	4	1	1	6
Williamson, 2014[32]	UK	4	2	1	7
Fukuda, 2011[33]	Japan	4	1	1	6
Ando, 2004[35]	Japan	3	2	2	7
Nakamura, 2009[36]	Japan	3	2	2	7
Shiono, 2013[37]	Japan	4	1	1	6
Ferencz, 2006[38]	Hungary	3	2	1	6
Kumagai, 2006[39]	Japan	3	1	1	5
Schaal, 2009[40]	US	3	1	2	6
Lochhead, 2004[41]	UK	4	1	1	6
Nagai, 2007[42]	Japan	3	2	1	6
Mochizuki, 2014[43]	Japan	3	2	1	6
Karacorlu, 2005[44]	Turkey	3	1	1	5
Nomoto, 2008[45]	Japan	3	1	2	6
Tsipursky, 2013[46]	US	4	1	2	7
Fu, 2014[49]	China	3	2	1	6
Kumar, 2011[50]	India	4	1	1	6
Selton, 2012[51]	France	3	2	1	6
Brasil, 2006[54]	Brazil	3	2	1	6
Rüfer, 2007[52]	Germany	3	1	1	5
Meyer, 2008[53]	Germany	3	1	1	5

NOS Scale: Newcastle-Ottowa Scale.

Inconsistent Test Results We did an inconsistency test for the closure of the IMH, forming 5 triangular closed loops, namely BBG-ICG-TA, BBG-ICG-no dye, BBG-TA-no dye, BBG-ICG-TB, and ICG-TA-no dye. The result of the inconsistency test showed that the impact factor (IF) was in the range of 0.12-0.95 and 95%CI was in the range of 0.00-3.92. Inconsistent test results of postoperative visual acuity improvement showed two closed loops, BBG-ICG-TB and ICG-TA-no dye. The results of the IF were in the range of 0.09-1.78 and 95%CI was in the range of 0.00-4.69. The results of BCVA showed two triangular closed loops, BBG-ICG-TA and ICG-TA-no dye. The results of the IF were in the range of 0.17-0.27 and 95%CI was in the range of 0.00-2.30.

Funnel Plot and Publication Bias The different points in the funnel plot represented a direct comparison between the five treatments, and the number of identical color points

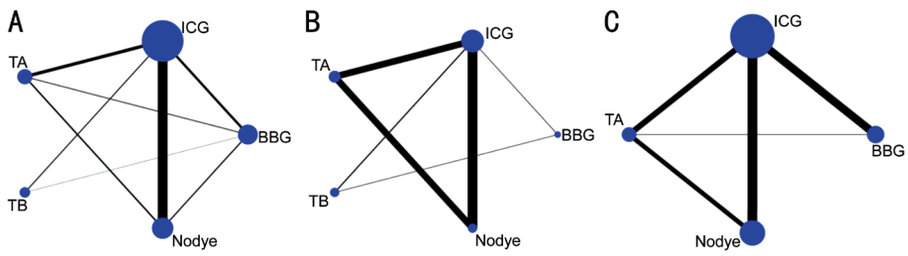

Figure 3 Network structure for different treatments was included in the network Meta-analysis A: Primary IMH closure rate; B: Rate of improved visual acuity; C: Postoperative visual acuity (logMAR). ICG: Indocyanine green; BBG: Brilliant blue G; TB: Trypan blue; TA: Triamcinolone acetonide; logMAR: Logarithm of the minimal angle of resolution.

