5-Fluoro-Uracil and Low Molecular Weight Heparin in the Management of Proliferative Vitreo-retinopathy

Col VS Gurunadh*, Brig A Banarji⁺, Col S Patyal[#], Col TS Ahluwalia^{**}, Col AK Upadhyay⁺⁺,
Col M Bhadauria (Retd)^{##}

Abstract

Background: Proliferative vitreo-retinopathy (PVR) is the most common cause of failed repair of a primary rhegmatogenous retinal detachment (RRD). The success rates for the surgery of complicated RRD has doubled with improved vitreous techniques from 35-40% to approximately 65-75% at six months. However, despite these advances, recurrent vitreo-retinal traction leads to re-detachment in more than one-fourths of the initially successful cases. The use of adjunctive treatments to prevent cellular proliferation holds promise for the prevention of PVR or recurrences after surgery. One focus has been on the use of intra-vitreous antimetabolites to prevent the occurrence of PVR.

Methods: Thirty patients of complicated retinal detachment associated with PVR, C1 or more were managed by vitreo-retinal (VR) surgery with the addition of 250 µg / ml of 5-fluorouracil (5FU) and 1 IU / ml of low molecular weight heparin (LMWH) to the vitreous infusion. The patients were examined for any evidence of PVR till 180 days as also for any systemic or other ophthalmic complication.

Result: Out of the 30 cases in the study group, 25 (83.34%) cases had retinal settlement at the end of six weeks, which is similar to the outcomes of conventional VR surgery. There was no case of any serious complication.

Conclusion: The addition of LMWH and 5FU did not enhance the outcome of VR surgery.

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Key Words : Proliferative vitreo-retinopathy; Rhegmatogenous retinal detachment; 5-fluorouracil;
Low molecular weight heparin

Introduction

Proliferative vitreo-retinopathy (PVR) is the most common cause of failed repair of a primary rhegmatogenous retinal detachment (RRD) and occurs when cellular proliferation creates traction on the retina usually leading to a recurrent RRD. PVR is a non-neoplastic intraocular growth resulting from an excessive inflammatory reaction after a retinal break. On a microscopic level, PVR consists of dense glial membranes consisting of retinal pigment epithelial cells, glial cells and inflammatory cells with complex layered architectures and focal glial 'pegs' extending to the inner retina from the membranes. The cells have contractile properties and exert traction directly on the retina or through the vitreous gel leading to retinal traction and retinal breaks. Traction is the key feature in the pathogenesis of PVR. Breakdown of blood ocular barrier is another key feature associated with PVR. This causes increased cytokine release in the vitreous and often precedes clinically recognisable PVR. The PVR process is self propagating which contributes to more

inflammation and worsening breakdown of blood-ocular barrier [1].

The success for the surgery of RRD depends upon attaining the closure of the causative break, relieving traction upon the retina either by scleral buckling or by a thorough dissection of the epiretinal membranes, or by both and minimizing the recurrence of traction. In complicated RRD there is a greater amount of these traction forces. Conventional re-attachment surgeries consisting of scleral buckling are successful in most situations wherein proliferative vitreo-retinopathy is minimal and the buckling process has been successful in relieving the vitreo-retinal traction. The situation is different when RRD is complicated by severe PVR. The surgical procedures consist not only in relieving the tractions but also to keep the retina in a continuous state of attachment from inside.

The introduction of vitreous surgical techniques have facilitated intraoperative re-attachment of retinæ with severe PVR that were thought to be otherwise untreatable by conventional methods of scleral buckling

*#Associate Professor, ⁺Professor & Head (Department of Ophthalmology), AFMC, Pune-40. ^{**}Senior Advisor (Ophthalmology), Command Hospital (Northern Command), C/o 56 APO. ⁺⁺Senior Advisor (Ophthalmology) AFCE, Delhi Cantt. ^{##}CMO, Sitapur Eye Hospital, Sitapur (UP).

surgeries. The introduction of ancillary techniques like peroperative and postoperative long acting intravitreal tamponading agents have nearly doubled the success rate of PVR surgery from 35-40% to approximately 65-75% at six months. Despite these advances, recurrent vitreo-retinal traction leads to re-detachment in more than one-fourths of the initially successful cases. As a result, there is an need to tackle the problem of PVR through some other means [2].

To improve the prognosis of retinal detachment surgery, recent research has focused on the use of intra-vitreous pharmacological agents to control proliferation and to break the pathophysiology of the formation of PVR [2]. But none of these agents are used routinely in clinical practice owing to concerns about retinal toxicity. However, if risk factors for the development of PVR could be identified, these potentially toxic intra-vitreous treatments could be targeted at those patients at greatest risk. A similar principle is used to maximize efficacy and minimize side effects of anti-scarring therapy in glaucoma filtration surgery [3]. The use of 5-fluorouracil (5FU) and low molecular weight heparin (LMWH) is promising and by far these agents are among the very few which have been used in humans. Studies on the safety and efficacy of adjuvant combination therapy using 5FU and LMWH for prevention of PVR after vitrectomy and retinal reattachment surgery has been done in England, France and Venezuela [4-6]. Are these two agents 5FU and LMWH useful? Can they be used to enhance the re-attachment rate of RRD with PVR? There is a paucity of such work in Indian literature. A study was therefore undertaken to assess the efficacy and safety of 5FU and LMWH in the management of PVR.

