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Original Article

5-Fluorouracyl added infusion fluid in patients with recurrent rhegmatogeneous retinal detachment

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Abstract

Purpose: To compare the efficacy of 5-fluorouracil (5-FU) added the infusion fluid with a control group in the event of grade C PVR in recurrent retinal detachment (RD).
Methods: The records of the patients with recurrent retinal detachment with grade C PVR who underwent vitrectomy for retinal detachment surgery between April 2003 and October 2004 were reviewed retrospectively for this comparative study. The recurrent retinal detachment patients with grade C PVR who underwent vitrectomy and had a minimum post-operative follow-up period of 12 months were included. The patients were divided into two groups as study and control groups. 5-FU (200 microgram/ml) and low-molecular-weight-heparin (LMWH) (5 IU/ml) was added into the infusion solution of the study group. Primary outcome measure of this study was the single operation anatomical success at month 12.
Results: A total of 43 eyes of 43 patients were included. The control group was consisted of 26 eyes (60.5%) and the 5-FU group was consisted of 17 eyes (39.5%). At month 12, single operation anatomical success was obtained in 14 of the 26 patients (53.8%) in the control group and in 16 of the 17 patients (94.1%) in the 5-FU group ($p = 0.005$).
Conclusion: Favorable outcomes were obtained in the patients with recurrent RD and grade C PVR in whom 5-FU and LMWH added infusion fluid which was used during vitrectomy.

Keywords: Proliferative vitreoretinopathy, Retinal detachment, Vitrectomy, 5-Fluorouracil

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Introduction

Proliferative vitreoretinopathy (PVR) is the most important complication of retinal detachment (RD).[1–4] It can be detected during the late presentation of RD and also can complicate the post-operative period after a surgery for RD and lead to surgical failure.[1–4] PVR is an abnormal process of scar formation of the detached retina secondary to proliferation of contractile cells and formation of epiretinal and subretinal membranes.[1–4] It also may also cause intraretinal foreshortening. PVR is detected in about 5–10% of all RD cases and is the main cause of redetachment after surgery in most of the cases.[1–4]

The current treatment of RD associated with PVR is vitrectomy.[1,7–14] Several surgical techniques and use of surgical adjuvant drugs were described for the treatment of PVR.[7–14] Adding scleral buckle, performing membrane peeling, using retinotomy-retinectomy techniques, using heavy perflu-

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orocarbon liquids and advanced tamponades such as silicone oil/perfluorocarbon gases are the introduced advances in surgery.[7–14] Various adjuvant drugs and drug delivery methods were assessed for the treatment of PVR such as steroids, antineoplastic agents and antigrowth factors.[1,9–14] Intravitreal steroids were found to be effective in some animal studies; however, in human studies this beneficial effect was not demonstrated clearly.[13] Antineoplastic and antiproliferative agents such as 5-fluorouracil (5-FU), taxol, colchicine, daunorubicin, mitomycin, etc. are the explored adjuvants for PVR treatment.[1,9–13,15–18] 5-FU is one of the most evaluated agents which acts on DNA synthesis by inhibition of thymidine formation.[1,15–18] The efficacy of 5-FU in the prevention of PVR in RD cases was evaluated in previous studies.[15–18] In these studies 5-FU and low-molecular-weight-heparin (LMWH) were added into the infusion solution which was used in vitreoretinal surgery and the surgical outcomes were compared with a placebo group. The outcomes were controversial in these studies.[15–18] Asaria et al[15] reported that a perioperative infusion of 5-FU and LMWH reduced the rate of PVR in primary RD patients with a high-risk of PVR whereas Wickham et al[17] did not reach this result in patients with primary RD who underwent vitrectomy. Charters et al evaluated the efficacy of 5-FU and LWMH to improve the outcome of the surgery for established PVR and reported that the adjuvant treatment did not significantly increase the success rate of vitreoretinal surgery in these cases.[16] This controversy has led us to conduct this study and the aim of this study was to compare the efficacy of 5-FU and LMWH in the infusion fluid with a control group in the event of grade C PVR in recurrent RRD cases.