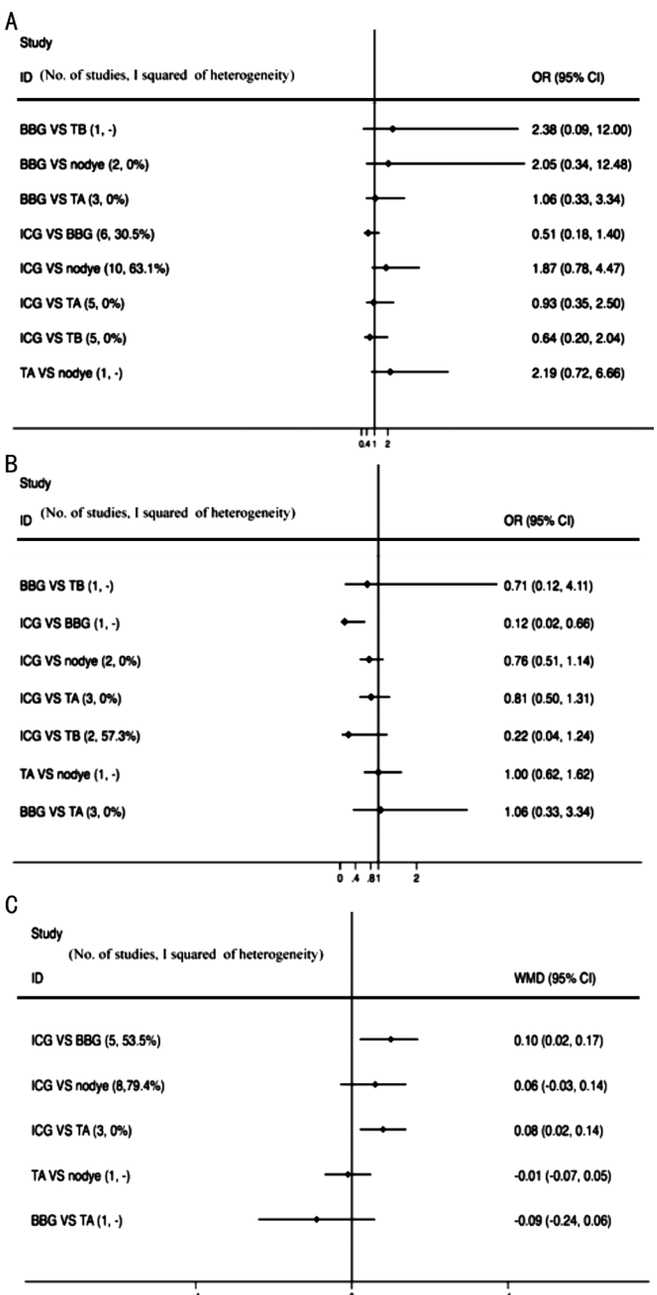

Figure 4 Forest plot of results of the pairwise Meta-analysis A: Primary MH closure rate; B: Rate of improved visual acuity; C: Postoperative visual acuity (logMAR). WMD: Weighted mean difference.

represented the same pairwise direct comparison from the original study. Comparison adjusted funnel plots were roughly symmetrical for the outcome Figure 7, it showed that there was a small possibility of small sample size effects or publication bias.

DISCUSSION

This network Meta-analysis study was mainly for patients with IMH, to analyze and summarize the postoperative primary MH closure rate and the rate of vision improvement and BCVA for ILM peeling with ICG, BBG, TB, TA, and no dye. It included 2514 eyes from 29 studies. Forest plots showed the postoperative IMH closure effect of BBG was better than no dye and it was statistically significant. The improvement rate of visual acuity after using BBG was significantly higher than the ICG group, and the TB group was significantly higher than the ICG, TA, and no dye groups. The differences between groups were not statistically significant. Ranking probability of therapeutic effects showed that for the rate of IMH closure, the rank from the best to the worse treatment was BBG, TB, TA, ICG, and no dye. The rank of the rate of improvement for visual acuity from the best to the worse treatment was BBG, TB, no dye, TA, and ICG. The results for visual acuity after ILM peeling with no dye were similar to the BBG and TA groups, but better than the ICG group. Comparison adjusted funnel plots were roughly symmetrical and showed that there was only a small possibility of small sample size effects or publication bias.

In 1996, Yooh *et al*[55] performed ultrastructural analysis of ILM tissue exfoliated during MH surgery, which suggested that ILM tissue became the only pulling force in stage 4 MH with posterior vitreous detachment or after posterior vitreous detachment[31]. ILM acted as a proliferating scaffold for various cellular components, such as RPE cells[56]. ILM peeling released tangential traction around the macula, which could cause centripetal motion of the tissue to close the MH[57].

