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# Comparison of indocyanine green and brilliant blue G to assist internal limiting membrane peeling during macular hole surgery: a systematic review and meta – analysis

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## 对比吲哚青绿和亮蓝辅助内界膜剥除治疗黄斑 裂孔疗效的 Meta 分析

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## 摘要

**目的**:对比术中应用吲哚青绿与亮蓝辅助内界膜剥除对特 发性黄斑裂孔术后临床疗效的影响。

方法:搜集世界范围内应用吲哚青绿和亮蓝辅助内界膜剥除治疗特发性黄斑裂孔的临床对照试验的英文及中文文献。计算机检索 PubMed, Ovid, ScineceDirect, NGC, EBSCO, EMBASE, CNKI, , CBM 数据库。由两位系统评价员做独立文献筛查、质量评价和资料提取,并交叉核对,不同意见时经过讨论或请第三者裁决。使用统计软件 Rev Man 5.3 完成 Meta 分析。

结果:经筛选最后纳入7篇文献,均是以应用吲哚青绿对 比亮蓝辅助内界膜剥除治疗特发性黄斑裂孔的临床对照 试验,包括受试患者598例,通过比较术后3个主要临床 指标:最佳矫正视力,裂孔闭合率和术后并发症,发现亮蓝 辅助内界膜剥除组的术后6mo最佳矫正视力高于吲哚青 绿组,差别有统计学意义[Z=2.10(P=0.04),OR=0.10, 95% CI(0.01,0.19)];在术后裂孔闭合率和并发症方 面,两组比较无明显差别(P>0.05)。

结论:亮蓝辅助内界膜剥除治疗特发性黄斑裂孔术后短期 内视力恢复快,优于吲哚青绿,是较理想的内界膜染色剂。 建议进行大样本、长期随访的高质量临床试验,提供更佳 的循证医学证据。

关键词:吲哚青绿;亮蓝;特发性黄斑裂孔;内界膜剥除; Meta分析

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#### Abstract

• AIM: To evaluate the outcomes of indocyanine green compared with brilliant blue G used for internal limiting membrane (ILM) peeling in macular hole surgery.

• METHODS: All studies about indocyanine green compared with brilliant blue G for assisting internal limiting membrane peeling during macular hole surgery all over the world were searched. PubMed, Ovid, ScineceDirect, NGC, EBSCO, EMBASE, CNKI, CBM were searched. Two reviewers independently screened the studies for eligibility, evaluated the quality and extracted the data from the eligible studies, with confirmation by cross - checking. Divergence of opinion was settled by discussion or consulted by the expert. Meta-analysis was processed by Rev Man 5.3.

• RESULTS: Seven trials on indocyanine green compared with brilliant blue G for assisting internal limiting membrane peeling during macular hole surgery involving 598 cases met the inclusion criteria in meta-analysis. The baseline of patients' characteristics were comparable in all studies. By comparing the three common criteria, including best corrected visual acuity (BCVA), macular hole closure rate and postoperative complications, we found that brilliant blue G was better than indocyanine green on improving best corrected visual acuity at 6mo postoperatively [Z=2.10(P=0.04), OR=0.10, 95% CI(0.)]01, 0. 19)]. While there was no statistical difference between two groups on macular hole closure rate Z=0.69 (P=0.49), OR = 0.95, 95% CI (0.82, 1.10)]. And there were no statistical differences in term of postoperative complications between two groups(P > 0.05).

• CONCLUSION: The available evidence indicates that the short - term recovery of best corrected visual acuity is significantly better in brilliant blue G (BBG) group than in indocyanine green (ICG) group, especially at 6mo after surgery. The long - term prognosis of BCVA which one

study only reported need further study. There were no significant differences on macular hole closure rate and adverse events between two groups. The results indicate that BBG is preferable to ICG for use during macular hole surgery.

