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Evaluation of retinal functional changes after macular hole surgery using heavy brilliant blue G dye for internal limiting membrane staining: A prospective, single blind, randomized controlled trial

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Purpose: To evaluate retinal functional changes after idiopathic macular hole (MH) surgery using heavy brilliant blue G (hBBG) dye for internal limiting membrane (ILM) staining. **Methods:** Forty-four eyes with idiopathic MH were randomized into two groups – 24 eyes undergoing vitrectomy with ILM peeling using hBBG staining and 20 eyes without staining; anatomical and functional status (with microperimetry (MP)) at baseline and during postoperative follow-up were noted and compared. **Results:** All eyes had closure of MH postoperatively and overall baseline MP indices (average threshold, AT; foveal sensitivity, FS) improved significantly at 6 weeks and 6 months of follow-up. AT and FS showed significant improvement at 6 weeks and 6 months from baseline in both individual groups ($P < 0.001$). Intergroup comparison showed that there was no statistically significant difference in AT and FS values at any point of time (baseline, 6 weeks, 6 months) between staining and no-stain group. No eyes in our cohort had any unexplained visual loss. **Conclusion:** Functional parameters of macula improved significantly after successful MH surgery using hBBG for staining the ILM.

Key words: Heavy brilliant blue G, ILM, internal limiting membrane, macular hole, pars plana vitrectomy

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Surgical techniques for macular holes (MHs) have evolved over the last decade, and today, MHs have the best success rates of any retinal surgical condition. MH surgery involves small gauge vitrectomy with internal limiting membrane (ILM) peeling. Brilliant blue G (BBG) is one of the frontrunners among the currently available dyes used for the staining of the ILM during vitrectomy for several macular pathologies.[1,2] BBG dye has been used as an alternative to indocyanine green which has been shown to be toxic to retina, and different formulations of BBG dye with polyethylene glycol, trypan blue, etc., are commercially available. We have previously demonstrated that BBG can be made "heavy" by using 10% dextrose normal saline (DNS).[3] Heavy BBG (hBBG) is isotonic and directly sediments on the posterior pole without dispersing in the vitreous cavity. Moreover, less dye is needed in terms of both volume and concentration.[3] It also obviates the need for a fluid air exchange (FAE) as required for trypan blue, since the staining effect is almost instantaneous. In this study, we attempted to analyze the functional improvement in patients undergoing MH surgery with hBBG-assisted ILM peeling, to evaluate the safety profile of hBBG in macular surgeries.

Methods

This prospective, single-blind randomized controlled trial (RCT) evaluated 44 eyes of 42 patients, diagnosed with idiopathic full thickness MH and operated at the Retina Clinic of Aravind Eye Hospital, Madurai between November 2018 and October 2019. The study was conducted after obtaining ethical clearance from the Institutional Review Board (AMRF Institutional Ethics Committee RES2018036CLI) and clinical trial registration (CTRI/2018/09/015712) was done. The study adhered to the tenets of the Declaration of Helsinki and informed consent was taken from each patient. Patients were randomized using computer-generated random number tables. The study recruited idiopathic full thickness MHs of OCT staging 2 or more with minimum hole diameter <800 μm. Exclusion criteria included postoperative reopened MHs, MHs with type 2 closure postoperatively, secondary MHs (e.g., traumatic), and other indications of ILM peeling (e.g., vitreomacular traction, epiretinal membrane, diabetic macular edema). Lens changes requiring combined cataract surgery along with MH surgery were also excluded. Eyes with either clear lens or pseudophakia were included in the study. Eyes having any other macular pathology, refractive error (> ±6 D), and with previous vitreoretinal surgery were excluded. Preoperatively, all subjects underwent baseline investigations including best-corrected visual acuity (BCVA) by Snellen chart, intraocular pressure (IOP) by noncontact tonometry (Topcon corporation, Tokyo, Japan), anterior and posterior segment examination, spectral domain optical coherence tomography performed

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using Spectralis HRA (Heidelberg engineering, Heidelberg, Germany) and microperimetry (MP) (macular analyzer integrity assessment (MAIA), CenterVue, Padova, Italy).

Subjects were randomized into two groups: group A, staining with hBBG group and group B, no staining group. All surgeries were performed by three senior vitreoretinal surgeons (NBK, RPR, KK), all experienced in ILM peeling with and without ILM staining with dye. All eyes underwent a 23-gauge three-port pars plana vitrectomy with triamcinolone-assisted removal of the posterior hyaloid interface. All subjects were explained about the safety and nature of the dye used for ILM staining, and informed consents were obtained preoperatively; however, the subjects were blinded regarding the dye used in their surgeries.

