

# Predictive factors for anterior chamber fibrin formation after vitreoretinal surgery

## *Fatores preditivos para formação de fibrina na câmara anterior após cirurgia vitreoretiniana*

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### ABSTRACT

**Purpose:** The aim of this study was to investigate possible predictive factors related to anterior chamber fibrin formation after vitreoretinal surgery in a large series of patients. **Methods:** The data of 185 eyes of 185 patients submitted to vitreoretinal surgery was reviewed. The following variables were evaluated: the postoperatively presence of fibrin, age, diabetes mellitus, the vitrectomy system gauge (20, 23 or 25 gauge), the type of vitreous substitute, the influence of prior surgical procedures and the combination with cataract extraction. To evaluate predictive factors for anterior chamber fibrin formation, univariate analysis was performed. A multivariate stepwise logistic regression model was adjusted to investigate factors associated with fibrin formation ( $p < 0.05$ ). **Results:** Fibrinoid anterior chamber reaction was found in 12 (6.4%) patients. For multivariate logistic regression analysis, balanced salt solution (BSS), the chance of fibrin occurrence was 5 times greater (odds ratio 4.83, CI 95% 1.302 - 17.892;  $p = 0.019$ ), while combination with phacoemulsification increased the chance of fibrin formation by 20 times (odds ratio 20, CI 95% 2.480 - 161.347;  $p = 0.005$ ). No significant difference was found regarding other variables. **Conclusion:** Anterior chamber fibrin formation is an unwanted complication after vitreoretinal surgery. Factors such as combined performance of phacoemulsification and the use of balanced salt solution as a vitreous substitute may predispose the occurrence of this complication.

**Keywords:** Cataract/surgery; Fibrin; Phacoemulsification/adverse effects; Vitrectomy/adverse effects; Tissue plasminogen activator; Vitreoretinal surgery

### RESUMO

**Objetivo:** Avaliar os possíveis fatores relacionados à formação de fibrina na câmara anterior após cirurgia vitreoretiniana em uma grande série de casos. **Métodos:** Foi realizado um estudo retrospectivo, observacional, caso-controle, onde os dados de 185 olhos de 185 pacientes submetidos à cirurgia vitreoretiniana foram avaliados. Os seguintes dados foram analisados: presença ou não de fibrina na câmara anterior na primeira semana de pós-operatório, idade, presença ou não de diabetes mellitus, calibre do sistema de vitrectomia utilizado (20,23 ou 25 gauge), substituto vítreo, a influência de cirurgias oftalmológicas prévias e a realização de cirurgia de catarata combinada. Para avaliação dos fatores preditivos para formação de fibrina, a análise univariada foi realizada. O modelo de regressão logística multivariada foi utilizado para investigar os fatores associados com a formação de fibrina ( $p < 0,05$ ). **Resultados:** A presença de fibrina na câmara anterior foi encontrada em 12 (6,4%) pacientes. Pela análise de regressão logística multivariada, o uso de solução salina balanceada (BSS) como substituto vítreo, a chance da presença de fibrina foi 5 vezes maior (odds ratio 4,83, IC 95% 1,302 – 17,892;  $p = 0,019$ ), enquanto que a realização de cirurgia facoemulsificação combinada aumentou a chance de formação de fibrina 20 vezes (odds ratio 20, IC 95% 2,480 – 161,347;  $p = 0,005$ ). Nenhuma diferença estatisticamente significativa foi encontrada para as outras variáveis. **Conclusão:** A formação de fibrina na câmara é uma complicação indesejada após cirurgia vitreoretiniana. Fatores como realização de cirurgia de facoemulsificação combinada e o uso de BSS como substituto vítreo podem predispor a esta complicação.

