TITLE

Postoperative aqueous humour flare as a surrogate marker for proliferative vitreoretinopathy development

RUNNING HEAD

Aqueous humour flare as a surrogate marker for PVR

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ABSTRACT

Purpose

As some surgical procedures have been shown to increase postoperative flare values and thus contribute to blood-ocular barrier breakdown, retinal reattachment surgery might influence the risk of developing proliferative vitreoretinopathy (PVR). Therefore, we investigated whether postoperative aqueous flare values are a surrogate marker for the development of postoperative PVR.

Methods

We prospectively included 195 patients with primary rhegmatogenous retinal detachment (RRD) and measured aqueous laser flare preoperatively, and at two and six weeks postoperatively. Postoperative PVR was defined as reoperation for redetachment due to PVR membranes, within six months of initial surgery. Logistic regression and ROC analysis determined whether higher postoperative flare values were associated with an increased risk of developing PVR later on.

Results

Reoperation for postoperative PVR was needed in 12 (6.2%) patients; in 18 (9.2%) reoperation was not related to PVR. The median flare value for patients who would develop PVR was significantly higher than that of patients who would not develop PVR, both at two weeks (p=.001) and six weeks (p<0.001) postoperatively. Logistic regression analyses showed that a higher flare value significantly increased the odds of developing PVR, either at two weeks (odds ratio (OR) 1.027; 95%CI: 1.010-1.044) or six weeks (OR 1.076; 95%CI: 1.038-1.115).

Conclusion

Flare values both at two and six weeks postoperatively seem a good surrogate marker in terms of sensitivity and specificity for the development of postoperative PVR. The two-week value would be more useful in terms of early recognition of high-risk patients and hence give the possibility to better study effects of treatment methods.

Keywords: laser flare, retinal detachment, proliferative vitreoretinopathy (PVR)

INTRODUCTION

Anterior chamber aqueous flare – a surrogate marker for inflammation – has been proposed as a predictor for proliferative vitreoretinopathy (PVR) in patients with a rhegmatogenous retinal detachment (RRD)(Conart et al. 2016, Hoerster et al. 2013, Schroder et al. 2012). In contrast to previous reports, we recently reported that the preoperative aqueous flare value ~~measured before surgery~~ is not a strong predictor for the development of PVR postoperatively (Mulder et al. 2017).

Although a minority of patients without a history of ocular disease presents with PVR prior to retinal reattachment surgery, in industrialis~~z~~ed countries 5-10% of patients typically develop PVR in two weeks to six months after surgery. ~~Although advances in surgical techniques have improved anatomical success~~ Some of these surgical procedures ~~used to reattach the retina~~ have been shown to increase postoperative flare values and thus ~~to~~ contribute to blood-ocular barrier breakdown (Bali et al. 2010, Hoshi et al. 2012, Jumper et al. 2006, Veckeneer et al. 2001). Therefore, retinal reattachment surgery is thought to possibly influence the risk of developing postoperative PVR (Cowley et al. 1989).

The flare value after surgery might therefore be a better indication of the development of postoperative PVR than the preoperative flare value. We investigated whether postoperative aqueous flare values or a change in aqueous flare values from preoperative to postoperative are a surrogate marker for the development of postoperative PVR.

METHODS

Patients

From January 2014 until October 2014 we included 208 patients with RRD admitted to the Rotterdam Eye Hospital, the Netherlands. Patients with additional ocular pathologies such as active uveitis, active vasculitis, retinal vein occlusion, diabetic macular oedema, proliferative diabetic retinopathy, exudative age-related macular degeneration, and primary PVR grade C or higher, were excluded. Postoperative PVR was defined as reoperation for redetachment due to PVR membranes, within six months of initial surgery. This information was extracted from the patient's file or, when not conclusive, by contacting either the patient or his/her current physician. The standardised surgical reports of the reoperations and the patient's file were evaluated by one vitreoretinal surgeon (masked to flare values) who scored each reoperation as either not PVR related or PVR related.