• KEYWORDS: indocyanine green; brilliant blue G; macular hole; internal limiting membrane peeling; metaanalysis

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#### INTRODUCTION

ince a report that the macular hole closure rate was improved by staining the internal limiting membrane (ILM) with indocyanine green (ICG) for better visual identification in macular hole surgery<sup>[1-2]</sup>, several dyes have been widely used as vital stains to make the ILM more visible<sup>[3-4]</sup>. Because ICG is potentially toxic to retina in high concentrations<sup>[5]</sup> and visual field defects have also been found after surgery using ICG<sup>[6]</sup>. Brilliant blue G (BBG) has emerged as an alternative dye which was later found to be more effective in staining the ILM<sup>[7]</sup>. A few studies<sup>[8-14]</sup> have ever compared the microstructure and function of eyes with macular hole after ILM peeling using different dyes. The toxicity and safety profiles of the dyes have been investigated to determine which dye is the safest. However, there are no exact conclusions of which one of them is preferred in the surgery of macular hole. We performed a meta-analysis to compare the effect of indocynine green versus brilliant blue G during macular hole surgery.

#### MATERIALS AND METHODS

Eight kinds of relevant databases, including PubMed (1966-2016), Ovid (1984-2016), ScineceDirect (1990-2016), NGC (Guideline Index) (1998 - 2016), EBSCO (1975 -2016), EMBASE (1984 - 2016), the Chinese biological medical (CBM) literature on CD-ROM database (1978-2016), China National Knowledge Infrastructure (CNKI) (1995-2016) and Cochrane Central Register of Controlled Trials, were searched. We performed computerized literature searches for relevant available articles published through Jan. 2016. The search included studies published both in the English and Chinese language. Searches comprised a combination of the following key words "indocyanine green", "brilliant blue G", "macular hole", and "internal limiting membrane peeling". Inclusion criteria comprised: 1) randomized control trials (RCTs), or case control studies; 2) the use of ICG or BBG for internal limiting membrane peel; 3) studies containing sufficient information on BCVA, macular hole closure rate or postoperative complications. Exclusion criteria were: 1) studies with insufficient data; 2)



Figure 1 Flow diagram of the study selection formeta analysis.

non – controlled study; 3) other adjuvants used for ILM peeling; 4) non-human experiments, 5) short-term (less than three months) studies.

**Document Screeningand Information Extracted** The screening was strictly in accordance with inclusion and exclusion criteria. Two reviewers independently screened the studies for eligibility, evaluated the quality and extracted the data from the eligible studies, with confirmation by cross – checking. Divergences of opinion were settled by discussion or consulted by the expert (Jia YD). The lack of information through communicating with the author would be added. Data from the literature included basic information, the patient baseline, interventions, the outcome indicators, the use of statistical methods and results, the author's conclusions, and so on.

Qualitative Assessment Because randomized control trials and non-RCTs were included in this meta-analysis, the Downs and Black (D&B) quality method, which is appropriate for RCTs and non-RCTs, was used to assess the qualities of the studies<sup>[15]</sup>. The D&B Scale comprises 27 criteria that evaluate the reporting, external validity, internal validity, selection biases, and power of the studies. Based on quality score, each study is grouped into one of four levels: 26-28, 20-25, 15-19, and  $\leq 14^{[16]}$ . Higher scores indicate higher quality. Because few studies reported the study's power, this parameter was omitted. Thus, the quality of each study was considered excellent (21-23), good (15-20), fair (10 - 14), and poor  $(\leq 9)$  by the two independent reviewers, and disagreements were resolved through discussion with a third reviewer (Zhang LL).

**Statistical Methods** The statistical software Rev Man 5.3 was used for meta – analysis, recommended by Cochrane Collaboration. For continuous variables, using the same measurement unit, outcomes were analyzed by weighted mean difference (WMD), if not by standardized mean difference (SMD), for dichotomous variables by odds ratio (OR), risk ratio (RR) or risk difference (RD), and 95% confidence interval (CI) should be showed. Chi–square test ( $\alpha = 0.1$ ) was used for heterogeneity test. If homogeneity was found, we used the fixed effect model. If heterogeneity was found, we analyzed the cause of heterogeneity, or proceed to sub–group analysis or sensitivity analysis. Data which could not be

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### Figure 2 Forest plot from the meta-analysis of BCVA (LogMAR) comparing ICG with BBG at 3mo postoperatively.