**Descritores:** Catarata/cirurgia; Fibrina; Facoemulsificação/efeitos adversos; Vitrectomia/efeitos adversos; Ativador de plasminogênio tecidual; Cirurgia vitreoretiniana

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## INTRODUCTION

Inflammatory reaction of the anterior segment associated with alterations of the blood-aqueous barrier are common events in the postoperative period of intraocular eye surgery<sup>(1)</sup>. These events are usually easily managed with the use of topical anti-inflammatory medication for a few days or weeks. Anterior chamber fibrin formation after intraocular surgeries, on the other hand, is a rare and potentially serious complication that may lead to visual loss from posterior capsule opacification, posterior synechiae, intraocular lens decentration, intraocular hypertension and pupillary seclusion<sup>(1,2)</sup>. The incidence of anterior chamber fibrin formation is estimated around 2% after cataract extraction and intraocular lens implantation<sup>(3)</sup>, but with the advent of modern small-incision cataract surgery, it is probable that this incidence is much lower nowadays. However, some special situations can lead to an increased risk of developing anterior chamber fibrin formation after intraocular surgeries, such as in children, diabetic patients, eyes with uveitis, penetrating ocular trauma or complicated surgeries with extensive manipulation, cataract surgery with posterior capsule ruptured and combined surgical procedures<sup>(4-7)</sup>.

The occurrence of anterior chamber fibrin reaction after vitreoretinal surgery is an important complication, especially because of posterior segment visualization impairment. Several previous studies have evaluated the efficacy of recombinant tissue plasminogen activator (t-PA) in case of anterior chamber fibrinoid formation after vitreoretinal surgery<sup>(2,8-10)</sup>. However, none of them evaluated in detail the main factors involved in the development of fibrin in anterior chamber after vitreoretinal surgery. The aim of this study was therefore to investigate possible predictive factors associated with the formation of fibrin in the anterior chamber in patients submitted to vitreoretinal surgery.

## METHODS

A retrospective, consecutive, observational study was conducted between January 2009 and August 2010. The data from all patients undergoing vitreoretinal surgery (pars plana vitrectomy, associated or not intraocular lens implantation) were reviewed. The following variables were evaluated: presence of fibrin in anterior chamber within the first 3 days after surgery, age, presence of diabetes, the gauge of the vitrectomy system (20, 23 or 25), the type of vitreous substitute (balanced salt solution – BSS, gas or silicone oil), the influence of prior surgical procedures and the association with cataract surgery at the time of vitreoretinal surgery. All patients included in the study had complete medical records.

For statistical analysis, the comparison between groups was performed using the Student *t* test, chi-square or Fischer's exact tests, for categorical variables and Student's *t* test or Mann-Whitney test for continuous variables. Using the variables with  $p < 0.10$  in the univariate model, a multivariate stepwise logistic regression model was adjusted to investigate factors associated with fibrin formation. A *p* value less than 0.05 was considered statistically significant. In all regression analysis, the presence of anterior chamber fibrin formation was considered as the dependent variable, whereas patient's age, presence of diabetes, the vitrectomy system gauge, the type of vitreous substitute and the association with cataract surgery were considered as independent variables.

## RESULTS

A total of 185 eyes of 185 patients submitted to vitreoretinal surgery between January 2009 and August 2010 were included. The mean age was 59.75 years  $\pm$  15.90 SD. One hundred and four (56.21%) patients were male and 69 (37.29%) diabetic. In 86 (46.48%) a 20-gauge incision was used; in 87 (47%) a 23-gauge and in 12 (6.48%), a 25-gauge incision was performed. In 50 (27%) BSS was the vitreous substitute, in 48 (26%) intraocular gas (C3F8 or SF6) and in 87 (47%) silicone oil. Regarding prior surgical procedures, 7 (3.78%) patients had previous vitrectomy followed by silicone oil removal. Phacoemulsification was performed combined with vitreoretinal surgery in 66 (35.7%) patients. The two most frequent diagnoses were rhegmatogenous retinal detachment (72 cases - 38.91%) and proliferative diabetic retinopathy associated with vitreous hemorrhage with or without tractional retinal detachment (48 cases - 25.9%). Table 1 shows the distribution of patients according to the diagnosis.