The study followed the tenets of the Declaration of Helsinki and was approved by the institutional review board. All patients gave written informed consent. This patient cohort has been part of a previously published report with a different research question exclusively on preoperative measurements (Mulder et al. 2017).

Flare measurements

Aqueous laser flare of the anterior chamber was measured preoperatively and during regular postoperative visits at two and six weeks with a Kowa FM-500 Laser Flare Meter (Kowa Company Ltd.

Tokyo, Japan). We performed seven measurements 15 minutes after instillation of 0.5% tropicamide eye drops. The highest and the lowest value were discarded, leaving an average of five measurements. In addition, we recorded the preoperative and postoperative lens status, the extent of retinal detachment, number of horseshoe tears, presence of curled edges during surgery, type of surgery, and medication history. In all patients undergoing a vitrectomy procedure triamcinolone (Kenacort®) was used to visualize the vitreous during vitreous removal. Standard treatment after surgery consisted of a subconjunctival injection of betamethasone (Celestone® 4mg) ~~after surgery consisted~~ and of four times daily prednisolone acetate eye drops (Pred Forte®) which were tapered over four weeks. Deviations from this protocol were also recorded.

Sample size

From previous measurements and other studies, it was known that flare values do not follow a normal distribution and that non-inflamed healthy eyes have (10log-transformed) flare values of 0.7 ± 0.3 (Bali et al. 2010, Shah et al. 1991, Veckeneer et al. 2001). For the purpose of the sample size calculation of the original study it was assumed that the standard deviation (SD) would be slightly higher (SD=0.4) (Mulder et al. 2017). The incidence of PVR was estimated at 10%, the two-sided significance level was set at α=0.05, power at P=0.80, and a factor two increase in flare value was thought to be clinically relevant. This led to a sample size of 176 eyes of which at least 16 eyes were expected to develop postoperative PVR.

Statistical analysis

Since aqueous flare values are not normally distributed we looked at median flare values and used non-parametric tests. Patients who required reoperation for another indication than PVR were displayed as a separate group but for the logistic regression and ROC analysis they were included in the uncomplicated RRD group. Median flare values of the three groups were compared using a Kruskal-Wallis test with pairwise comparisons for both time points (two and six weeks).

We performed logistic regression to assess to what extent a higher postoperative flare value at either two or six weeks increased the risk of postoperative PVR development. ROC analysis was used to test the sensitivity and specificity of postoperative flare values in discriminating between PVR and no PVR development, and to define the optimal cut-off point. A Mann-Whitney U-test was used to compare the individual changes in flare values from preoperative to two weeks postoperatively between the two groups.

Statistical analyses were performed with IBM SPSS statistics version 21 (IBM Corp., Armonk, NY, USA).

RESULTS

We included 208 patients of which five patients were excluded due to other ocular pathology than RRD, three had preoperative PVR, two patients were lost to follow-up, two had multiple failed flare measurements and one received only laser treatment. The characteristics of the remaining 195 patients are shown in **Table 1**. Thirty patients (15%) underwent reoperation, out of whom four patients had a persistent detachment (reoperation within one week) and 12 patients (6.2%) developed postoperative PVR for which surgery was performed. The remaining 14 patients had redetachments caused by new breaks (n= 8), not completely closed old breaks (n= 4), a macular hole (n= 1) or giant tear (n= 1), without any signs of traction due to epiretinal membranes or subretinal strands. The median time until reoperation was 49 days (range 12-183 days) for patients who had developed PVR and 20 days (range 2-139 days) for reoperation due to other reasons.

Postoperative flare values

At two weeks postoperatively, the pairwise comparisons showed a significant difference between patients who would develop PVR postoperatively and patients with uncomplicated RRD (adjusted p= 0.001; n= 10 vs. n=162). The median flare value of patients with a reoperation due to other reasons (n=12) did not differ significantly from the two other groups (adjusted p= 0.526 and p= 0.176), at two weeks postoperatively. At six weeks, the flare values of patients who would develop PVR (n= 8) remained higher than those of patients who received a reoperation for another reason (adjusted p = 0.002; n= 5) and of patients with uncomplicated RRD (adjusted p < 0.001; n= 164).