	ICG				BBG			Mean Difference	Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year		IV, Rar	ndom, 9	5% CI	
Baba 2012	0.37	0.27	28	0.25	0.3	35	18.9%	0.12 [-0.02, 0.26]	2012			-		
Kadonosono 2013	0.18	0.3	21	0.18	0.1	19	19.5%	0.00 [-0.14, 0.14]	2013		-	-		
Mochizuki 2014	0.57	0.36	61	0.37	0.2	15	19.6%	0.20 [0.06, 0.34]	2014			-	-	
Machida 2014	0.23	0.16	16	0.26	0.24	16	18.9%	-0.03 [-0.17, 0.11]	2014		-			
Williamson 2014	0.71	0.53	209	0.52	0.43	109	23.0%	0.19 [0.08, 0.30]	2014			-	-	
Total (95% CI) Heterogeneity: Tau² =	0.01: Ch	i² = 10	335 ).09. df	= 4 (P =	= 0.04)	194 :  ² = 60	<b>100.0%</b>	0.10 [0.01, 0.19]	-			•	► 	
	eterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 10.09, df = 4 (P = 0.04); l <sup>2</sup> = 60% est for overall effect: Z = 2.10 (P = 0.04) ICG_BBG								0.5					

#### Figure 3 Forest plot from the meta-analysis of BCVA (LogMAR) comparing ICG with BBG at 6mo postoperatively.

	ICG			BBG				Mean Difference		Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI Y	Year	IV. Random, 95% Cl			
Machida 2014	0.21	0.16	16	0.26	0.22	16	50.2%	-0.05 [-0.18, 0.08] 2	2014				
Mochizuki 2014	0.44	0.35	60	0.33	0.2	15	49.8%	0.11 [-0.02, 0.24] 2	2014				
Total (95% CI)			76			31	100.0%	0.03 [ 0.13, 0.19]		+			
Heterogeneity: Tau² = Test for overall effect:			-	-0.5 -0.25 0 0.25 0.5 ICG EBG									

Figure 4 Forest plot from the meta-analysis of BCVA (LogMAR) comparing ICG with BBG at 1y postoperatively.

incorporated into the meta-analysis adopted descriptive study. The results of meta-analysis were explained by forest plot. The potential publication bias was showed by funnel plot, and was assessed by Egger regression asymmetry test and Begg adjusted rank correlation test.

#### RESULTS

Literature Search and Results Filter Seven trials included two RCTs<sup>[8-9]</sup> and five case control trials<sup>[10-14]</sup>, involving a total of 598 eyes, of which 368 eyes underwent vitrectomy with internal limiting membrane peeling using indocyanine green and 230 eyes using BBG (Figure 1).

**Comparison on BCVA at 3mo postoperatively between two groups** The seven trials included in the study, of which two<sup>[13-14]</sup> didn't report BCVA at 3mo postoperatively, one<sup>[8]</sup> only reported retinal nerve fiber layer thickness after surgery. By ommiting the three trials, the remaining four trials<sup>[9-12]</sup> were included in the meta-analysis. Heterogeneity test: P =0.08, the random – effects model was adopted. The pooled estimate of mean difference (MD) was 0.05, and the 95% *CI* was (-0.04, 0.15). The result (Figure 2) suggested that although the average best corrected visual acuity was better in BBG group than in ICG group at 3mo after surgery, but the difference had no statistical significance (P=0.27). **Comparison on BCVA at 6mo postoperatively between two groups** Six trials<sup>[8-9,11-14]</sup> reported BCVA of ICG and BBG group at 6mo postoperatively. But BCVA in one trial<sup>[10]</sup> reported by Baba T was measured using a decimal visual acuity chart, didn't been convented to the logMAR units for statistical analysis, therefore a sub – group analysis was performed on other five trials. The pooled estimate of MD was 0.10, and the 95% *CI* was (0.01, 0.19). The result (Figure 3) suggested that the average BCVA was better in BBG group than in ICG group at 6mo after surgery, the difference had statistical significance (P = 0.04). The result of sub–group analysis was in agreement with that reported by Baba T.