The presence of fibrin in anterior chamber was found in 12 patients (6.5%) of 185 patients. The presence of intraocular fibrin was graded as slight (several fibrin strands), moderate (compact fibrin aggregates), or severe (fibrin membranes or clots)<sup>(3)</sup>. In 8 patients fibrin was graded as moderate and in 4 as severe (table 2).

In all cases, the presence of fibrin was observed in the first postoperative day. All patients with fibrinoid reaction underwent 25mcg/0.1mL of t-PA (Ophtalmos, São Paulo, Brazil) intracameral injection under aseptic conditions. In all, there was a rapid absorption of fibrin, with improvement of symptoms within the first 24 hours (figure 1). No complications or adverse side effects possibly related to t-PA were observed.

Table 2 shows the clinical characteristics of 12 patients who developed fibrinoid reaction. The mean age was 56.50  $\pm$  15.41 and 57.05  $\pm$  15.96 for the 173 patients without fibrinoid reaction. No statistically significant difference between groups regarding age or gender was found. Table 3 shows the comparison results between the two groups. Among patients who had developed fibrin in anterior chamber, BSS was used as vitreous substitute in 8 (6.7%) ( $p=0.004$ ), in 11 (91.7%) phacoemulsification combined with vitreoretinal surgery was performed ( $p<0.001$ ) and in 3(25%) the silicone oil was removed, indicating a significant association with these three variables (table 3 and 4).

Table 1

### Distribution of patients according to the diagnosis in 185 patients submitted to vitreoretinal surgery

Diagnosis	n	%
Macular holes	15	8.1
IOFB	3	1.6
DM, VH, tractional RD	48	25.9
Rhegmatogenous RD	72	38.9
Endophthalmitis	6	3.2
Misdirection glaucom	1	0.5
HV	10	5.4
ERM	19	10.3
Retained lens fragments 4	2.2	
Vitreous opacities	7	3.8
<b>Total</b>	<b>185</b>	<b>10</b>

IOFB: intraocular foreign body; DM: diabetes mellitus; VH: vitreous hemorrhage; RD: retinal detachment; ERM: epiretinal membrane

**Table 2**  
**Clinical characteristics of 12 patients submitted to vitreoretinal surgery and anterior chamber fibrin formation**

Patient	Age	Sex	Eye	Diagnosis	Surgical procedure	Gauge	Diabetes	Vitreous substitute
1	80	M	OS	Rhegmatogenous RD	Phacoemulsification + IOL + Silicone oil removal	20	No	BSS
2	64	F	OS	DM, VH, tractional RD	Phacoemulsification + IOL + PPV	20	No	Silicone oil
3	25	M	OS	Rhegmatogenous RD	Phacoemulsification + IOL + Silicone oil removal	20	No	BSS
4	58	F	OS	DM, VH, tractional RD	Phacoemulsification + IOL + PPV	20	Yes	Gas
5	53	F	OD	ERM	Phacoemulsification + IOL + PPV	25	No	BSS
6	63	F	OD	DM, VH, tractional RD	Phacoemulsification + IOL + PPV	23	Yes	BSS
7	64	M	OS	Rhegmatogenous RD	Phacoemulsification + IOL + Silicone oil removal	20	No	BSS
8	41	F	OD	Rhegmatogenous RD	Phacoemulsification + IOL + PPV	23	No	Gas
9	76	M	OD	Retained lens fragments	Phacoemulsification + IOL + PPV	23	No	BSS
10	61	F	OS	ERM	Phacoemulsification + IOL + PPV	23	No	BSS
11	41	M	OS	Vitreous opacities	Phacoemulsification + IOL + PPV	23	No	BSS
12	52	M	OD	Rhegmatogenous RD	PPV	23	No	Gas

M: male; F: female; OD: right eye; OS: left eye; RD: retinal detachment; DM: diabetes mellitus; VH: vitreous hemorrhage; ERM: epiretinal membrane; IOL: intraocular lens; PPV: pars plana vitrectomy; BSS: balanced salt solution

**Table 3**

**Comparison between groups submitted to vitreoretinal surgery according to the presence or absence of anterior chamber fibrin formation**