Material and Methods

Thirty patients of complicated retinal detachment (RD) associated with PVR, C1 or more reporting to this hospital were included in this study and were managed by Vitreo-retinal (VR) surgery.

The following patients were excluded from the study

- a. Complicated cases of RD which would settle with scleral buckling surgery alone
- b. RD with PVR less than C1
- c. Previous vitreous surgery
- d. Patients less than 40 years of age
- e. Phakic eyes
- f. Cases with bilateral involvement

Detailed ophthalmic examination comprising of best corrected visual acuity (BCVA), detailed slit lamp biomicroscopy including anterior vitreous, fundus evaluation, applanation tonometry and pre-operative fundus photography was done. A detailed general physical examination was done in all patients. From the time the patient

first reported and was diagnosed with retinal detachment, the patient was put on topical steroid eye drops thrice daily and topical 2% homatropine eye drops twice daily. One day prior to the day of surgery, ciprofloxacin eye drops were instilled every 6 hours. Systemic oral antibiotic in the form of ciprofloxacin 500 mg tablet 12 hourly was started one day before surgery.

All surgeries were performed under peribulbar local anaesthesia using 7 ml of 0.5% Inj Bupivacaine and 3 ml of 2% Inj Lignocaine with 75 IU/ml of Hyaluronidase.

Enrolled eyes were subjected to VR surgery. A broad buckle was placed in all cases, if not already in place. A scleral buckle was chosen to ensure that the peripheral retina had adequate support from the buckle and the buckle closed all peripheral retinal breaks. The minimum buckle used was MIRA 276. Then the mattress sutures for the scleral buckle were placed in each quadrant. The callipers were set 3 mm wider than the width of the buckling material to obtain good invagination of the sclera from the buckle. The suture bites were placed at two-thirds the depth of the sclera. The scleral buckle was placed through the pre-placed mattress sutures, and these were later permanently tied to create a high buckling effect.

Three sclerotomies of 20 gauge sizes were made at the pars plana, 3 mm away from the limbus since the eyes were either aphakic or pseudophakic. The infusion cannula was placed first infero-temporally. The infusion cannula was secured by placing pre-placed sutures of 6-0/7-0 vicryl. A 6 mm cannula was used. The infusion port was made first and to the first infusion fluid (of 500 ml of Ringer lactate) 250 µg / ml of 5FU and 1 IU / ml of LMWH was added. The superior ports were used for the vitrectomy and endo-illuminator.

A lens ring was secured to the eye so that various contact lenses (Lander's lenses) could be placed on the eye to facilitate membrane dissection and other procedures. Alternatively, a hand-held infusion contact lens was used.

Standard VR surgery was then performed. Per fluorocarbon liquid (PFCL) was used when necessary to settle the retina. The PFCL used was per fluoro-n-octane. Once the retina was settled either with PFCL or without it, laser photocoagulation was then performed around the retinal breaks or any area suspected of having retinal breaks. The laser photocoagulation was placed by using the laser indirect ophthalmoscope delivery system or with an endolaser probe. The laser used was 532 Alcon Eyelite. Laser photocoagulation was also applied posterior to the edge of the buckle all over. The retina was then re-examined to be certain that it was supported by the buckle and that the laser photocoagulation completely surrounded the retinal breaks. PFCL if injected was then exchanged with air.

Upon removal of the PFCL, intraocular tamponade was achieved by exchanging the air with C₃F₈ or with silicon oil. If the dissection was lengthy and the retino-retinal adhesions were tough, then silicon oil was used. Whenever silicon oil was used in aphakic eyes, an Ando's iridectomy was performed. The same was also done in pseudophakic eyes if the zonular integrity was doubtful.

Patients were administered ciprofloxacin 500 mg tablets 12 hourly from a day prior to the surgery till the 5th post operative day. Ciprofloxacin eye drops were administered two hourly for 10 days. Steroid-antibiotic eye drops were administered two hourly for 14 days followed by tapering as per the progress of the case. Strict prone positioning was advised in the postoperative period depending upon the tamponading agent used.

Postoperatively all patients were examined daily for first three days, subsequently on day 7, 10, 14, 21, 28, 35 and thereafter every four weeks till six months. In those cases where silicon oil had been used as tamponade, it was removed only if there were signs of emulsification. On each postoperative visit the BCVA was estimated. Intra-ocular pressure was measured with applanation tonometer. Decongestive measures were instituted if required. Slit lamp biomicroscopy and binocular indirect ophthalmoscopy was done for status of retinal settlement, evidence of PVR and evidence of any intra-ocular inflammation.

