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Official Title

Comparison of peroperative methotrexate infusion with postoperative intra silicon oil methotrexate injections for prevention of proliferative vitreoretinopathy development after vitrectomy for rhegmatogenous retinal detachment repair.

Brief Title

Comparing Methotrexate Usage Techniques to Prevent Proliferative Vitreoretinopaty After Retinal Detachment Vitrectomy.

Topic of interest: Role of Methotrexate in the prevention of proliferative vitreoretinopathy development after pars plana vitrectomy for rhegmatogenous retinal detachment.

Research gap: A comparison of different dosing regimens of methotrexate is not available.

Research question.

Which methotrexate dosing strategy is more effective in preventing PVR after retinal detachment surgery (PPV): perioperative infusion or sequential postoperative injections?

Introduction

Retinal detachment is one of the major causes of irreversible blindness [1]. Increasing number of aging population, increasing myopia and increased number of cataract surgeries are resulting in increased incidence of retinal detachment [2,3].

Surgical intervention is essential for the treatment of rhegmatogenous retinal detachment. With increase in expertise of surgeons and refined gadgets, pars plana vitrectomy is the most commonly performed surgical procedure for the treatment of rhegmatogenous retinal detachment [4].

PVR is a major cause of retinal detachment surgery failure [5]. Many approaches have been attempted to stop the development of PVR [6]. Methotrexate infusion during pars plana vitrectomy has been tried. It has shown encouraging results in terms of prevention of development of PVR [7]. Serial methotrexate intrasilicon oil injections are utilized. They also have showed promising results in terms of prevention of PVR [8].

PVR develops in response to inflammatory cascade. PVR develops during initial postoperative period particularly 60 to 90 days after retinal detachment surgery [9].

Peroperative infusion of methotrexate provide loading dose. It is though that retinal tissues absorb methotrexate that prevents formation of PVR. This could be beneficial in the immediate postoperative period in stopping the development of PVR, but long-term prevention could not be provided. Half-life of intravitreal methotrexate is 3 to 5 days [10]. Repeated doses of methotrexate should be needed to prevent the development of PVR in the first 2 to 3 months after pars plana vitrectomy. According to our **hypothesis**, repeated intrasilicon oil methotrexate injection should prevent PVR formation to a greater extent than per operative methotrexate infusion.

Objective of this interventional trial is to compare the efficacy of repeated intrasilicon oil Methotrexate injections with per operatively Methotrexate infusion in the prevention of Proliferative Vitreoretinopathy

Key words: Injection, Methotrexate, Proliferative vitreoretinopathy, Retinal detachment, Vitrectomy

Methodology

This interventional trial will be conducted at the Sahiwal Teaching Hospital, Sahiwal and Ali Fatima Teaching Hospital Lahore from March 2024 to May 2025. The study will follow the guidelines of the Declaration of Helsinki. The study protocol will be approved by institutional review boards of respective hospitals. Written informed consent will be taken from all the subjects. The first subject will be recruited in March 2024 and the last subject will be recruited in February 2025. Three more months will be required to complete the final follow-up of the last subject.

The study will include rhegmatogenous retinal detachments patients of both sexes between 20 and 70 years of age.

Exclusion criteria will include the presence of proliferative vitreoretinopathy grade C, previous retinal detachment surgery in the same eye, penetrating ocular trauma, intraocular foreign bodies, previous glaucoma filtration surgery, allergy to methotrexate, and pregnant and lactating women.

A detailed history of the patients' presenting complaints, duration of symptoms, and risk factors for retinal detachment will be gathered. Comprehensive ocular examination, including visual acuity, intraocular pressure, and examination of the anterior and posterior segments, will be performed. The extent of retinal detachment, location of retinal breaks, and presence of PVR will be documented.

Sampling method will be simple random sampling. Sample size will be calculated by using online software.

RESULTS

Dichotomous Endpoint, Two Independent Sample Study

Sample Size	
Group 1	60
Group 2	60
Total	**120**

Study Parameters	
Incidence, group 1	12%
Incidence, group 2	0%
Alpha	0.05
Beta	0.2
Power	0.8

View Power Calculations

$$N_1 = \left\{ z_{1-\alpha/2} * \sqrt{\bar{p} * \bar{q} * (1 + \frac{1}{k})} + z_{1-\beta} * \sqrt{p_1 * q_1 + (\frac{p_2 * q_2}{k})} \right\}^2 / \Delta^2$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + k p_2}{1 + K}$$

$$\bar{q} = 1 - \bar{p}$$

$$N_1 = \left\{ 1.96 * \sqrt{0.06 * 0.94 * (1 + \frac{1}{1})} + 0.84 * \sqrt{0.12 * 0.88 + (\frac{0 * 1}{1})} \right\}^2 / 0.12^2$$

$$N_1 = 60$$

$$N_2 = K * N_1 = 60$$

p_1, p_2 = proportion (incidence) of groups #1 and #2
$\Delta = |p_2 - p_1|$ = absolute difference between two proportions
n_1 = sample size for group #1
n_2 = sample size for group #2
α = probability of type I error (usually 0.05)
β = probability of type II error (usually 0.2)
z = critical Z value for a given α or β
K = ratio of sample size for group #2 to group #1

Using lottery methods patients will be divided into two groups with 60 subjects in each group. Group 1 will be regarded as control group and per operative methotrexate infusion will be used by mixing 75 mg of methotrexate into one litre of BSS solution. Group 2 will be regarded as the study group and will receive 500 µg of intra-silicon oil methotrexate at the end of the surgery and then at 1st, 2^{nd}, 3^{rd} , 4^{th} and 6^{th} post operative weeks.

