Brilliant Blue G versus Triamcinolone-Assisted
ILM Peeling: A Comparative Evaluation in
Macular Hole Surgery

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ABSTRACT

Purpose: To evaluate and compare the anatomical and functional outcomes of internal limiting membrane (ILM) peeling in macular hole surgery (MHS) assisted by Brilliant Blue G (BBG) or triamcinolone acetonide (TA).

Study design: Retrospective, non-randomized, interventional single center study.

Methods: 51 eyes of 51 patients with idiopathic macular holes (≥ stage 2) who underwent MHS at our center were included. An OCT evaluation of hole status was followed by pars plana vitrectomy for each of these eyes. Those who underwent TA-assisted ILM peeling were considered as group 1 (n = 26) and those with BBG-assisted ILM peeling were considered as group 2 (n = 25). The primary outcome measures included anatomical hole closure, postoperative visual acuity and operative complications for either group.

Results: Anatomical hole closure was achieved in 46 eyes (90%). The mean postoperative follow-up duration was 15.9 ± 2.3 months. The mean preoperative visual acuity was 1.0702 ± 0.37 Log MAR (equivalent to 20/240) and the final acuity was 0.7122 ± 0.22 Log MAR (equivalent to 20/100) (p < 0.0001). There were no significant postoperative complications apart from progression of nuclear sclerosis in 8/35 phakic eyes. After adjusting for age and preoperative visual acuity, there was no significant difference between the two groups with respect to hole closure rate and postoperative visual acuity.

Conclusion: BBG-assisted ILM peeling offers an effective alternative to triamcinolone with the added advantage of marked enhancement of vitreoretinal interface contrast with comparable hole closure rates and visual outcomes.

Keywords: ILM Peel, BBG dye, Macular holes, Triamcinolone.

INTRODUCTION

Internal limiting membrane (ILM) peeling is an essential step in various vitreoretinal surgeries, including macular hole surgery.1-3 It relieves the tangential traction4 over the fovea, which contributes significantly to macular hole formation and thus improves the anatomical and functional outcomes of the surgery.1,2,5-7 However, the ILM being an optically clear structure at the vitreoretinal interface is difficult to identify. The procedure of ILM peeling may be facilitated and its safety improved by enhancing the contrast between ILM and the surrounding retina using vital dyes, a procedure called as chromovitrectomy.8 The challenge lies in selecting a dye which stains the ILM selectively without affecting the macular function. Various dyes which have been used for the same, including indocyanine green (ICG), trypan blue (TB), triamcinolone acetonide crystals (TA) and the recently introduced dye Brilliant Blue G (BBG).9-12

ICG and TB were among the first dyes used, however, there are conflicting reports of retinal toxicity, including apoptotic retinal cell death in vitro.13-16 The introduction of BBG, which has minimal toxicity and good staining properties, has provided vitreoretinal surgeons with the most versatile dye almost outdating ICG and TB. TA continues to remain a routinely used dependable and safe surgical adjuvant for ILM peeling. This study compared the anatomical and functional outcomes of ILM peeling in macular hole surgery assisted by a novel dye BBG or TA.

MATERIALS AND METHODS

We studied 51 patients in this retrospective, comparative, non-randomized, single center, interventional study. Patients with idiopathic macular holes of stage 2 or more, who underwent BBG or TA assisted ILM peeling, were included in the study. Patients with stage 1 macular hole, failed macular holes, post-traumatic macular holes and those who did not follow-up and were unable to maintain postoperative prone positioning were excluded from the study. Eyes with previous vitreous surgery or poor visual potential were also excluded. All patients
underwent a detailed ophthalmic and systemic evaluation. The best-corrected visual acuity was recorded using Snellen’s chart and converted to Log MAR equivalent. Optical coherence tomography (OCT) (Stratus OCT, version 4, Carl Zeiss Meditec, Inc) was done for all patients to determine the stage of macular hole. Patients with posterior subcapsular cataracts that could have affected the visualization during macular hole surgery underwent first stage phacoemulsification and vitrectomy was performed two weeks later. Those who underwent TA-assisted ILM peeling were considered as group 1 and those with BBG-assisted ILM peeling were considered as group 2.