In 2002, TB was firstly used in vitreoretinal surgery[58]. TB is a high molecular weight reactive dye with a weight of 960.8, which makes the lens anterior capsule, preretinal membrane[59-60], and ILM more visible and able to form a high affinity with the retinal epithelium, improving the surgical effect[61]. Brazitikos *et al*[62] observed 35 eyes of intraoperative

A: Primary MH closure rate

nodye	2.47 (0.64,9.47)	2.08 (0.74,5.81)	1.69 (0.91,3.13)	**2.82 (1.08,7.32)**
0.41 (0.11,1.56)	**TB**	0.84 (0.18,3.85)	0.69 (0.21,2.28)	1.14 (0.27,4.78)
0.48 (0.17,1.35)	1.19 (0.26,5.44)	**TA**	0.82 (0.32,2.11)	1.36 (0.48,3.83)
0.59 (0.32,1.09)	1.46 (0.44,4.84)	1.23 (0.47,3.17)	**ICG**	1.66 (0.72,3.82)
0.36 (0.14,0.92)	0.88 (0.21,3.67)	0.74 (0.26,2.08)	0.60 (0.26,1.38)	**BBG**

B: Rate of improved visual acuity

nodye	**3.47 (1.04,11.58)**	0.98 (0.62,1.55)	0.76 (0.51,1.12)	4.09 (0.80,20.82)
0.29 (0.09,0.96)	**TB**	**0.28 (0.08,0.97)**	**0.22 (0.07,0.69)**	1.18 (0.23,6.05)
1.02 (0.65,1.60)	**3.53 (1.03,12.13)**	**TA**	0.77 (0.48,1.23)	4.17 (0.80,21.65)
1.32 (0.90,1.94)	**4.57 (1.46,14.32)**	1.29 (0.81,2.07)	**ICG**	**5.39 (1.11,26.20)**
0.24 (0.05,1.24)	0.85 (0.17,4.34)	0.24 (0.05,1.25)	**0.19 (0.04,0.90)**	**BBG**

C: Postoperative visual acuity (logMAR)

nodye	0.03 (-0.75,0.82)	0.35 (-0.11,0.80)	0.01 (-0.73,0.76)
-0.03 (-0.82,0.75)	**TA**	0.31 (-0.39,1.02)	-0.02 (-0.88,0.84)
-0.35 (-0.80,0.11)	-0.31 (-1.02,0.39)	**ICG**	-0.33 (-0.93,0.26)
-0.01 (-0.76,0.73)	0.02 (-0.84,0.88)	0.33 (-0.26,0.93)	**BBG**

Figure 5 Odds relative with 95%CI of the network Meta-analysis for different dyes in the surgery of IMH Different dyes in the middle block (in blue) divide the graph into upper and lower triangles, for the lower triangle, the efficacy estimate is the ratio of the column interventions to the row interventions. A, B: In case that 95%CI does not include 1, if OR>1, it favors the column interventions, in contrast, if OR<1, it favors the row interventions. C: It is different from A and B, in case that the 95%CI does not include 0, if OR<0, it favors the column interventions, in contrast, if OR>0, it favors the row interventions. The upper triangle is symmetrical to the lower triangle. The efficacy estimate is the ratio of the row interventions to the column interventions. The results are mutually reciprocal. Boxes highlighted show significant difference. OR: Odds relative; CI: Credible intervals; IMH: Idiopathic macular hole; ICG: Indocyanine green; BBG: Brilliant blue G; TB: Trypan blue; TA: Triamcinolone acetonide; logMAR: Logarithm of the minimal angle of resolution.