Protocol for ILM staining

In group A, ILM was stained with hBBG, which was prepared by mixing BBG 0.05% dye (Ocublue Plus, Aurolab, Madurai, India) with 10% DNS in the ratio 2:1, as described previously by Shukla D *et al*.[3] This resulted in a final concentration of dextrose 3.33% and BBG 0.033%. The relative densities of hBBG and conventional BBG in Ringer's Lactate solution have been shown to be 0.9801 and 0.9726. This small increase in density results in significantly greater precipitation of hBBG in Ringer's Lactate solution which leads to better staining of the ILM. The dye was allowed to stay for 1 min with all the ports plugged and was aspirated afterwards. ILM was peeled with an ILM peeling forceps for an area of about 2 disc-diameter (DD) around the fovea with "pinch and peel" technique. This was followed by fluid-air exchange, drying of macular surface with a flute needle, injection of 2 mL of 100% expansile SF6, and postoperative prone positioning for 2 weeks.[4]

In group B, no staining of ILM was done. Undiluted, preservative-free triamcinolone acetate suspension (Aurocort, Aurolabs, Madurai, India) was injected after inducing PVD and was allowed to settle over the posterior pole for 1–2 min, followed by removal of free flowing steroid particles by active aspiration. ILM was then peeled about 2 DD around the fovea with ILM peeling forceps with "pinch and peel" technique, without staining the ILM. TA particles remain adherent to the flap of ILM, thus providing contrast from the underlying retina, which is devoid of TA. After peeling the ILM, fluid-air exchange was done, posterior pole dried by a flute needle, and 2 mL 100% SF6 gas injected.[4] All subjects were advised postoperative face down positioning for 2 weeks.

Protocol for MP

MP was done in a dark room by a single trained technician on the preoperative day, with the MAIA microperimeter (CenterVue, Padova, Italy). Sensitivity values were obtained by a 4-2-1 staircase strategy and with the sparse grid stimulus distribution, consisting of 37 points in three concentric circles of 2, 6, and 10 degrees diameter. The results of foveal sensitivity (FS) and average macular threshold within 6 degrees were recorded for analysis.

Follow-up protocol

Postoperatively BCVA, IOP, slit-lamp examination, OCT (Spectralis HRA) were repeated at 2 weeks, 6 weeks, and 6 months. MP was repeated for all subjects postoperatively by the same technician at 6 weeks and at 6 months.

Outcome measures

Primary outcome measure for the study was the postoperative change in average threshold (AT) and FS parameters on MP in the two study groups. Secondarily change in postoperative BCVA was also evaluated.

Statistical analysis

Data were entered into Microsoft Excel (Microsoft Inc.) spreadsheet and was analyzed by Stata software version 8.1 (Stata Statistical Software: College Station TX: Stata Corp LP). Wilcoxon signed-rank test, paired *t*-test, and Mann–Whitney U-test were used for comparing variables, depending on their parametricity. A *P* value of less than 0.05 was considered statistically significant. Snellen visual acuity was converted to logarithm of minimal angle of resolution (logMAR) for ease of analysis.

Results

This RCT included 24 eyes of 23 patients in group A and 20 eyes of 19 patients in group B. The demographic details of the two study groups are also summarized in Table 1. There was no statistical difference in between two groups in terms of patients' age, duration of symptoms, MH size, and preoperative BCVA. In group A, 18 out of 24 eyes were pseudophakic (75%), while rest 6 were phakic with clear lens. In group B, 16 out of 20 eyes were pseudophakic (80%), rest 4 were phakic with clear lens. In both groups, all eyes had closure of MHs at final follow-up of 6 months.

In group A, AT improved from 17.14 ± 3.39 dB preoperatively to 18 ± 2.95 dB at 6 weeks follow-up ($P = 0.17$) and 19.78 ± 3.07 dB at 6 months follow-up ($P < 0.001$) [Table 2]. FS improved from median of 15.0 dB preoperatively to 15.4 dB at 6 weeks follow-up ($P = 0.05$) and 17.3 dB at 6 months follow-up ($P < 0.001$). BCVA improved from baseline 0.724 ± 0.16 logMAR to 0.726 ± 0.16 logMAR at 6 weeks follow-up ($P = 0.86$) and 0.704 ± 0.168 logMAR at 6 months follow-up ($P = 0.21$). The average foveal fixation stability improved from 62.6 ± 23.57% before surgery to 72.29 ± 15.8% at the final follow-up, although not significantly ($P = 0.101$).