Methods

The records of the patients with recurrent retinal detachment with grade C PVR who underwent vitrectomy for retinal detachment surgery between April 2003 and October 2004 were reviewed for this retrospective comparative study. A written informed consent was obtained from all patients before the treatment and the study adhered to the tenets of the Declaration of Helsinki. Institutional ethical board approval was obtained for the study.

The recurrent retinal detachment patients who underwent vitrectomy for grade C PVR with a minimum post-operative follow-up period of 12 months were included. The patients who had milder degrees of PVR, or did not complete a follow-up period of at least six months after silicone oil removal (if silicone oil was used as a tamponade), or had a history of trauma were not included. All of the patients were operated previously and undergone vitrectomy+encircling scleral buckle or only encircling scleral buckle surgeries. Data collected from the patients included age, gender, visual acuity, complications, functional and anatomical outcomes of the surgeries. All patients underwent an examination including measurement of best corrected visual acuity (BCVA) via a projection chart in decimals, biomicroscopy, measurement of intraocular pressure (IOP) via applanation tonometry, and fundus examination. The examinations were repeated at post-operative day 1, week 1, month 1, 3, 6, and 12. Functional success was defined to have a postoperative BCVA $\geq$ 1.3 LogMAR, and anatomical success was defined to have an attached retina at postoperative month 12. Silicone oil was permanently left in vitreous cavity in some patients, these patients was not accepted to obtain anatomical success.

Surgical technique

A 20- or 23-gauge transconjunctival vitrectomy with the Accurus system (Alcon Surgical, Ft. Worth, TX) and a wide-field viewing system was used. The phakic patients with a significant cataract underwent a combined phacoemulsification and vitrectomy procedure, whereas the patients without significant lens opacity did not undergo phacoemulsification. Standard 3 port vitrectomy sclerotomies for infusion, endoillumination, and vitreous cutter were prepared and vitreous was completely removed. Vitreous base shaving was performed, vitreoretinal traction was released around all of the breaks. All of the preretinal and some of subretinal membranes which caused stiffness of the retina were removed without the aid of any dye. After removing all of the membranes retinectomy was performed if retinal stiffness was not still resolved. Subretinal fluid was drained via a flute needle from the existing breaks with or without the assistance of a heavy perfluorocarbon fluid, endolaser photocoagulation was applied to all of the breaks. If the patient showed diffuse retinal degenerations of tears all around the retina then 360-degree barrier laser photocoagulation was applied. Air-fluid exchange was performed and suitable tamponade was exchanged with air at the end of the surgery. Sclerotomies were checked in regard to leakage and all leaking sclerotomies were sutured with 7/0 polyglactine suture. The choice of endotamponade was made according to the surgeons' preferences, but mostly silicon oil was used as the cases were all complicated. Silicon oil was planned to be removed after postoperative month 3 according to the patients' clinical situations. The patients were divided into 2 groups as study and control groups. 5-fluorouracyl (200 microgram/ml) and DMAH (5 IU/ml) was added into the infusion solution of the study group.

Primary outcome measure of this study was the anatomical success at the last follow-up visit.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 21.0). Visual acuity was converted to the logarithm of the minimum angle of resolution (LogMAR) for statistical analysis. The continuous variables were expressed as means ± standard deviation (SD). The categorical variables were expressed as number (n) and percentages (%). Categorical variables were presented as numbers and percentages, while numerical variables were expressed as the mean and standard deviation. First the data was analyzed in terms of normal distribution using Shapiro-Vilk test. As the distribution of the data was found to be normal, the visual acuity and the CRT values between baseline and the other time points were assessed with repeated measures test. The differences between the two groups were assessed with independent t test. Categorical variables were compared using chi-square test. A p value <0.05 was considered statistically significant.