	Without fibrin (n=173)	With fibrin (n=12)	p-value
Age	59.98 ± 15.96	56.50 ± 15.41	0.465(*)
Sex (M/F)	98/75	1	0.654(**)
Vitreous substitutes			
BSS	42 (24.3%)	8 (66.7%)	0.004(***)
Gas	42 (24.3%)	3 (25%)	<0.0001(***)
Silicone oil	86 (46.48%)	1 (8.3%)	<0.0001(***)
Phacoemulsification	55 (31.8%)	11 (91.7%)	<0.0001(***)
Gauge			
20	81 (46.8%)	5 (41.7%)	
23	81 (46.8%)	6 (50.0%)	0.925(**)
25	11 (6.4%)	1 (8.3%)	
Diabetes	67 (38.7%)	2 (16.7%)	0.216(***)
Prior surgery			
Silicone oil removal	4 (2.3%)	3 (25.0%)	0.006(***)

M: male; F: female; BSS: balanced salt solution; (\*) Student t test; (\*\*) Chi-square test; (\*\*\*) Fisher test; significant values are in italic (p<0.05)

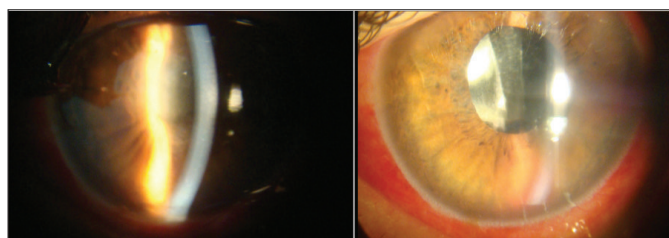


Figure 1: left - Patient with fibrin in anterior chamber in the first post-operative of vitrectomy combined with phacoemulsification with intraocular lens implantation; right - same patient three hours after intracameral injection of 25mcg/0,1mL of t-PA; note the good response to treatment, with improvement and better visualization of the anterior segment (patient 5, table 2)

**Table 4**

**Odds ratio and confidence intervals (CI) 95% of the analyzed variables (univariate model)**

Variable	Odds ratio	CI 95%	p-value
Age	0.99	(0.95; 1.02)	0.464
Sex			
F	1	-	-
M	0.77	(0.24; 2.47)	0.654
BSS			
No	1	-	-
Yes	6.24	(1.79; 21.76)	0.004
Gas			
No	1	-	-
Yes	1.04	(0.27;4.02)	0.771
Silicone oil			
No	1	-	-
Yes	0.09	(0.01;0.73)	0.013
Phacoemulsification			
No	1	-	-
Yes	23.6	(2.97; 187.39)	0.003
Gauge			
20	1	-	-
23	1.2	(0.35; 4.09)	0.771
25	1.47	(0.16; 13.80)	0.735
Diabetes			
No	1	-	-
Yes	0.32	(0.07; 1.49)	0.145
Prior surgical procedure			
Silicone oil removal			
No	1	-	-
Yes	14.08	(2.73;72.62)	0.002

M: male. F: female. BSS: balanced salt solution. Significant values are in italic (p<0.05)

In order to determine whether the variables were risk or protective factors for anterior chamber fibrin formation, the odds ratio was estimated in the usual manner (table 4). The presence

of fibrin was considered the variable dependent and the phacoemulsification, the vitreous substitute (BSS, gas or silicone oil), the gauge of vitrectomy system used (20, 23 or 25), the silicone oil removal and the presence of diabetes mellitus were considered independent variables. It was found that use of BSS, the silicone oil removal and the concomitant performances of phacoemulsification were associated with the presence of fibrin. The patients in which BSS was used, the chance of fibrin formation was six times higher than those in which BSS was not used (*odds ratio* 6.24, CI 95% 1.79 - 21.76;  $p=0.004$ ). In patients submitted to silicone oil removal, the chance of fibrin formation was 14 times higher (*odds ratio* 14.08, CI 95% 2.73 - 72.62;  $p=0.002$ ). In patients who underwent phacoemulsification combined vitreoretinal surgery, the chance of fibrin formation was 24 times higher than patients undergoing vitreoretinal surgery without cataract extraction (*odds ratio* 23.6, CI 95% 2.97 - 187.39;  $p=0.003$ ) (Table 4).

