Comparison of the Effect of Adjuvant 5-Fluorouracil, Low Molecular Weight Heparin and Daunomycin in Combination with Triamcinolone during Vitrectomy in Advanced Retinal Detachment

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Abstract

Purpose: To compare the success rate of adjunctive 5-fluorouracil (5-FU) and low molecular weight heparin (LMWH), and daunomycin in combination with triamcinolone during vitrectomy in eyes with retinal detachment (RD) and proliferative vitreoretinopathy (PVR).

Methods: In this prospective randomized clinical trial, 69 eyes from 69 patients with RD and PVR (grade B or C) randomized to 3 groups. Group 1: received 5-FU and LMWH (200 microgram/ml 5-FU and 5 IU/ml LMWH, Fragmin); group 2: received daunomycin (0.5 mg) in 500 cc infusion fluid; and group 3: control group. In all patients, 0.1 cc intravitreal triamcinolone was used during vitrectomy. The patients visited on day 1, week 1, month 1, 3 and 6. Best corrected visual acuity (BCVA) and retinal status compared in the 3 groups.

Results: Complete data were available for 60 out of 69 patients. Thirty five patients (58.3%) were male and 25 patients (41.7%) were female. The patient age range was 19-84 years and the mean age was 49. The groups did not have significant difference in age, sex, duration of detachment, severity of PVR, preoperative visual acuity (V/A), lens status, type of tamponade and encircling band and buckle. Postoperative V/A and retina status also was the same in the 3 groups.

Conclusion: Perioperative infusion of 5-FU, LMWH and daunomycin does not significantly increase the success rate of patients with RD and PVR comparing to control group. Although visual acuity improvement and retina reattachment rate in group 1 and 2 were better than control group, but statistical analysis failed to show significant difference between the 3 groups.

Keywords: retinal detachment, proliferative vitreoretinopathy, daunomycin, 5-Fluorouracil, low molecular weight heparin, deep vitrectomy

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Introduction

Despite advances in vitreoretinal surgical techniques, proliferative vitreoretinopathy (PVR) remains a significant complication of rhegmatogenous retinal detachment (RD).[1] The success rate of RD surgery has now reached over 90%.[2,3] PVR occurs in 5% to 10% of all rhegmatogenous RDs[4] and is implicated in postsurgical redetachment over 75% of the time.[5] PVR is a wound healing response resulting in the formation of a membrane on both side of the retina and vitreous base.[6] Contraction of the resulting scar tissue leads to redetachment and failure of surgery. It is a complex process involving cellular proliferation of a variety of cells and secretion and remodeling of the extracellular matrix.[7]

The main stimulator for cellular metaplesia and proliferation in PVR is a retinal break, which result in the migration of retinal pigment epithelial (RPE) and glial cells and implantation of them on the retina and in the vitreous.[8,9]

The severity of cellular proliferation is directly related to the extent of retinal damage, severity of damage to the blood retinal barrier and interaction between glial and RPE cells and growth factors.[10]

Laboratory and clinical studies suggest that pharmacologic adjuvant therapy can modify the proliferative disease process and improve the success of surgery.[6]

There are a number of studies showing a potential benefit of a variety of pharmacologic interventions, including 5-fluorouracil (5-FU),[5] low molecular weight heparin (LMWH),[5] daunomycin[11] and steroids.[12]

This prospective, controlled, randomized clinical trial was undertaken to determine whether adjuvant therapy using intraoperative infusion of 5-FU, LMWH or daunomycin in combination with triamcinolone increase success rate after deep vitrectomy in RD patients.

Methods

A total of 69 patients (69 eyes) with rhegmatogenous RD in whom primary vitrectomy was considered necessary for a number of reasons including giant retinal tear, posterior retinal break, the presence of preoperative PVR and media opacities, were enrolled into this study between June 22,

2005 and April 20, 2006. Patients with the following conditions were excluded: age less than 18 years, pregnancy and lactation, diabetic retinopathy, glaucoma, uveitis, history of posterior segment trauma, any corneal opacity sufficient to impair surgical view, attached macula, and history of bleeding tendency. Informed consent was obtained from all participating patients.

A full medical and ophthalmic history was taken and an examination performed on all patients. Specific attention was paid to risk factors such as age, duration of symptoms, vitreous hemorrhage, preoperative lens status, preoperative PVR, previous operations and size of RD. All details were recorded into a specific file. If present, PVR was graded according to the updated classification published by the Retina Society in 1991.[13] The best corrected visual acuity (BCVA) was measured using the Snellen acuity chart and then transformed on a logMAR scale.

Randomization was carried out after the patient had been scheduled for surgery. Randomization was performed according to the randomization table.

According to the randomization table, the patients assigned to one of the three groups: Group 1, using 5-FU and LMWH; group 2, using daunomycin and group 3, was control group.