Since eight patients required reoperation before their evaluation visit at two weeks and nine patients required reoperation before their evaluation visit at six weeks, the flare values of those visits are missing. **Figure 1** shows the median flare values over time for the three mentioned groups. The whiskers represent the interquartile ranges.

Postoperative flare value and risk of PVR development

We tested whether a higher flare value at either two or six weeks after surgery was a surrogate marker for a future PVR redetachment. Patients requiring reoperation due to other reasons than PVR were included in the uncomplicated group. The logistic regression analysis showed a significant result for both time points (see **Table 2**).

Sensitivity, specificity, and positive predictive value

The ROC analysis showed high area under the ROC curves for both the two-week postoperative values (0.84; 95% CI: 0.76 – 0.93) and the six-week postoperative values (0.92; 95% CI: 0.86 – 0.97). A cut-off value of 34 pc/ms two weeks postoperatively led to both a sensitivity and specificity of 80% (see **Figure 2**). For the values obtained at six weeks, the optimal cut-off value was 27 pc/ms, with an accompanying sensitivity and specificity of 100% and 83%. A cut-off of 27 pc/ms for the two-week postoperative values, showed 85% sensitivity and 69% specificity. The probability that a patient with a flare value above 27 pc/ms at two or six weeks postoperatively developed a PVR redetachment – the positive predictive value – was 14.5 and 22 percent. The positive predictive value with a cut-off of 34 pc/ms two weeks postoperatively was 18%.

Absolute change in flare values from preoperatively to two weeks postoperatively

We calculated the individual absolute change in pc/ms from the preoperative value to the two-week flare value for patients who would not develop PVR (uncomplicated RRD) – including patients with reoperations due to other reasons—and for patients who would later develop postoperative PVR. A positive value in **Figure 3** means that the flare value increased after surgery and a negative value means a decrease in flare value. **Figure 3** shows that the flare value in patients who would later develop postoperative PVR increased in half of the patients and decreased in the other half. In patients who would not develop PVR, the flare value increased slightly in most cases. The distribution of differences was not significantly different between the two groups (Mann-Whitney U p= 0.672). One factor that potentially could contribute to a large drop in the flare value postoperatively is the reversal of hypotony. Three patients presented with an IOP ≤ 4mmHg preoperatively of which one developed PVR. In this patient, the flare value changed from 43 pc/ms preoperatively to 37 pc/ms two weeks postoperatively.

DISCUSSION

The logistic regression showed that a higher postoperative flare value at either two or six weeks increased the chance of developing postoperative PVR. The ROC analysis provided insight into the optimal cut-off values, which is a balance between not missing any patients who will develop postoperative PVR (sensitivity) and not labelling too many patients incorrectly as high-risk patients (specificity). The area under the ROC curve showed a better result for the six-week values, due to reaching 100% sensitivity and a good specificity. The accompanying cut-off value was 27 pc/ms. None of the eight patients who had not yet developed postoperative PVR at that point had a flare value below this value and 28 out of 183 patients who would not develop PVR had a flare value above 27 pc/ms (specificity 83%). For the two-week values, the optimum was 80% sensitivity with 80% specificity and an accompanying cut-off value of 34 pc/ms.

Although the ROC analyses showed high sensitivity and specificity at a cut-off value of 34 pc/ms and 27 pc/ms at two and six weeks postoperatively, this led to positive predictive values of only 18% and 22%. Most probably, the main reason for this was the low prevalence of postoperative PVR in our study (6.2%). However, using these cut-off values for postoperative flare would still improve the selection of patients at high risk by approximately 3.5 times.

