Saudi Journal of Ophthalmology (2014) 28, 257–261

Original article

# Effect of intraoperative 5-fluorouracil and low molecular weight heparin on the outcome of high-risk proliferative vitreoretinopathy

Sunil Ganekal, FRCS [a,*]; Syril Dorairaj, MD [b]

## Abstract

*Purpose:* To evaluate the efficacy of a combination of 5-fluorouracil (5-FU) and low molecular weight heparin (LMWH) during vitrectomy, as adjuvants in preventing proliferative vitreoretinopathy (PVR).
*Design:* Double-blind, prospective, randomized placebo-controlled trial.
*Methods:* Forty consecutive patients diagnosed with rhegmatogenous retinal detachment with high-risk PVR, were randomized to study and control groups ($n = 20$ each). Study group (group 1) patients underwent vitrectomy with the use of both intraoperative 5-FU (0.2 mg/ml) and LMWH (5 IU/ml). In the control group (group 2), a similar surgery was performed without the use of adjuvants. Patients were evaluated at 1 month, 3 months and 6 months after surgery. Postoperative retinal reattachment, recurrence of PVR, best-corrected visual acuity and complications at the end of 6 months were compared between the two groups. A *Chi-square statistical* analysis was used on all of the outcome measures.
*Results:* At 6 months post-surgery, 62.5% of patients had reattached retina. There was no significant difference (*Chi-square* test showed $x^2 = 0.106$, $P = 0.7447$, $P > 0.05$) in retinal reattachment in both of the groups. The rate of postoperative PVR in the control group was 55%; in the study group, the rate was 45% (the *Chi-square* test showed $x^2 = 0.4$, $P = 0.5271$, $P > 0.05$), which proves statistically insignificant. In addition, there was no statistically significant difference in visual outcomes between the two groups (*Chi-square* test showed $x^2 = 0.1002$, $P > 0.05$), no significant difference in the complication rate and drug toxicity was noted between two groups.
*Conclusions:* This study fails to prove the efficacy of the intraoperative use of 5-FU and LMWH in combination as an antiproliferative regiment for the prevention of postoperative PVR or improvement in final visual acuity. At the same time, no significant complications could be attributed to the treatment.

**Keywords**: Rhegmatogenous retinal detachment, Proliferative vitreoretinopathy, Low molecular weight heparin, 5-Fluorouracil


http://dx.doi.org/10.1016/j.sjopt.2014.03.005

## Introduction

PVR is an anomalous scarring process of the detached retina due to the growth and contraction of cellular membranes within the vitreous cavity and on both sides of the retinal surface. Despite improvements in the primary success rate of retinal detachment surgery,[1] PVR remains the most common cause of failure, with a reported incidence of 5.1–11.7%.[2–8] PVR is responsible for the failure of more than 75% of cases in retinal detachment surgery.[9–11] Although

Received 22 October 2013; received in revised form 24 February 2014; accepted 11 March 2014; available online 21 March 2014.

[a] Department of Ophthalmology, JJM Medical College, Davangere 577004, Karnataka, India
[b] Department of Ophthalmology, Mayo Clinic, Jacksonville, FL 32224, USA

* Corresponding author. Tel./fax: +91 (8192) 220088.
e-mail address: drgsunil@yahoo.com (S. Ganekal).

Peer review under responsibility of Saudi Ophthalmological Society, King Saud University

Production and hosting by Elsevier

Access this article online:
www.saudiophthaljournal.com
www.sciencedirect.com

advances in the management of PVR have improved the anatomical success rate of surgery, multiple surgical interventions are often necessary to treat PVR, and final visual results are often disappointing, with visual prognosis remaining poor.[12–15] An improved understanding of the pathophysiology of PVR has led to the use of adjunctive therapies to prevent PVR, simplify its surgical management and improve outcomes. Low molecular weight Heparin has been shown to reduce postoperative fibrin after vitrectomy.[16] Heparin binds to fibronectin and to a wide range of growth factors, including acidic and basic fibroblast growth factors and platelet derived growth factors.[17] 5-FU inhibits DNA synthesis, inhibits fibroblast proliferation and has been effective in reducing rates of PVR in animal models.[18] The actions of 5-FU and LMWH occur at different stages of the PVR process, and using these agents in conjunction may produce a synergistic effect.

In a randomized controlled study of high-risk retinal detachment cases, identified using a risk assessment algorithm,[19–20] adjunctive therapy with 5FU and LMWH decreased the incidence of PVR from 26.4% in the control group to 12.6% in the treatment group.[21] Conversely, a further study of patients with established PVR using the aforementioned adjunctive combination, showed no significant treatment effect.[22] These varied results emphasize the importance of developing treatments aimed at well-defined clinical subgroups of PVR development.