The surgical technique consisted of three-port pars plana vitrectomy using 23-gauge Accurus Vitrectomy system (Alcon Labs Inc., Fort Worth, TX). In both groups, the core vitrectomy was performed followed by the placement of nondilute TA [(concentration 40 mg/mL; preservative free—Retilone (Cipla, Mumbai, India)] into the vitreous cavity. The posterior hyaloid was separated using the vitrector with aspiration. In group 1, the additional nondilute TA suspension was put and allowed to settle over the posterior pole to remove the ILM. This was followed by removing the free flowing particles using active aspiration. In group 2, after detaching the posterior hyaloid, the TA crystals were thoroughly washed out and 0.5 ml of 0.05% Brilliant Blue G dye (Ocublue Plus, Aurolab, Aravind Eye Care System, Madurai, India) was then injected in the fluid filled vitreous cavity and kept for 15 seconds. Excess dye was aspirated with the vitrector. In both the groups, the ILM peel, the foremost step for the success of MHS, 1,2,5-7 acts by relieving tangential traction4 caused by the presence of postoperative details included best-corrected visual acuity at most recent visit, status of macular hole, lens status, and any complications. Visual acuities were converted to logarithm of minimum angle of resolution (Log MAR) for statistical analysis. The data was organized in a Microsoft excel sheet and statistical analysis was performed for various parameters comparing the two groups using Stata 9.0 software. Alpha error was taken as 0.05, implying a p-value of 0.05 to be statistically significant. Analysis of covariance (ANCOVA) was applied for adjusting age and preoperative visual acuity.

RESULTS
Fifty-one eyes of 51 patients were included in the study of which 28 (55%) patients were female. 35 eyes were phakic, 16 eyes were pseudophakic. The mean follow-up was 15.9 ± 2.3 months. Five eyes (10%) had stage 2 macular hole, 27 eyes (53%) had stage 3 macular hole and 19 eyes (37%) had stage 4 macular hole. The mean overall preoperative visual acuity was 1.0702 ± 0.37 Log MAR (equivalent to 20/240). At the most recent postoperative visit, the mean best-corrected visual acuity improved to 0.7122 ± 0.22 Log MAR (equivalent to 20/100) which was statistically significant (p < 0.0001). Anatomic macular hole closure was achieved in 46 eyes (90%). There were no cases of postoperative retinal detachment or endophthalmitis. Though 15 patients required topical glaucoma medication for a short duration in the postoperative period, none required surgical intervention for glaucoma. Of the 35 phakic eyes, eight had visually significant progression of nuclear sclerosis during follow-up. All affected patients underwent successful phacoemulsification and IOL implantation, and the macular hole remained closed.

Both the groups were similar with respect to the baseline preoperative clinical characteristics, such as sex, duration of macular hole and stage of macular hole on OCT (Table 1). However, they differed with respect to age and preoperative visual acuity (Tables 1 and 2). Statistically significant difference was found in pre- and postoperative visual acuity in both the groups (p = 0.001). However, after adjusting for age and preoperative visual acuity no statistical significant difference was found in postoperative visual acuity between the two groups (p = 0.788) (Table 2). Also no significant difference was found in hole closure (p = 0.668). No major complications were noted in either group.

DISCUSSION
ILM peeling, the foremost step for the success of MHS, 1,2,5-7 acts by relieving tangential traction caused by the presence of

### Table 1: Comparison of preoperative and postoperative characteristics of BBG-assisted vs TA-assisted ILM peeling

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 26)</th>
<th>Group 2 (n = 25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean)</td>
<td>56.92 ± 9.07</td>
<td>61.2 ± 4.04</td>
<td>0.035</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>11:15</td>
<td>12:13</td>
<td>0.683</td>
</tr>
<tr>
<td>Stages of macular hole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>17</td>
<td>10</td>
<td>0.139</td>
</tr>
<tr>
<td>Stage 4</td>
<td>8</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Follow-up (months) mean</td>
<td>15.84 ± 2.58</td>
<td>16.12 ± 2.10</td>
<td>0.681</td>
</tr>
<tr>
<td>Anatomical hole closure</td>
<td>24</td>
<td>22</td>
<td>0.668</td>
</tr>
<tr>
<td>Duration of symptoms median (months) (range)</td>
<td>7 (3-16)</td>
<td>6 (3-24)</td>
<td>0.457</td>
</tr>
</tbody>
</table>
contractile cells on the inner surface of the ILM.\textsuperscript{17,18} It also prevents future epiretinal membrane formation as ILM serves as a scaffold for glial cell proliferation and thus improving long-term visual results. ILM peeling has also been found to increase cytokine release which stimulates glial cells to cause hole closure when direct apposition is not possible as in cases of large macular holes.\textsuperscript{19}