Although the six-week ~~results were~~measurements proved to be a better marker for later PVR than the two-week measurements~~results~~, the two-week measurements~~results~~ would be more useful in terms of earl~~y~~ier recognition of ~~a~~ high ~~-~~risk ~~patient~~ for PVR and subsequently ~~give~~ the possibility to start a treatment. Moreover, at two weeks less patients will have already experienced a PVR redetachment. Postoperative therapeutic options would be the administration of oral drugs or injections when such a treatment would be available and effective(Ahmadieh et al. 2008, Ahmadieh et al. 2015, Chang et al. 2008, Fekrat et al. 1995, Jonas et al. 2003, Koerner et al. 2012, Mulder et al. 2016). Both postoperative measurements could be used by ophthalmologists ~~or~~to monitor inflammation and study treatment methods.

The absolute flare value was a better surrogate marker for postoperative PVR development than the change in flare value. While the overall trend in flare values was an increase after surgery followed by a decrease towards six weeks, the individual changes from the preoperative flare value to the postoperative flare value at two weeks did not show a clear trend. This was highlighted in the ten patients who would later develop PVR: flare values increased in five cases~~,~~ but decreased in the five other cases.

The absence of a clear trend might be the result of specific proceedings and choices by the surgeon and/or patient during surgery and early postoperative phase. Patients who underwent a vitrectomy procedure seemed to have higher postoperative flare values than patients who underwent scleral buckling, independent of the number of quadrants detachment (data not shown). In addition, factors such as the occurrence of complications, duration of surgery, choice of vital dyes, manipulation due to indentation and the use of antibiotics and/or steroids, may influence the inflammatory response.

Figuring out the individual importance of these factors would require an extremely large sample size, whereas the postoperative flare value represents the sum of these factors.

Adding the outcome of postoperative aqueous flare measurements to existing risk prediction models could possibly increase its value. The size of a detachment is a well-known risk factor for the development of PVR, but the size of the detachment is also correlated to flare (Conart et al. 2016, Schroder et al. 2012). In our study, this association was the strongest for preoperative flare and higher number of quadrants detachment ($r_s = 0.42$, $p < 0.001$), for postoperative flare this association was weak ($r_s = 0.20$, $p = 0.005$). In addition, correcting for the number of quadrants detachment in the logistic regression analysis did not change the odds ratio for the postoperative flare value (data not shown).

These results should, however, be interpreted with caution due to a lower prevalence of postoperative PVR in our sample than anticipated. In conclusion, postoperative flare values two weeks after RRDD surgery are a reasonable surrogate marker for the development of postoperative PVR. Despite the fact that these results should be validated in other cohorts including more patients with postoperative PVR, flare measurements could already be of importance in estimating the chance of PVR development after RRDD surgery~~, particularly in the setting of a treatment trial where it would allow the recruitment of patients at increased risk of PVR.~~

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CONTRIBUTOR STATEMENT

- The conception or design of the work: VCM, EHCD, JCM
- Data acquisition: VCM, EHCD, IM and Annemiek Krijnen.
- Analysis and interpretation of data: VCM, EHCD, ECLH, JCM
- Drafting the work: VCM
- Revising the work: EHCD, IM, ECLH, JCM
- Final approval of the version published: VCM, EHCD, IM, ECLH, JCM
- Agreement to be accountable for all aspects of the work VCM, EHCD, IM, ECLH, JCM

Support: Frank Verbraak (lender Flare meter)

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FIGURE LEGENDS

Fig. 1 Median flare values over time for the three different groups of patients with a rhegmatogenous retinal detachment. The whiskers represent the interquartile ranges (25-75%)

Fig. 2 ROC analyses of flare values at two and six weeks postoperatively and postoperative proliferative vitreoretinopathy (PVR) development. Patients requiring reoperation due to other reasons than PVR are included in the uncomplicated group

Fig. 3 Histogram of absolute differences between the preoperative value and postoperative value at 2 weeks. A positive value means an increase after surgery; a negative value a decrease after surgery

TABLE LEGENDS

Tab. 1 Patient characteristics of 195 patients with a rhegmatogenous retinal detachment

Tab. 2 Results from logistic regression comparing uncomplicated rhegmatogenous retinal detachment patients with patients who developed proliferative vitreoretinopathy.