We report the results of a further randomized prospective study on adjunctive 5-FU and LMWH, undertaken to determine the efficacy of this combination in improving the outcome of surgery for established high-risk PVR. The use of adjunctive medication was aimed at preventing reproliferation and, thereby, reducing the number of reoperations and potentially improving the visual outcome of surgery.

## Materials and methods

Forty eyes of 40 consecutive patients with PVR who underwent vitrectomy for retinal detachment (RD) between January 2009 and April 2010 were enrolled in the study.

The study was approved by local research ethics committee. Patients were randomly divided into 2 groups: 20 patients in the study group (group 1) and 20 patients in the control group (group 2). In group 1, all 20 patients underwent surgery for PVR with the use of intraoperative 5-FU and LMWH. In group 2, a similar surgery was performed on all 20 patients without the use of 5-FU or LMWH.

Inclusion criteria for the study required all patients with rhegmatogenous retinal detachment with high risk PVR to have a minimum follow-up of 3 months. An updated classification of retinal detachment with PVR by the Retina Society Terminology Committee was used to classify preoperative PVR.[23] A preoperative scoring system for high risk PVR was used, as described by Asaria et.al. [PVR score = 2.88 × (Grade C PVR) + 1.85 × (Grade B PVR) + 2.92 × (aphakia) + 1.77 × (anterior uveitis) + 1.23 × (quadrants of detachment) + 0.83 × (vitreous hemorrhage) + 23 × (previous cryotherapy)].[19] If the total score was >6.33, the patient was considered at high risk for PVR and was included in the study for randomization.

Patients with proliferative diabetic retinopathy, bleeding diathesis, hepatic and renal failure, glaucoma, giant retinal tear, posterior penetrating trauma, corneal opacity sufficient to impair surgical view, no light perception vision, inability to give informed consent, inability to complete follow-up, and unwillingness to accept randomization were excluded from the study.

At the time of recruitment, patients were given an information sheet with a complete and thorough explanation of the trial. Upon recruitment, details of medical and ophthalmic examinations were recorded. Data collected at the preoperative clinical assessment included best-corrected visual acuity, refractive status, intraocular pressure (IOP) (mmHg), corneal clarity, presence of anterior segment inflammation, lens status, presence of vitreous hemorrhage, number of retinal breaks, and extent of retinal detachment (recorded in clock hours). Vitreous hemorrhage was recorded as present if a hemorrhage was observed in the vitreous base, vitreous gel, or on the retinal surface. On the day of surgery, non-trial personnel randomized recruited patients to the group 1 and group 2 using a computer-generated weighted coin method.

The basic steps of surgery were same for both the groups and all surgeries were performed by a single surgeon (SG). For young and uncooperative patients, general anesthesia was used; for adults, peribulbar anesthesia along with mild anxiolytics was used. A standard 3-port pars plana vitrectomy was performed, along with lensectomy for lens opacity or the management of anterior PVR. Elimination of traction sufficient to allow retinal reattachment was achieved by epiretinal membrane peeling or relaxing retinotomy and retinectomy. Retinopexy was applied to treat retinal breaks using endolaser and/or cryotherapy. A scleral buckle or encircling band was used in relevant cases. 6 o'clock iridotomy was done for aphakic siliconized eyes. Air, perflouropropane (C3F8) gas and silicone oil were used for internal tamponade. Postoperative prone positioning was advised in all the patients.

In patients allocated to the group 1, intraoperative 5-FU (0.2 mg/ml) and LMWH (5 IU/ml) were added to the infusion fluid (100 mg of 5-FU and 2500 units of LMWH in 500 ml bottle), while a normal saline placebo was added to the fluid of group 2 patients. In cases lasting for more than one hour, the infusion bag was replaced with a new, identical infusion. After surgery, clinical data were recorded at 1 month, 3 months and 6 months. Patient characteristics for the treatment groups were tabulated to check for any major dissimilarity at baseline. Postoperatively both the groups were compared for best corrected visual acuity, retinal reattachment, recurrence of PVR, need for additional operations and complications.

## Results

Mean age of the patients was 28.5 ± 6.8 years in group 1 and 38.5 ± 7.2 years in group 2. Majority of the patients were males in group 1 ($n = 18$) as well as in group 2 ($n = 13$). Eight percent of the patients in group 1 and 75% of the patients in group 2 had previously undergone an intraocular surgery (Fig. 1). Risk factors for the development of recurrent PVR in both groups are shown in Table 1. Table 2 shows the details of the surgical procedures performed in both groups. Secondary vitrectomy was performed for failed sclera buckling and a repeat vitrectomy was performed for recurrent retinal detachments. Silicone oil (group 1, $n = 16$; group 2, $n = 12$), C3F8 gas (group 1, $n = 1$; group 2, $n = 2$) and air