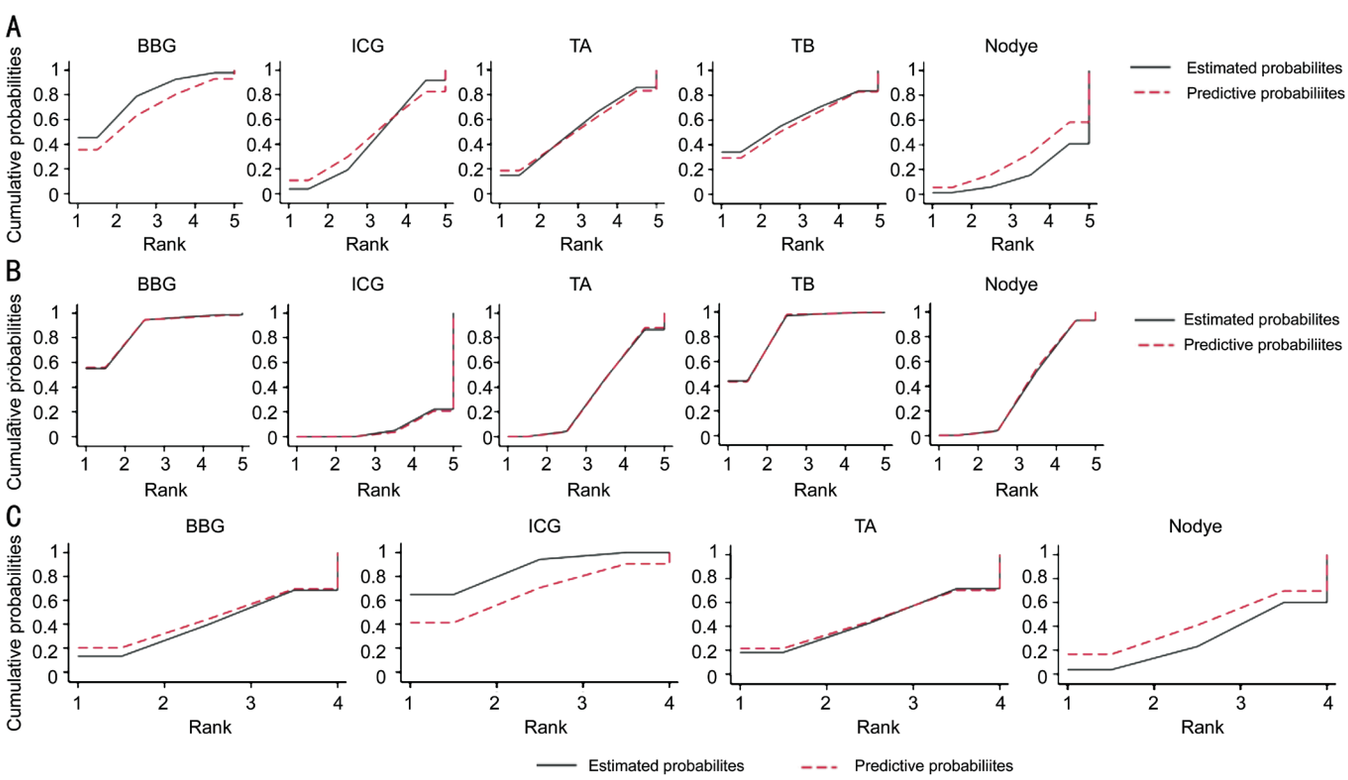

Figure 6 Ranking of therapeutic effects included in the network Meta-analysis A: Primary MH closure rate; B: Rate of improved visual acuity; C: Postoperative visual acuity (logMAR).

