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Interventions for Proliferative Vitreoretinopathy

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CLINICAL QUESTION What is the efficacy of pharmacologic interventions in preventing proliferative vitreoretinopathy?

BOTTOM LINE There is limited high-quality evidence to support currently available pharmacological options for prevention of proliferative vitreoretinopathy.

Introduction

Proliferative vitreoretinopathy (PVR) is a complication of rhegmatogenous and other types of retinal detachments (RD) and a leading cause of surgical failure. It is characterized by proliferative cellular membranes that grow on the surface or under the retina and can extend into the vitreous.[1] PVR-associated fibrocellullar proliferation and formation of contractile membranes lead to retinal traction.[2] PVR affects approximately 4000 patients a year with a US incidence of 5% to 10% of all RD.[3,4] It is the most common cause of surgical failure in rhegmatogenous retinal detachment (RRD) cases and often leads to poor visual outcomes. Adjuvant agents have been used to suppress the inflammation leading to PVR,[5,6] but there are no agents approved by regulatory authorities for the prevention of PVR.

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Summary of Findings

As of 2023, only 1 Cochrane review has been published on pharmacologic PVR interventions. We examined systematic reviews regarding pharmacologic interventions for PVR.[7-9] The available evidence is based on studies examining methotrexate, corticosteroids, and 5-fluorouracil (5-FU) with heparin.

In the methotrexate studies, all patients received 1 intravitreal injection intraoperatively, and in some studies, patients received additional injections after surgery with notable heterogeneity in injection regimens and patient characteristics. Though more robust studies are required, the current literature suggests that methotrexate improves best-corrected visual acuity (BCVA) irrespective of dosing schedule. No difference in retinal reattachment rates was observed, with 80% for methotrexate recipients compared with 83% in control groups. Of interest, a phase 3 randomized clinical trial (RCT), the GUARD trial, is assessing the rate of PVR after a series of 13 postoperative intravitreal injections of methotrexate over 16 weeks. The rate of RD over 6 months was reduced compared with historical control.[3] Final results have not been published in a peer-reviewed journal, and use of a historical control is a confounding factor. Corticosteroids have been used for PVR given their antiproliferative properties. A meta-analysis of 4 RCTs revealed no difference in recurrence rate of PVR. However, when considering only grade A and B PVR, the incidence of PVR recurrence in the steroid group was reduced (**Table**). Furthermore, the steroid group demonstrated a reduction in macular edema 6 months after surgery (relative risk [RR], 0.64; 95% CI, 0.47-0.88; $P = .007$). Retinal reattachment rate did not differ from that in controls (RR, 1.07; 95% CI, 0.99-1.15; $P = .10$).

Evidence Profile

No. of studies overall: 14

No. of randomized clinical trials: 7

No. of observational studies: 7 (methotrexate studies)

Study years: 1997-2022

Date of literature search: Up to September 12, 2023

No. of patients: 1541

Male: 66.6% **Female:** 33.4% (not reported in 1 study)

Race and ethnicity: Not reported

Age, range: 18-93 years

Setting: Outpatient clinics in Iran, Peru, Egypt, US, UK, and Switzerland

Comparisons: Interventions for proliferative vitreoretinopathy in various contexts vs surgical retinal reattachment, with varying dosages or timing regimens

Primary outcomes: Best-corrected visual acuity, retinal reattachment rate at 6 months, development of postoperative proliferative vitreoretinopathy within 6 months

Secondary outcomes: Intraocular pressure, macular edema, reoperation after primary surgery, epiretinal membrane, change in visual acuity, complication rates

A Cochrane review examining 5-FU/heparin was published in 2013 and included 2 RCTs. One study demonstrated benefit of 5-FU/heparin in reducing postoperative PVR, but another RCT showed no difference; no definitive recommendation could be given.