Results

A total of 43 eyes of 43 patients were included. The mean age was 52.9 ± 14.4 years (range 21–73 years). Twenty-nine patients (67.4%) were men and 14 (32.6%) were women. The mean follow-up period was 13.9 ± 2.8 months (range 12–41 months). The control group was consisted of 26 eyes (60.5%) and the 5-FU group was consisted of 17 eyes (39.5%). The general characteristics of the two groups were summarized in Table 1.

Anatomical outcomes

Single operation anatomical success was obtained in 14 of the 26 patients (53.8%) in the control group and in 16 of the 17 patients (94.1%) in the 5-FU group (p = 0.005). Recurrent retinal detachment was detected in 12 patients (46.2%) in the control group and in only one patient (%5.9) in the 5-FU group. The reason was PVR in all of the recurrent RRDs and the final anatomical success increased to 65.4% after a mean of 1.5 ± 0.67 vitrectomy procedures in the control group, but did not change in the 5-FU group in which none of the patients did not undergo reoperation and remained as 95.1%. In the control group at the last follow-up visit, 17 patients (65.4%) had an attached retina, 4 (15.4%) had attached retina under silicone oil, 2 (7.7%) had detached retina without tamponade, and 3 (11.5%) had detached retina under silicone oil endotamponade. Whereas, 16 patients (94.1%) showed attached retina and only one patient (5.9%) showed detached retina under silicone oil endotamponade in the 5-FU group.

Visual outcomes

The visual outcomes of the two groups were summarized in Table 2. The mean baseline BCVA was 1.58 ± 0.30 LogMAR (range 0.5–1.7) and 1.62 ± 0.23 LogMAR (range 1.0–2.0) in the control and 5-FU groups, respectively (p = 0.5). In-group analysis showed that, the change in mean BCVA from baseline to month 1, 3, 6, 12, and last visit was not statistically different in control group (p > 0.05 for all); however, it was statistically better at all of the time points in 5-FU group (p < 0.05 for all). Intergroup analysis revealed that the change in mean BCVA from baseline was statistically better in 5-FU group than control group at month 1 (p = 0.03), month 12 (p = 0.02), and at the last follow-up visit (p = 0.04). Functional success (BCVA $\geq$ 1.3 LogMAR) was achieved in 6 of the 26 eyes (23.0%) in control group and in 10 of the 17 eyes (58.8%) (p = 0.02).

Tamponades, lens status, intraocular pressure and re-operation

The tamponade choice was similar between the two groups (Table 1) (p = 0.1).

Baseline lens status (p = 0.9) and need for combined surgery (p = 0.3) was similar between the two groups (Table 1).

The mean baseline and last IOP was 13.4 ± 4.9 mmHg (range 4–23 mmHg) and 13.9 ± 4.3 mmHg (range 5–22 mmHg) in the control group (p = 0.8). The mean baseline and last IOP was 14.9 ± 4.7 mmHg (range 7–25 mmHg) and 14.4 ± 2.8 mmHg (range 9–20 mmHg) in the 5-FU group (p = 0.7). The IOP at the last follow-up was <6 mmHg in only one eye in the control group (3.8%) and in none of the eyes in the 5-FU group (p = 0.4). None of the eyes show signs of phthisis bulbi at the last follow-up visit. Early IOP elevation was detected in 6 eyes (23.1%) in the control group and 3 eyes (17.6%) in the 5-FU group (p = 0.6). Only 3 eyes (11.5%) in the control group and 2 eyes (11.8%) in the 5-FU group showed prolonged IOP elevation and required chronic antiglaucomatous medication during the follow-up (p = 0.9).

The number of required reoperations was 1.5 ± 0.67 (range 0–2) and 0 in control and 5-FU groups, respectively (p = 0.04).

Table 1. General characteristics of the study groups.