**Comparison on BCVA at 1y postoperatively between two groups** Of the seven trials included in the study, only two<sup>[9,11]</sup> trials reported BCVA at 1y postoperatively. The pooled estimate of MD was 0.03, and the 95% *CI* was (-0.13, 0.19). The result (Figure 4) suggested that the average BCVA was not significantly different between the two groups at 1y after surgery (P=0.71). As the number of the trials had only two, this result had insufficient evidence which needed further study.

**Comparison on macular hole closure rate between two groups** Two<sup>[8,12]</sup> of the seven trials didn't report macular hole closure rate afer surgery, thus the remaining five trials



Figure 5 Forest plot from the meta-analysis of macular hole closure rate comparing ICG with BBG postoperatively.



Figure 6 Forest plot from the meta-analysis of adverse events comparing ICG with BBG postoperatively.

were included. The five trials<sup>[9-11,13-14]</sup> all reported the initial closure rate after surgery, one<sup>[11]</sup> of which reported the final closure rate also. The pooled estimate of relative risk (RR) was 0.95, and the 95% *CI* was (0.82, 1.10), Z=0.69, *P* = 0.49, (Figure 5). This suggested that between the ICG and BBG groups, the initial macular hole closure rates weren't significantly different.

Adverse Events Three trials<sup>[8-9,13]</sup> included in the literature didn't describe adverse events, and the remaining four trials described adverse events which included retinal detachment, reopening of the macular hole(MH), macular pucker, retinal tear, intraocular hypotension, intraocular hypertension and endophthalmitis. Mochizuki *et al*<sup>[11]</sup> reported that a retinal tear</sup>in the peripheral retina occurred in 2 eyes in BBG group intraoperatively, 11 eyes in ICG group, and reopening of the macular hole occurred in 1 eye in ICG group. Baba et  $al^{[10]}$ reported the MH was closed in all cases after the initial surgery in ICG group, and two eyes in BBG group required a second surgery. Shukla et  $al^{[14]}$  and Kadonosono et  $al^{[12]}$  both reported that none of the patients developed any intraoperative or postoperative complications. The four trials<sup>[10-12,14]</sup> were included in meta-analysis. Heterogeneity test: P=0.64, the fixed-effects model was adopted and the effect size for metaanalysis was RD. The pooled estimate of RD was 0, and the 95% CI was (-0.07, 0.07), Z = 0.08, P = 0.94 (Figure 6). The result suggested that compared with BBG group, ICG group had no difference in the incidence of adverse events.

**Comparison on retinal nerve fiber layer thickness between two groups** Only one trail<sup>[8]</sup> demonstrated that a transient increase of the retinal nerve fibre layer (RNFL) thickness was



Figure 7 Funnel plot of publication bias.

seen in the mean overall and sectoral thicknesses except for the nasal/inferior sector at 1 mo after surgery in two groups. Then, the thickness gradually decreased and returned to the baseline level in all sectors except for the nasal/inferior sector. The differences in the RNFL thickness between the two groups weren't significant for at least 12mo postoperatively.

**Publication Bias** The publication bias of the study reporting comparison on BCVA at 6mo postoperatively between two groups was shown in the funnel plot (Figure 7). There was no evidence of publication bias (Begg's test, P=0.142; Egger's test, P=0.433).