The surgery included an encircling band and/or buckle (if necessary) and standard three-port pars plana vitrectomy together with lensectomy in some eyes for management of lens opacity or anterior PVR. In the group 1, at the beginning of operation, and only in the first 500 cc of infusion fluid, 100 mg 5-FU (200 microgram/ml) and 2500 IU (5 IU/ml) LMWH (Fragmin) was added. In the group 2, 0.5 mg of daunomycin was added to the first 500 cc of infusion fluid and in the group 3, 2 cc of distilled water added to the infusion fluid.

In all of patients, 0.1 cc of triamcinolone was injected into the vitreous cavity during creation of posterior vitreous detachment and vitrectomy. 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 only. Endolaser or indirect laser was preferred and in cases which adequate

retinopexy was not possible by laser, cryotherapy was used. Internal tamponade was achieved using either intraocular gas (SF6) or five thousands-centristoke silicone oil. Four patients were treated with SF6 in the group 1, 3 patients in the group 2, and 2 patients in the group 3. The rest of patients were treated with silicone oil. The surgeon was blind to the group of patients.

Data were collected before and during surgery and at control visits after 1 day, 1 week, 1 month, 3 months and 6 months postoperatively. None of the patients had silicone removal during follow-up period.

The main outcome measurement was attachment of retina (posterior to equator) and change in BCVA. All statistical analysis were carried out using the computer software program SPSS.

Results

A total of 69 patients (69 eyes) were recruited to take part in the study. There were 22 patients in the group 1, 24 patients in the group 2, and 22 patients in the group 3. Seven patients were lost to follow-up (2 patients from the group 1, 3 patients from the group 2, and 2 patients from the group 3), and unfortunately, 1 patient died one month after operation. Also, 1 patient developed corneoscleral laceration due to sharp truama which underwent corneoscleral laceration repair but excluded from the study.

Complete data were available for 60 patients (20 patients in each group). The baseline characteristics of the 3 groups were similar and are presented in table 1.

Of the 60 patients, 35 were male (58.3%) and 25 female (41.7%). The mean age was 49 years (range 19-84 years). The mean age in the 3 groups was similar (p value=0.65). The mean duration of RD was 7, 6.8, and 6.4 weeks in the group 1, 2, and 3 respectively. There is no statistical difference between the 3 groups in the duration of symptoms (p value=0.860, Anova test). There was no statistical difference in the extent of RD, which expressed as the number of involved quadrants, between the 3 groups (p value=0.69, Kruskal- Wallis test). Regarding lens status, the patients were divided into 2 groups: phakic and non phakic (including pseudophakia and those for whom lensectomy was done during vitrectomy).

There were 4 phakic eyes in each group. The mean duration of follow-up in the 3 groups was 6.5 months (range 4-10 months) and there was no statistical difference between the 3 groups (p value=0.53, one-way Anova test). There was no statistical difference between the 3 groups in the used intraocular tamponade (p value=0.676; chi-square test) and grade of PVR (p value=0.62; chi-square test).

Table 1. Baseline characteristics of patients

Characteristic	Group 1	Group 2	Group 3
Number	20	20	20
Gender			
Male	12 (60%)	11 (55%)	12 (60%)
Female	8 (40%)	9 (45%)	8 (40%)
Age (yrs)			
mean (SD)	48.6 (15.8)	51.6 (13.6)	47.2 (16.7)
Lens status			
Phakic	4 (20%)	4 (20%)	4 (20%)
Aphakic	16 (80%)	16 (80%)	16 (80%)
Mean logMAR visual acuity	2.43	2.44	2.47
Grade of PVR			
Grade B	8 (40%)	10 (50%)	11 (55%)
Grade C	12 (60%)	10 (50%)	9 (45%)
Duration of RD (week)			
mean (SD)	7 (3.78)	6.8 (3.12)	6.4 (3.62)
Extent of RD			
2 quadrants	1 (5%)	0 (0%)	2 (10%)
3 quadrants	2 (10%)	4 (20%)	3 (15%)
4 quadrants	17 (85%)	16 (80%)	15 (75%)
Previous operations	2 (10%)	3 (15%)	5 (25%)

Group 1: 5-FU and LMWH
Group 2: daunomycin
Group 3: control group
SD: standard deviation

From the point of encircling band and buckle, the patients divided into 4 groups: 1-encircling band, 2-buckle, 3-both of them, and 4-none of them. Encircling band and buckle status in the 3 groups are shown in table 2. There was no statistical difference between the 3 groups from this point (p value=0.62, chi-square test).