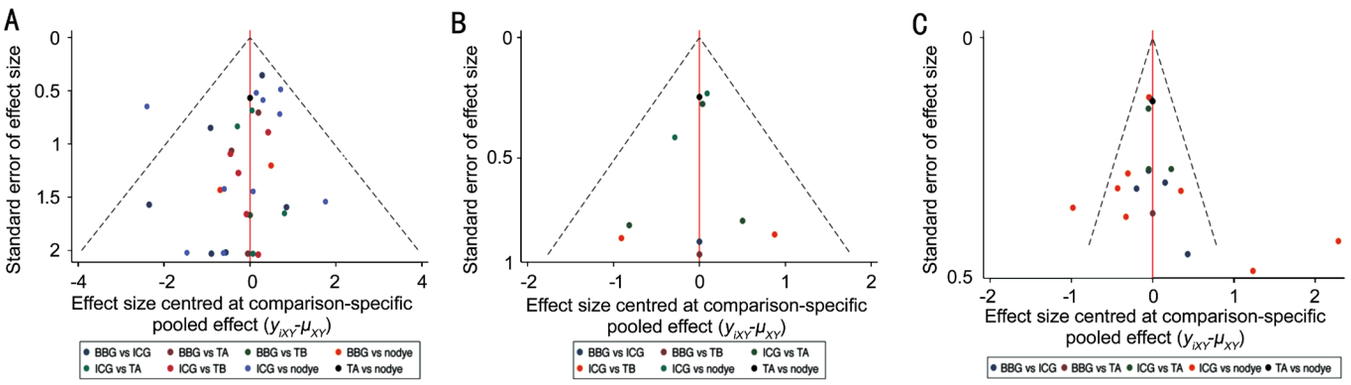

Figure 7 A comparison-adjusted funnel plot representing the same pairwise direct comparison from the original study A: Primary MH closure rate; B: Rate of improved visual acuity; C: Postoperative visual acuity (logMAR).

Table 3 Summary of main findings of pairwise and network-analysis

Parameters	Direct pairwise Meta-analysis				Network Meta-analysis
	No. of samples	OR/WMD (95%CI)	*P*	Heterogeneity I^2	OR/WMD (95%CI)
Primary MH closure rate					
IGG *vs* BBG	572	0.51 (0.18-1.40)	0.229	30.5%	0.6 (0.26-1.38)
TA *vs* BBG	162	1.06 (0.33-3.34)	0.623	0	0.74 (0.26-2.08)
TB *vs* BBG	35	2.38 (0.09-62.7)	-	100%	0.88 (0.21-3.67)
No dye *vs* BBG	12	2.05 (0.34-12.48)	0.526	0	0.36 (0.14-0.92)
TA *vs* ICG	427	0.93 (0.35-2.50)	0.833	0	1.23 (0.47-3.17)
TB *vs* ICG	187	0.64 (0.20-2.04)	0.912	0	1.46 (0.44-4.84)
No dye *vs* ICG	1171	1.87 (0.78-4.47)	0.008	63.1%	0.59 (0.32-1.09)
TB *vs* TA	-	-	-	-	1.19 (0.26-5.44)
No dye *vs* TA	306	2.19 (0.72-6.66)	-	0	0.48 (0.17-1.35)
No dye *vs* TB	-	-	-	-	0.41 (0.11-1.56)
Rate of improved visual acuity					
IGG *vs* BBG	30	0.12 (0.02-0.66)	-	0	0.19 (0.04-0.90)
TA *vs* BBG	-	-	-	-	0.24 (0.05-1.25)
TB *vs* BBG	35	0.71 (0.12-4.11)	-	100%	0.85 (0.17-4.34)
No dye *vs* BBG	-	-	-	-	0.24 (0.05-1.24)
TA *vs* ICG	313	0.81 (0.50-1.31)	0.46	0	1.29 (0.81-2.07)
TB *vs* ICG	73	0.22 (0.04-1.24)	0.126	57.3%	4.57 (1.46-14.32)
No dye *vs* ICG	518	0.76 (0.51-1.14)	0.428	0	1.32 (0.09-1.94)
TB *vs* TA	-	-	-	-	3.53 (1.03-12.13)
No dye *vs* TA	306	1.00 (0.62-1.62)	-	0	1.02 (0.65-1.60)
No dye *vs* TB	-	-	-	-	0.29 (0.09-0.96)
Postoperative visual acuity (logMAR)					
IGG *vs* BBG	531	0.10 (0.02-0.17)	0.072	53.5%	0.33 (-0.28-0.95)
TA *vs* BBG	36	-0.09 (-0.24-0.06)	-	100%	0.01 (-0.88-0.89)
No dye *vs* BBG	-	-	-	-	-0.08 (-0.86-0.70)
TA *vs* ICG	365	0.08 (0.02-0.14)	0.536	0	-0.33 (-1.05-0.40)
No dye *vs* ICG	648	0.06 (-0.03-0.14)	0.00	79.4%	-0.41 (-0.91-0.08)
No dye *vs* TA	306	-0.01 (-0.07-0.05)	-	100%	-0.09 (-0.91-0.73)

OR: Odds ratio; WMD: Weighted mean difference.