Lately, many vital dyes have been introduced to stain the ILM facilitating the procedure of peeling and increasing safety margins.\textsuperscript{9,10} ICG did not gain wide acceptance with the surgeons due to its toxicity to retina.\textsuperscript{13,14} Trypan blue, a remarkable bio stain, can also lead to dose-dependent retinal damage, comprising apoptotic retinal cell death.\textsuperscript{15,16,20-24} At present, both TA and BBG have been found to be relatively non-toxic to the retina; TA-assisted ILM peeling has been shown to be safe and effective in macular hole surgery.\textsuperscript{9,25,28}

BBG, also known as Coomassie or acid blue with the formula C\textsubscript{47}H\textsubscript{48}N\textsubscript{3}O\textsubscript{7}S\textsubscript{2}Na\textsubscript{2}, has recently been reported as a safe tool for chromovitrectomy by Enaida et al.\textsuperscript{29} It has been used for protein staining in biological fields as it binds nonspecifically to most proteins. Although, the pharmacological function of BBG still remains unconfirmed, there is a long history of biologic use in which no apparent toxicity has been reported.\textsuperscript{30}

Furthermore, BBG offers numerous advantages. It stains ILM more strongly as compared to other vital dyes which are being considered as an alternative for staining intraocular structures as ILM, ERMs and lens capsule.\textsuperscript{9,10} It is easier to handle; is produced in granular form that can be easily dissolved with intraocular irrigating fluid and has a stable pH.\textsuperscript{28} Osmolarity of BBG is similar to intraocular irrigating solutions. Thus, it causes minimal cytotoxicity.\textsuperscript{28} In our experience, it does not cause any posterior capsular staining, being a non-fluorescent dye, it has little possibility of phototoxicity.\textsuperscript{28} It is a potent antagonist to purinergic nucleotide receptor (P2X7) which is involved in proliferation of cells and thus, thought to improve postoperative results by reducing fibrous formation and microglial proliferation (ERM).\textsuperscript{28} Histological examination has revealed that BBG promotes no major toxic changes in the inner and outer nuclear layer cells, nerve fiber layer, RPE and choriocapillaries and also successful separation of the ILM occurs in cases of peeling without remnants of retinal cells. No apoptotic cell death of the retinal cell has been detected, and the amplitude of electroretinogram waves demonstrates no remarkable reduction in rat’s eyes.\textsuperscript{30,31}

Intraoperatively, we observed that BBG offers a distinct advantage over TA as it effectively stains ILM with a single application within a few seconds in a fluid (BSS) filled eye. TA does not stain ILM and tend to get dispersed within the vitreous cavity, and repeated injections are at times required. The ILM is identified by the fine crystals of TA layered over it. TA is particulate and it tends to stick to the forceps platform, making it occasionally necessary to clean the tips during the procedure while BBG is produced in a granular form and hence can be easily dissolved with intraocular irrigating fluid. However, we feel that TA would be a better alternative in cases where ILM peeling has to be carried out for macular hole with retinal detachment as is often associated with myopic retinal detachments. Theoretically, BBG may get access into the subretinal space in such cases and may remain long enough to cause retinal toxicity.

Our study revealed an overall primary anatomical closure rate of 90% which is comparable to other reports on ILM peeling performed for macular hole closure.\textsuperscript{7,26,32} The best corrected visual acuity improved from a mean of 1.0907 Log MAR (equivalent to 20/240) to a mean of 0.7173 Log MAR (equivalent to 20/100) (p = 0.001). These results compare favorably with other studies involving various techniques of ILM peeling using other stains.\textsuperscript{26,32} No significant differences in the anatomical hole closure rate and postoperative BCVA were found between the two groups (Tables 1 and 2). Thirty-four eyes (67%) had improvement of two or more lines. Around one fourth of phakic patients developed progression of nuclear sclerosis, a known complication of pars plana vitrectomy.\textsuperscript{33} No reopening of hole was noted throughout the follow-up period, including those who underwent cataract extraction and IOL implantation. The sample size and non-randomization proved to be the main limitations of this study, although the follow-up was reasonably adequate. To the best of our knowledge, this is the first study comparing BBG and TA-assisted ILM peeling. BBG-assisted ILM peeling seems to provide excellent anatomic and visual results in idiopathic macular hole surgery and compares favorably with other methods of ILM peeling. No significant outcome difference was noted between BBG and TA-assisted group, suggesting that either of the two staining techniques are relatively nontoxic and highly effective in macular hole surgery. Furthermore, BBG might offer an additional advantage over TA by providing marked enhancement of contrast at vitreoretinal interface due to its superior staining properties.\textsuperscript{9,10}
REFERENCES