Table 2. Band and buckle status in the three groups

	Group 1	Group 2	Group 3
Band	15 (75.0%)	16 (80.0%)	13 (65%)
Buckle	1 (5.0%)	1(5%)	2(10%)
Both	1 (5.0%)	2(10%)	4(20%)
None	3 (15%)	1(5%)	1(5.0%)

Group 1: 5-FU and LMWH
Group 2: daunomycin
Group 3: control group

Table 3 shows the final changes in visual acuity (VA) and postoperative status of the retina in the 3 groups. The mean preoperative visual acuities of the 3 groups were not statistically different between the 3 groups (p value=0.91, Anova test). Postoperatively, the mean logMAR visual acuity was 1.69, 1.60 and 1.82 in the group 1, 2, and 3 respectively. There was no statistical difference between the 3 groups in post operative VA (p value=0.55, Anova test). The mean improvement in post operative VA for the 3 groups was 0.74 logMAR, but there was no significant difference in VA improvement between the 3 groups (p value=0.67, Anova test). At the end of follow-up period, the retina was attached in 80%, 85%, and 65% in the group 1, group 2, and control group, respectively, which was similar in the 3 groups (p value=0.29).

None of the patients had intraocular pressure greater than 21 mmHg or significant surgical complication.

Table 3. Postoperative retina status and mean visual acuity

	Group 1	Group 2	Group 3
logMAR VA Mean (SD)	1.69 (0.7)	1.60 (0.44)	1.80 (0.68)
Retina status On	16 (80%)	17 (85%)	13 (65%)
Off	4 (20%)	3 (15%)	7 (35%)

Group 1: 5-FU and LMWH
Group 2: daunomycin
Group 3: control group
SD: standard deviation

Discussion

The principal aim of this study was to compare the efficacy of the combination of 5-FU and LMWH, and daunomycin (alone), given as a perioperative infusion, with control group in improving the outcome of surgery for complicated RDs. In pharmacologic treatment of PVR, because of blood retinal barrier and corneal epithelium, systemic or topical administration of drugs cannot give rise to adequate intraocular concentration of drugs.[14] The adjunctive medications used in this study were selected on the basis of their availability, proven safety in previous nonrandomized clinical trials,[11,15-18] ease of administration as a perioperative infusion, and their potential to produce complementary pharmacological effects to prevent intraocular cellular

proliferation. 5-FU is known to have antiproliferative effects on several ocular cell types, including RPE cells, and it has been shown that short exposure to 5-FU produce a long-term inhibition of proliferation in vitro and in vivo.[19,20]

LMWH, which theoretically has less potential for hematologic complications than heparin,[20] reduces fibrin after vitrectomy,[18] is antiproliferative to RPE and other cell types, and can reduce the effect of fibrogenic growth factors.[20]

Daunomycin is an anthracycline antibiotic, which very effectively arrests cell proliferation and cell migration but not contraction in vitro.[21] Danumycin had shown convincing results in the prevention of experimental PVR.[22] Its action is independent of the cell cycle and, importantly, requires only a short exposure time to suppress cellular proliferation of fibroblasts and RPE cells completely.[23]

In this study, there was no statistical difference between the 3 groups in preoperative baseline data such as: age, sex, duration and size of detachment, and grade of PVR.

The anatomic success rate of RD surgery in this study was 80%, 85%, and 76% in the group 1, 2, and 3, respectively; which was similar in the 3 groups (p value=0.29).

Wiedmann et al[11] used adjunctive daunomycin in the treatment of PVR. They found that the rate of anatomic success after 6 months failed to show significance, but some benefit of the adjunctive treatment exist, especially a tendency toward increased rate of reattachment and a significant reduction in the number of reoperations. In Wiedmann's study, all patients had PVR grade C2 or greater, but in this study, only 52% of patients had PVR grade C.

Asaria et al[6] used a combination of 5-FU and LMWH as adjuvant combination therapy in patients who were high risk to develop PVR. They concluded that there is a significant reduction in the incidence of post operative PVR and in the reoperation rate resulting from PVR. After that, Charteris et al[1] used the same medication as Asaria, but their study failed to show significant increase in the success rate of vitreoretinal surgery for established PVR.

The mean age in 3 studies of Wiedmann, Charteris and Asaria was 62.9, 65.8 and 63

years, respectively. The mean age in this study was 49.1 years, which indicates the younger population.

In this study, the male/female ratio was 58.3/41.7, which is similar to Wiedmann study (57/43).

The postoperative VAs in the 3 groups were similar (p value=0.53) but the improvement in VA in the group 1 and 2 (0.74 and 0.82 logMAR, respectively) were more than improvement in the group 3 (0.65 logMAR). This shows that the results in the treatment groups are better than the control group but, may be due to small sample, statistical analysis failed to show significant difference between the 3 groups.

Recently, Wickham et al showed that adjuvant therapy with 5-FU and LMWH does not improve the anatomic or visual success rate of unselected primary RDs undergoing vitrectomy.[24]

Conclusion

Perioperative infusion of 5-FU, LMWH and daunomycin does not significantly increase the success rate of patients with RD and PVR comparing to control group. Although visual acuity improvement and retina reattachment rate in the group 1 and 2 were better than the control group, but statistical analysis failed to show significant difference between the 3 groups. It is advised that the study repeated in a large volume of sample.

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