Discussion

Systematic reviews suggest methotrexate may improve BCVA outcomes. Corticosteroids may warrant consideration in grade A and B PVR, with limited evidence for grade C. The Cochrane review for 5-FU/heparin lacked consistent evidence to make a recommendation. In summary, the evidence regarding the benefit of pharmacotherapies is still limited in quality, and there is no firm evidence for one pharmacotherapy over standard RRD reattachment.

Limitations

Conclusions were based on a few studies with a small number of patients. For methotrexate, the absence of a control group in some studies coupled with substantial heterogeneity in patient characteristics and dosing regimens made it difficult to determine success. Corticosteroids and 5-FU/heparin had similar limitations because of small sample

Table. Summary of the Evidence

Context of pharmacologic use	Successful retinal attachment rates, No./total No. of patients (%)	Postoperative PVR rate, RR (95% CI)[a]	Study outcome	Quality of evidence
Methotrexate[b]				
Intraoperative injection in primary RD repair and established PVR	21/22 (95)	NA	Rate of retinal reattachment within 6 mo	Low to very low
Intraoperative methotrexate infusion	Established PVR: 31/42 (74) Primary RD with high risk of PVR: 27/35 (77) Primary RD with no risk of PVR: 23/24 (95)	NA		
Intraoperative and postoperative weekly injections for 4-8 wk in primary RD repair and established PVR	6/7 (85) after 3 mo	NA		
Corticosteroids[c]				
Intraoperative TA injection in primary RD repair with PVR grade C or established PVR	32/38 (84)	Grade A, B, and C PVR: RR, 0.87 (0.70-1.08); $P = .19$ Grade A and B PVR: RR, 0.67 (0.46-0.99); $P = .04$	Rate of retinal reattachment at 6 mo	Moderate
Intraoperative and 4-mo postoperative injection of slow-release dexamethasone in established PVR	34/69 (49)			
Postoperative oral prednisolone for 10 d in primary RRD repair with PVR grade A or B	3/4 (75)			
Oral prednisone from day of surgery to 15 d postoperative in primary RRD repair with or without grade A or B PVR	84/94 (89)			
5-Fluorouracil and low-molecular-weight heparin[d]				
Intraoperative intravitreal infusions in primary RRD repair	68/87 (78)	RR, 0.48 (0.25-0.92)	(1) Presence of PVR at 6 mo (2) Retinal attachment at 6 mo	"Good"
Intraoperative intravitreal infusions in primary RRD repair	269/327 (82)	RR, 1.45 (0.76-2.76)		

Abbreviations: NA, not applicable; PVR, proliferative vitreoretinopathy; RR, relative risk; RRD, rhegmatogenous retinal detachment; TA, triamcinolone acetonide.

[a] Relative risks are calculated to compare the pharmacologic group with the control group.

[b] Methotrexate: 250-400 µg; mean, 2.2 injections.

[c] Corticosteroids: 4 mg of TA, 1 mg/kg of oral prednisone, 0.7 mg of slow-release dexamethasone.

[d] 5-Fluorouracil, 200 µg/mL, and low-molecular-weight heparin, 5 IU/mL.

size, and the significant heterogeneity in the 5-FU/heparin studies precluded meta-analysis.

Comparison of Findings With Current Practice Guidelines

The current standard of care for PVR involves pars plana vitrectomy with surgical membrane peeling and retinal reattachment.[10] While corticosteroids may benefit grade A and B PVR, there is no consensus regarding the use of any pharmacologic intervention to reduce PVR in patients with more severe grade C PVR.

Areas in Need of Future Study

Given that PVR is the most common cause of failed surgery for RRD, randomized, adequately powered clinical trials using methods to reduce heterogeneity are warranted to investigate possible treatments. Patients who are offered adjunct pharmacologic agents commonly have had grade C PVR with multiple reattachment surgeries; therefore, clinical trials centered on this subgroup are needed. Currently, the decision to offer therapies with possible marginal benefit often rests on clinical equipoise.

ARTICLE INFORMATION

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