TB-assisted ILM peeling, and showed that ILM peeling with TB did not cause any changes in the thickness of the retinal nerve fiber layer at six months after surgery. TA is a kind of water-insoluble glucocorticoid[63]. As an anti-inflammatory drug[64-65], it has been used for the treatment of various ophthalmic diseases[61], and also for staining the posterior vitreous membrane and ILM. The deposition of TA particles on the surface of the retina acts as a "stain" because there are no white spots on the ILM, allowing the surgeon to see where the ILM is peeling[45]. Similarly, studies have found that TA has toxic effects on the RPE and retinal ganglion cells[66]. Furthermore, some studies have reported that ICG is more likely to cause a decrease in retinal function than other dyes such as TB and TA[67].

Several studies proved that BBG has less toxic effects on the retina than other dyes such as TB, ICG, and TA, the results of these studies were consistent with the current network meta-analysis[67]. Some experiments demonstrated that BBG had less retinal toxicity than ICG and other dyes[63]. Ejstrup *et al*[68] injected BBG, ICG, and TA into the eyes of pigs and found that the toxicity of ICG on the retina was much higher than that of BBG and TA. Creuzot-Garcher *et al*[69] injected BBG, TB, ICG, and TA into the eyes of rats. After one month it was observed that the electroretinogram of the rats had returned to normal in the BBG, TB, and TA groups. However, the rats being injected with ICG took a longer time to recover. Ueno *et al*[70] compared the toxicity of BBG, TB, and ICG, and found that BBG had the lowest toxicity on the retina, with the toxicity of BBG being lower than TB and the toxicity of TB being lower than ICG. The results of several clinical studies differed from our findings. Shukla *et al*[26] compared surgical outcomes with three dyes, BBG, TB, and ICG, six months postoperatively, visual improvement occurred in 80%, 85%, and 33% eyes (P=0.005). However, the results of our study found that the effect of BBG was better than the TB group, and the effect of TB was better than the ICG group. Nomoto *et al*[45] reported the results of MH surgery with TA-assisted ILM peeling and ICG-assisted ILM peeling. The rate of MH closure was similar with 98% for the TA group and 100% for the ICG group. The results of improved BCVA in the TA group were better than the ICG group, and the results of BCVA with 20/40 or better in the TA group were better than 59% in the ICG group, which was similar to our findings. Previous results of meta-analysis were also consistent with the results of this network meta-analysis. In 2016, Azuma *et al*[67] performed a systematic review showing that the BCVA in the BBG group was better than the ICG group and the BBG-free group. In 2012, another meta-analysis reported that VA improvement was less in the ICG group. The toxicity of visual field defects was greater in the ICG group compared with the non-ICG group[71]. However, these traditional meta-analyses only compared two therapeutic measures, and do not accurately compare multiple therapeutic measures.

Of the 29 studies included, the relevant qualified RCTs were numbered, the sample size was not sufficient and the RCTs did not clearly describe clearly how masking and allocation were completed. The other 24 studies were retrospective studies. The differences in the concentrations of BBG, ICG, and TB, and the time of face down position after surgery may also affect the results. There were few related studies on TB, and there was insufficient data in this meta-analysis. Some large samples randomized controlled and double-blind trials would be the best choice for inclusion in network meta-analysis, but there were few high-quality studies on topics related to this research. Overall, some more high quality RCTs with a longer duration and more comprehensive endpoints should be carried out in the future.

In conclusion, the results showed that the rate of MH closure after ILM peeling with dyes was better than without dyes. The dye with the highest safety was BBG, and TB was second, followed by TA which was better than ICG. This network meta-analysis systematically and objectively evaluated the efficacy of ICG, BBG, TB, TA, and no dye-assisted ILM peeling in the treatment of IMH. It allowed clear and comprehensive understanding of these dyes, which was beneficial in the selection of the best dye for ILM peeling of IMH.

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