#### DISCUSSION

Vitrectomy combined with ILM peeling is the main method for the treatment of idiopathic macular hole (IMH). The application of dyes can improve the resolution of ILM in the operation<sup>[17]</sup>, so that ILM peeling become simple and convenient. ICG is a kind of water soluble dye, which can be combined with type IV collagen and glycoprotein closely. Type IV collagen is the main component of ILM, ICG can effectively dye the ILM pale green, make the border of ILM clear in macular hole surgery<sup>[18]</sup>. Kadonosono *et al*<sup>[12]</sup> reported that indocyanine green provided a significantly higher contrast ratio than BBG by performing a color contrast ratio analysis. We can get a better visibility of ILM when stained with ICG.

However, fundamental researches have found that ICG was toxic to the retinal pigment epithelial cells, ganglion cells and optic nerve<sup>[19]</sup>. ICG can not only make the ILM stained, but also penetrate the human retinal epithelium layer and pigment epithelium layer<sup>[20]</sup>. Cases of visual field defects after ILM staining with ICG were reported<sup>[6]</sup>. Although the intraocular toxicity of ICG has been recognized, but if the reasonable control of the concentration, osmotic pressure and exposure time, toxicity will be greatly reduced<sup>[21]</sup>. With the application of advanced surgical equipment and the improvement of surgical experience, the risk of retinal toxicity caused by ICG is greatly reduced. Therefore, ICG is still used in the treatment of IMH. But the toxicity of low concentration ICG on the retina is still inevitable. According to the data collected here, the short - term recovery of BCVA was significantly better in BBG group than in ICG group, especially at 6mo after surgery, as a consequence of the toxicity of ICG on retina which delayed the recovery of visual function.

Moreover, Notomi *et al*<sup>[22]</sup> reported that photoreceptor apoptosis could be attenuated by BBG, a pharmacologic P2RX7 antagonist that acts by blocking the interaction between extracellular ATP and P2RX7. Pharmacologic inhibition of P2RX7 has been reported to result possibly in neuroprotection of photoreceptors in cases of subretinal hemorrhage<sup>[23]</sup>. These previous reports supported the result of present study that the short-term prognosis of VA was better in the BBG group than in the ICG group.

Although Mochizuki *et al*<sup>[11]</sup> reported that the magnitude of the improvement at 2y after surgery was significantly better in the BBG group than in the ICG group, but this was a retrospective study , and sample size was relatively limited. As the number of the long-term trial had only one, this result had insufficient evidence to reach a conclusion.

In this study, the closure rates and intraoperative/ postoperative complications didn't differ between ICG group and BBG group. The diameter of MH and duration of symptoms had been listed as factors affecting the hole closure and visual outcomes<sup>[24-25]</sup>. The macular hole closure rate and adverse events weren't significantly related to the type of vital stain. It had also been reported that early inner segment/outer segment (IS/OS) junction restoration affected the prognosis of the postoperative visual acuity<sup>[17]</sup>. As a result, the use of ICG and BBG appeared to yield similar macular hole closure rate. In addition, only one study<sup>[8]</sup> demonstrated that the RNFL thickness was significantly increased at 1 mo after MH surgery but then decreased to the baseline thickness in two groups. The degree of change of the RNFL thickness was not significantly related to the type of vital stain.

In conclusion, this meta-analysis outcomes revealed that the short-term recovery of the BCVA was significantly better in the BBG group than in the ICG group, especially at 6mo after surgery (P < 0.05). The long-term prognosis of BCVA which one study only reported needed further study. There was no significant difference on the macular closure rates and adverse events between two groups (P > 0.05). Based on these findings, the results indicated that BBG was preferable to ICG for use during macular hole surgery, which provided clinical practice from evidence-based medicine.

Limitations of this study This meta-analysis only included two randomized control trial (RCT) studies, other five studies were comparative and retrospective case series. We didn't get unpublished study and sample size was small. The concentration of ICG and BBG, follow – up time and measurement indicators were not totally consistent, which brought many difficulties to data analysis. These factors may cause bias. Because of the existing restrictions, it is suggested that a multi center, large sample, randomized controlled clinical study is required to be conducted, which might provide more convincing evidence for clinical practice. **REFERENCES** 

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