	Control, n, 25	5-FU, n, 18	p
Age, years	52.8 ± 15.0	52.9 ± 14.0	0.9
Gender (Female/Male)	19/7	10/7	0.5
Follow-up period	14.5 ± 3.3	13.1 ± 1.8	0.1
Lens status (Phakic/Pseudophakic/Aphakic)	18/4/4	11/3/3	0.9
First surgery (PPV + Scleral buckle/Scleral buckle)	15/11	10/7	0.5
Combined surgery with Phaco	19/7	14/3	0.3
Localization of RD (superior/inferior/total)	7/12/7	8/6/3	0.3
Status of macula, attached/detached, (% of attached macula)	2/14 (12.5%)	0/17 (0.0%)	0.3
PVR Severity, grade (C1/C2/C3/C4)	0/13/9/4	0/4/10/3	0.2
Baseline BCVA, LogMAR	1.58 ± 0.30	1.62 ± 0.23	0.6
Tamponade (SO/C3F8)	23/3	17/0	0.1
Functional Success (BCVA $\geq$ 1.3 LogMAR at the final visit) (%)	23.0%	58.8%	*0.01**
Final anatomical Success (%, retinal attachment at the final visit)	65.4%	94.1%	*0.03**

Abbreviations: n, number of patients, RD, retinal detachment, PVR, proliferative vitreoretinopathy, BCVA, best corrected visual acuity, SO, silicone oil, C3F8, perfluoropropane, p, P value. *Italic values shows statistically significance,* **chi-square test.*

Table 2. Visual acuity levels of the two study groups at different time points.

	Baseline	Month 1	Month 3	Month 6	Month 12	Last visit
Control group, Logmar	1.58 ± 0.30	1.57 ± 0.27	1.56 ± 0.24	1.47 ± 0.30	1.47 ± 0.33	1.42 ± 0.36
5-FU Group, Logmar	1.62 ± 0.23	1.53 ± 0.25	1.41 ± 0.25	1.35 ± 0.22	1.21 ± 0.34	1.16 ± 0.36

Complications

Early postoperative complications were mild-transient anterior chamber reaction (23.1% in the control group versus 5.9% in the 5-FU group, p = 0.1) and corneal edema (26.9% in the control group versus 17.6% in the 5-FU group, p = 0.4).