The results were tabulated and statistically analysed.

Results

The age range of the study group was from 46-70 years with a median of 60 years and a mean of 60.03 years (Table 1). There were 21 (70%) males in the study. Out of the 30 eyes 23 (76.67%) were pseudophakic eyes. The right eye was involved in 19 (63.34%) cases. The BCVA preoperatively was light perception in nine (30%) cases. The remaining had a BCVA of hand movements close to face. Postoperatively the retina remained settled at the end of 180 days in 25 (83.34%) cases. In the settled eyes the BCVA was between 3/60 to 6/60 in 50% of the cases. C_3F_8 was used as the postoperative tamponading agent in 20 (66.64%) cases.

Discussion

The study population consisted of retinal detachments associated with aphakia and pseudophakia. Hence the mean and median age of the study group of 60 years is in consonance with the normal age of cataractogenesis. The predominant male composition in this study group is in consonance with the higher risk seen in males for retinal detachment [7]. The majority eyes being pseudophakic reflects the changing trend in cataract surgery towards intraocular lens (IOL) implantation. The involvement of the right eye being more than the left is only a matter of chance. There were no patients with

bilateral involvement (they were excluded from the study as such). Being cases with PVR C1 or more, the BCVA was predictably hand movements close to face or light perception only. Out of the 30 cases in the study group, 25 (83.34%) cases had retinal settlement.

The aim of the study was to find out if 5FU and LMWH were effective in the reduction of PVR when used as a peri-operative additive in the infusate while performing vitreous surgery to settle retinal detachment with PVR. The basis for this study was the trial of Asaria et al [4], who reported good results with the use of these two chemical agents. While 5FU is antimetabolite, LMWH is an agent that prevents binding of cells to components of the extracellular matrix and collagen. The pharmacological basis for the intervention is logical. However the success rate of 83.34% is similar to most outcomes of VR surgery in the literature. There is no improvement in the outcome in this study. The findings of the study are similar to the reports of two studies done at Moorefield's eye hospital [8,9]. In one study these agents were used in cases with significant PVR like the present one and in the other they were used in all uncomplicated cases of RD. However, in the present study, only thirty eyes have been evaluated.

There were no serious complications. This vouches for the safety of the drugs when used intra-vitreally. This is also corroborated by the multiple studies of the Moorefield's group, the French and the Venezuelan workers [4,6,8,9]. Hence in cases with severe PVR, chances of a favourable outcome can be increased by adding 5FU and LMWH to the infusion fluid. There was no difference in the outcome either based on sex or the age of the patients. The bottom line for a favourable outcome in a case of PVR remains a meticulous VR surgery.

Conflicts of Interest

None identified

Intellectual Contribution of Authors

Study Concept : Col VS Gurnadh

Drafting & Manuscript Revision : Col VS Gurnadh, Brig A Banarji

Statistical Analysis : Col S Patyal, Col M Bhaduria (Retd)

Study Supervision : Col TS Ahluwalia, Col AK Upadhyay

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Table 1
Age and Sex distribution

Age group	M	F	Total	%
46-50	03	01	04	13.33
51-55	06	-	06	20
56-60	01	04	05	16.67
61-65	05	03	08	26.67
66-70	06	01	07	23.33
Total	21	09	30	100

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Quiz

Picture Quiz

Lt Col AR Rajan*, AA Bhavé†

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A nine year old girl presented with six days history of fever. On examination she had right cervical lymphadenopathy and an erythematous macular rash over her trunk and face. She was febrile (39.4°C) with proportionate tachycardia. Systemic examination including cardiovascular system was normal. Over the next 48 hours the fever persisted and she also developed bilateral nonexudative bulbar conjunctivitis (Fig.1). Examination of oropharyngeal mucosa revealed cheilitis, oral congestion and a strawberry tongue (Fig. 2). By the seventh day of fever she had also developed

erythematous swelling over her palms and soles. This was followed by desquamation seen at the fingertips of her hands and feet (Fig. 3). Haematological investigations revealed a leucocyte count of 14,600/mm³ with predominant neutrophils (72%). Her haemoglobin was 10.8g/dl. The erythrocyte sedimentation rate (ESR) was raised (46mm in 1st hour by Wintrobe's method) and the C-reactive protein was elevated (12mg/dl). Her platelet count was 4,25,000/mm³. All biochemical parameters and her electrocardiogram were normal..

What is your diagnosis?

Fig. 1 : Nonexudative bilateral bulbar conjunctivitis.

Fig. 2 : Mucosal changes including fissured lips, strawberry tongue and oropharyngeal congestion.

Fig. 3 : Desquamation of periungual skin .

Answer to Picture Quiz : pg. 166

*Classified Specialist (Paediatrics), Command Hospital (CC), Lucknow -226002. †Senior Research Scientist, CSMMU, Lucknow.

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