In group B, AT improved from 19.03 ± 3.12 dB preoperatively to 19.45 ± 2.85 dB at 6 weeks follow-up ($P = 0.29$) and 20.66 ± 0.66 dB at 6 months follow-up ($P < 0.001$). FS improved from median of 16.5 dB preoperatively to 17 dB at 6 weeks follow-up ($P = 0.02$) and 18.6 dB at 6 months follow-up ($P < 0.001$). BCVA changed from baseline 0.705 ± 0.17 logMAR to 0.726 ± 0.16 logMAR at 6 weeks ($P = 0.99$) and 0.696 ± 0.17 logMAR at 6 months follow-up ($P = 0.58$). The average foveal fixation stability improved from 67.9 ± 15.08% before surgery to 75.02 ± 11.72% at the final follow-up, although not significantly ($P = 0.103$).

When we compared BCVA between the two groups, there was no statistically significant difference in between the groups at any point of time. While comparing postoperative AT between the groups, there was no statistically significant difference at baseline ($P = 0.063$), 6 weeks ($P = 0.106$), and 6 months ($P = 0.216$). On comparing FS between the groups, there was no statistically significant difference at baseline ($P = 0.013$), 6 weeks ($P = 0.076$), and 6 months ($P = 0.066$). Till 6 months of follow-up, no patient showed any complication secondary to vitrectomy; no significant cataract due to surgery was observed till the last follow-up and none of the subjects showed raised IOP.

Discussion

ILM peeling for MHs was first started after Gass's theory on MH pathogenesis.[5,6] ILM contributes to 50% of retinal rigidity and may also lead to tangential due to the presence of contractile cells on inner surface of ILM.[7,8] Hence, ILM peeling relieves this tangential traction and also prevents glial tissue-induced epiretinal membrane formation and MH reopening postoperatively.[6,9,10] However, proper and meticulous peeling of ILM is difficult due to its thin and transparent structure. Several dyes have been introduced to stain the ILM to aid in its peeling;, however there is always a concern of injury to the neurosensory retina due to direct toxicity of the dye or due to dye-mediated phototoxicity. In this prospective RCT, we wanted to examine the safety profile of hBBG for ILM peeling surgery.

Table 1: Demographic and clinical features of subjects in the two study groups

	Group A n=24	Group B *n*=20	*P*
Mean age (years)	64±5.2	63±5.8	0.55
Duration of symptoms (months)	5.8±2	6±1.8	0.91
Macular hole size (μm)	563.16+152.63	547.6+148.27	0.73
Stage 2	6 (25%)	4 (20%)	0.69
Stage 3	10 (41.6%)	12 (50%)	0.58
Stage 4	8 (33.3%)	4 (20%)	0.32
Pre-op BCVA	0.724±0.16	0.705±0.16	0.67

Enaida *et al*.[11] in their clinical trial used 0.5 mL of 0.025% BBG dye (0.25 mg/mL) for staining the ILM followed by immediate washout. However, inconsistent and inadequate staining has been reported with this concentration of the dye.[12] Shukla *et al*.[3] first reported the use of hBBG to uniformly and effectively stain the ILM. They reported that only 0.1 mL, i.e., one-fifth of the volume used by Enaida *et al*., was sufficient to stain the ILM because the dye gravitated downwards and accumulated directly over the posterior pole. Moreover, a waiting time of 1–2 min was sufficient for good staining of ILM. Favorable anatomical outcomes were achieved by Shukla *et al*. in spite of reducing the volume, concentration, and duration of application of BBG dye before peeling the ILM.[3] However, they did not evaluate the functional outcomes after hole surgery using hBBG. Technically, ILM peeling without staining is much more challenging than dye-assisted peeling, since the ILM gets stained far better with the dye and this provides for better visualization of ILM and contrast during peeling and may reduce chances of mechanical trauma to the retina and risk of bleeding. To the best of our knowledge, no other study has evaluated the functional changes in the macula after hBBG-assisted ILM peeling in MHs.