This will be a single-blind study in which the subjects will be unaware of the intervention. Blinding will be maintained by ensuring that subjects are unaware of the dosing regimens they are receiving.

Standard pars plana vitrectomy will be performed by two surgeons, one surgeon at Sahiwal Teaching Hospital Sahiwal and other surgeon at Ali Fatima Teaching Hospital Lahore. Silicon oil will be used as post operative tamponade in all subjects. A combination of steroid and antibiotic eye drops will be administered eight times per day during the first postoperative week. The dosing will be tapered off during the next three weeks. Patients will be instructed to adopt the appropriate posture according to the location of retinal breaks.

Follow-up will be performed every week for three months. The development of PVR, occurrence of retinal detachment, intraocular pressure, and visual acuity will be noted. The posterior segment will be examined with the help of a superfield lens and wide-field contact lens for the development of PVR and occurrence of retinal detachment.

The primary outcomes will be the development of PVR and the recurrence of retinal detachment. All patients will be followed up until the development of one of the primary outcomes or completion of 3 month follow, whichever occurs earlier.

Improvement in visual acuity will be secondary outcome of the study. Final visual acuity will be measured at completion of 3 month follow up or meeting the primary outcome, whichever is earlier.

All information will be collected using a specially designed proforma and entered into SPSS version 26. Qualitative variables, such as sex, PVR development, recurrence of retinal detachment, and improvement in visual acuity, will be presented as frequencies and percentages. Quantitative variables, such as age and intraocular pressure, are presented as mean and standard deviation.

In this prospective study we shall investigate the differences in the development of proliferative vitreoretinopathy (PVR) between two distinct groups. Additionally, we shall compare the difference in the occurrence of re-detachment of the retina between these groups. Furthermore, we shall compare the improvement in visual acuity at the final follow-up visit between the two groups. As the variables involved will be qualitative (frequency of eyes with development of PVR, Frequency of eyes with retinal

re-detachment, and frequency of eyes with improved visual acuity), Pearson's chi-square test will be used to carry out the statistical analysis. Statistical significance will set at $P \leq 0.05$.

References

[1] Kunikata H, Abe T, Nakazawa T. Historical, current and future approaches to surgery for rhegmatogenous retinal detachment. The Tohoku Journal of Experimental Medicine. 2019;248(3):159-68. doi.org/10.1620/tjem.248.159

[2] van Leeuwen R, Haarman AE, Van De Put MA, Klaver CC, Los LI. Dutch Rhegmatogenous Retinal Detachment Study Group. Association of rhegmatogenous retinal detachment incidence with myopia prevalence in the Netherlands. JAMA ophthalmology. 2021;139(1):85-92. doi:10.1001/jamaophthalmol.2020.5114

[3] Park JY, Byun SJ, Woo SJ, Park KH, Park SJ. Increasing trend in rhegmatogenous retinal detachment in Korea from 2004 to 2015. BMC ophthalmology. 2021; 21:1-1. doi.org/10.1186/s12886-021-02157-1

[4] Sultan ZN, Agorogiannis EI, Iannetta D, Steel D, Sandinha T. Rhegmatogenous retinal detachment: a review of current practice in diagnosis and management. BMJ open ophthalmology. 2020;5(1): e000474. doi:10.1136/bmjophth-2020-000474

[5] Nagpal M, Juneja R, Talati S. Managing PVR in the era of small gauge surgery. Journal of Ophthalmology. 2021;2021: 10 pages. doi.org/10.1155/2021/8959153

[6] Schaub F, Abdullatif AM, Fauser S. Proliferative vitreoretinopathy prophylaxis: mission (im) possible. Der Ophthalmologe. 2021; 118:3-9. doi.org/10.1007/s00347-020-01173-8

[7] Jahangir S, Jahangir T, Ali MH, Lateef Q, Hamza U, Tayyab H, et al. Use of intravitreal methotrexate infusion in complicated retinal detachment for prevention of proliferative vitreoretinopathy in a pilot study. Cureus. 2021;13(8): e17439. doi: 10.7759/cureus.17439

[8] Roca JA, Yon-Mendoza A, Huamán N, Wu L. Adjunctive serial post-operative intravitreal methotrexate injections in the management of advanced proliferative vitreoretinopathy. Graefe's Archive for Clinical and Experimental Ophthalmology. 2021;259(10):2913-7. doi.org/10.1007/s00417-021-05206-z

[9] Xu K, Chin EK, Bennett SR, Williams DF, Ryan EH, Dev S, et al. Predictive factors for proliferative vitreoretinopathy formation after uncomplicated primary retinal detachment repair. Retina. 2019;39(8):1488-95. doi: 10.1097/IAE.0000000000002184

[10] El Baha S, Leila M, Amr A, Lolah M. Anatomical and functional outcomes of vitrectomy with/without intravitreal methotrexate infusion for management of proliferative vitreoretinopathy secondary to rhegmatogenous retinal detachment. Journal of Ophthalmology. 2021;2021: 10 pages, doi.org/10.1155/2021/3648134