Discussion

We evaluated the outcomes of adding 5-FU and LMWH into the infusion solution of the recurrent RD patients with grade C PVR who underwent secondary vitrectomy and compared the results with a control group in this study. Both of the anatomical and functional outcomes were better in 5-FU group than the control group. In the previous studies the anatomical success rate for RD associated with PVR was reported between 60 and 80% and the functional success (visual acuity $\geq$1.3 LogMAR) was reported between 40 and 80% with only vitrectomy with various surgical techniques in which adjuvant agents were not used.[1,3–5] Steroids, 5-FU, daunorubicin, retinoic acid, glucosamine, etoposide, bevacizumab and other several agents were used in the treatment of PVR along with vitrectomy.[9–18] Controversial outcomes were reported with all of these agents and some were found to be effective, some was not. The efficacy of 5-FU combined with LMWH was compared with placebo in the treatment of RD in previous studies.[15–18] Asaria et al, conducted a prospective randomized study which included 174 high-risk RD patients.[15] The patients were divided into two groups either to receive 5-FU and LMWH in the infusion solution during the surgery or not. There were 87 patients in each of the two groups. The included eyes were reported to have a risk of developing PVR and this risk was calculated on a regression formula depending on a previous study of risk factor analysis study which was previously performed by the same study group.[6] The baseline characteristics of the two study groups were similar and mostly expanding gases were used as endotamponade in both of the groups (more than 90%). The surgical outcomes were evaluated at post-operative month 6 and primary anatomical success rate was 78.2% in the 5-FU group and 71.2% in the placebo group which was reported as statistically significant. In addition, 19.5% of the 5-FU group and 25.3% of the placebo group required at least one or more reoperations after the first surgery. Interestingly the reason for the reoperation was PVR in 10.3% of the eyes in the 5-FU group and 18.4% of the eyes in the placebo group which was also statistically significant. The visual outcomes were parallel to the anatomical outcomes and 60% of the eyes in 5-FU group versus 45% of the eyes in the placebo group showed visual improvement. The postoperative complications were limited with only hyphema and was similar between the two groups. The same group evaluated the outcomes of adding 5-FU and LMWH into the infusion solution in RD patients with established PVR who underwent vitrectomy in another study which included 157 eyes with PVR.[16] All of the patients had stage C PVR and were randomized to either to receive 5-FU or not. The anatomical success rate was 56% in the 5-FU and 51% in the placebo group at months six which was not statistically significant. Retinal status at month 12 was also similar between the two groups and the retina was fully attached in 85% of the eyes in each group. Complications were glaucoma, hypotony, cataract formation and keratopathy and all were similar between the two study groups. Wickham et al conducted a larger study in order to evaluate the efficacy of 5-FU and LWMH in the treatment of unselected RD cases who underwent primary vitrectomy.[17] The study consisted of 641 patients from two centers. The primary outcome of the study was retinal attachment at postoperative month 6 similar to the previous studies. Baseline characteristics including gender, laterality, mean age, mean IOP, median visual acuity, corneal and lens status, presence of myopia, status of macula was all similar between the two groups. Applied surgical techniques was also assessed and the two groups did not differ in regards to used retinopexy technique, intraocular tamponade, and required additional procedures such as scleral buckling and membrane peeling. The primary success was 82.3% in the 5-FU group and 86.8% in the placebo group and the number of the patients who showed significant PVR at month 6 was also similar between the two groups. The median visual acuity at month 6 was 0.40 in both of the groups. The authors of the study concluded that the use of 5-FU and LMWH in unselected primary RD cases undergoing vitrectomy did not demonstrate an additional benefit and this combination was not suggested to be used in routine RD cases. In a more recent study by Ganekal and Dorairaj, the patients who were grouped as at high-risk PVR similar to the study by Asaria et al and randomized into two groups either to receive 5-FU and LMWH or not.[6,18] After a mean follow-up period of 6 months et al they reported that adding 5-FU and LMWH failed to prove efficacy in the prevention of PVR in contrast to Asaria et al. We used a technique which was similar to these discussed studies; however, the characteristics of the patients who were included in this study were different from all of them. We only included the patients who previously underwent an unsuccessful operation and had a recurrent RD with stage C PVR. Single anatomical success rate was better in our 5-FU group than the control group. We achieved 94.1% anatomical success with use of 5-FU and LMWH versus 53.8% without the use of this combination. The reason for unsuccessfulness was PVR in all of the remaining cases. Also, the patients in control group required a mean of 1.5 additional surgical interventions, whereas the patients in the 5-FU group did not require any. Visual outcomes were also significantly better in 5-FU group of our study. Functional success was achieved in 58.8% of the eyes in the 5-FU group and in only 23% of the eyes in the control group. Early postoperative complications were limited with anterior chamber reaction and corneal edema in both of the groups similar to the previous studies.

The main limitation of our study was its retrospective design and limited number of included patients. However, we evaluated a rather homogeneous special subgroup of recurrent RD patients in this comparative study and achieved positive outcomes in our adjuvant treatment arm which were two important strengths of our study.

Conclusions

In conclusion, the use of 5-FU and LWMH was assessed in previous studies. It was found to be effective in only a subgroup of primary RD patients who were calculated to be

high-risk patients for the development of PVR.[15–18] In this study we obtained significant favorable outcomes with the use of 5-FU and LMWH which were both added into the infusion solution during the vitrectomy surgery in patients with recurrent RD and grade C PVR. Therefore, we may suggest the use of these adjuvants in these advanced and complicated cases.

Conflict of interest

The authors declared that there is no conflict of interest.

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