In the hBBG group, although we observed a trend toward improvement in AT at 6 weeks follow-up, the change was not statistically significant. However, at 6 months follow-up, there was statistically significant improvement in AT. Improvement in FS was statistically significant at both 6 weeks and at 6 months. Intergroup comparison showed that there was no statistically significant difference in FS and AT values at any point of time (pre-op, 6 weeks, 6 months) between the two groups. The visual acuity change was also comparable between

Table 2: Comparison of parameters of postoperative functional improvement of macula at different time points in the two study groups

Group A				
Variable	***n***	**Mean±SD**	**Range**	***P*^t**
Average macular threshold (dB)				
Baseline	24	17.14±3.39	12.3-23.1	Baseline vs 6 weeks=0.17
6 weeks	24	18±2.95	13.4-23.8	Baseline vs 6 months <0.001
6 months	24	19.78±3.07	14-24.9	6 weeks vs 6 months <0.001
Variable	***n***	**Median**	**Interquartile range**	***P*^s**
Foveal sensitivity (dB)				
Baseline	24	15	12.45-16.45	Baseline vs 6 weeks=0.05
6 weeks	24	15.4	14.1-17.3	Baseline vs 6 months <0.001
6 months	24	17.3	15.8-19	6 weeks vs 6 months <0.001
Group B				
Variable	***n***	**Mean±SD**	**Range**	***P*^t**
Average macular threshold (dB)				
Baseline	20	19.03±3.12	14.6-25.6	Baseline vs 6 weeks=0.29
6 weeks	20	19.45±2.85	13-26	Baseline vs 6 months <0.001
6 months	20	20.66±0.663	15-27	6 weeks vs 6 months <0.001
Variable	***n***	**Median**	**IQ**	***P*^s**
Foveal sensitivity (dB)				
Baseline	20	16.5	14.2-18.5	Baseline vs 6 weeks=0.02
6 weeks	20	17	15.6-19	Baseline vs 6 months <0.001
6 months	20	18.6	16.5-20.1	6 weeks vs 6 months <0.001

T - independent sample t-test with post-hoc tests, S - Wilcoxon sign rank test with post-hoc tests, *Significant results are boldened and in italics

the two groups at all points of time. Triamcinolone acetonide although does not particularly stain the ILM, ILM peeling with TA without staining has been proven to be safe and effective in MH surgeries.[13-17] Previously, MHs in which ILM peeling was done assisted with TA have shown significant improvement in microperimetric indices postoperatively.[18,19]

Visual acuity assessment may be a basic requirement for foveal functional evaluation; however, it may underestimate the subclinical foveal functional changes in MH surgery patients.[20] In this regard, MP can help determination of point to point retinal sensitivity and provides specific functional information of the macula and visual restoration after hole surgery.[21-23] Previously, several authors have demonstrated significant improvements in functional parameters measured on MP after successful MH surgery with ILM peeling.[19,20,24-30] After postoperative closure of the MH, the fixation status of eyes may show a complex reorganization, and fixation may become more stable with follow-up.[31] Fixation stability is an important functional parameter in MH patients. In our study, we observed a similar trend toward recovery of fixation stability postsurgery till the final follow-up.

Our study may be limited by the fact that we have not performed a layer-wise OCT analysis of the patients and trying to correlate them to functional changes, and also by the intrinsic measurement errors and variability in the MP test. MP results may vary based on patient compliance and there may be a "learning factor" associated with each follow-up which may affect the actual degree of improvement during follow-up. Moreover, the visual acuity did not improve significantly in both the groups in our study, and this may be attributed to the shorter period of follow-up. This may be another limitation, since visual acuities have been shown to improve after a period of at least 1 year after MH surgeries.[32] However, since the objective of the study was to evaluate the immediate safety of hBBG in terms of macular toxicity, a period of 6 months of follow-up was adjudged to be suitable for the same to look for early functional derangements.

One of the major strengths of this study is its prospective design, and microperimetric analysis of MH eyes after hBBG-assisted ILM peeling. Moreover, the "heavy" BBG was indigenously and inexpensively formulated, unlike the expensive western alternatives (Brilliant Peel with heavy water and ILM Blue with polyethylene glycol) in the market. This is especially relevant in India at least, if not globally, because the latter dyes do not have such safety evaluations in spite of the cost.

Conclusion

To summarize, improvements in functional parameters were similar in both staining and no staining group till the 6 months follow-up period. The use of hBBG may obviate the need for FAE, thereby avoiding annoying residual bubbles and saving time. The hBBG technique for staining may also be evaluated in the future for patients with MH and retinal detachments or even in patients with long-standing macular detachments.

Ethical approval

All procedures performed were in accordance with the ethical standards of the Institutional Ethics Committee of Aravind Eye Hospital, Madurai, India and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical clearance from the Institutional Review Board (AMRF Institutional Ethics Committee RES2018036CLI) and clinical trial registration (CTRI/2018/09/015712).

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Conflicts of interest

There are no conflicts of interest.

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