For multivariate logistic regression analysis, variables with  $p<0.10$  in univariate models were selected. Therefore, the use of BSS, silicone oil removal and phacoemulsification were chosen. For the multivariate model, logistic regression analysis found that only BSS and phacoemulsification were associated with the fibrin formation (Table 5), while the silicone oil removal were not ( $p=0.17$ ). In patients that used BSS, the chance of fibrin occurrence was 5 times greater (*odds ratio* 4.83, CI 95% 1.302 - 17.892;  $p=0.019$ ), while in patients who underwent phacoemulsification, the chance of occurrence of fibrin was 20 times higher (*odds ratio* 20, CI 95% 2.480 - 161.347;  $p=0.005$ ).

**Table 5**  
**Odds ratio and confidence intervals 95% of the analyzed variables (multivariate model)**

Variable	<i>Odds ratio adjusted</i>	CI 95%	p-value
<b>BSS</b>			
No	1	-	-
Yes	4.83	(1.30; 17.89)	0.019
<b>Phacoemulsification</b>			
No	1	-	-
Yes	20	(2.48; 161.35)	0.005

CI: confidence intervals; M: male; F: female; BSS: salt balanced solution; Significant values are in italic ( $p<0.05$ )

## DISCUSSION

The importance of this present study was to assess the incidence of anterior chamber fibrin formation in patients submitted to vitreoretinal surgery and also which predictive factors were involved. Only a few previous studies evaluated the incidence of fibrinoid reaction after intraocular surgery. Heiligenhaus et al.<sup>(1)</sup> investigated in a multicenter, prospective, randomized study the effect of intracameral t-PA in patients with severe fibrinoid reaction after cataract surgery. These authors included 86 patients in this study, corresponding, approximately, to 2% of all cataracts performed during all period of the study, in the six participating centers. This work was conducted from 1993 to 1994, and included patients who underwent both phacoemulsification and extracapsular cataract extraction. Although we did not find recent studies assessing the incidence

of anterior chamber fibrin formation after modern cataract surgery using phacoemulsification, we believe the incidence is lower than that determined by those authors, due to major advances and improvements in surgical technique, intraocular lens and viscoelastic achieved in recent years.

The association between vitreoretinal surgery and fibrin formation was first described by Sebestyen<sup>(5)</sup>. This author evaluated 280 consecutive cases of vitrectomy in diabetic patients and in 15 eyes (5.35%) described the presence of fibrinoid reaction in the vitreous chamber, between the surface of the retina and the posterior iris plane. This author found that the combination of surgery to remove the lens, performing retinopexy with scleral buckling and the presence of retinal detachment preoperatively, could predispose to the occurrence of this complication. Performing multiple combined procedures at the same surgery would presumably lead to an increased vascular permeability, which results in a gelatinous material, resembling fibrin in the vitreous of diabetic patients.

In the present study, the incidence of fibrin formation (6%), was similar to that found by Sebestyen (5.35%)<sup>(5)</sup>. But it was surprising that, contrary to what suggested by this author, the presence of diabetes mellitus was not associated with an increased risk for fibrin formation. This can be explained, at least in part, by the fact that the majority of diabetic patients submitted to vitrectomy procedure were cases in severe stages, with a presence of vitreous hemorrhage, fibro-vascular proliferation and tractional retinal detachment, requiring the use silicone oil, in most cases. The silicone oil may acts as a mechanical barrier, preventing the free diffusion and circulation, in the vitreous chamber, of factors that can lead to fibrinoid anterior chamber reaction. In accordance with the hypothesis, in the present study, only one patient in which silicone oil was used developed fibrin. It should be pointed the strong association of fibrinoid reaction and the use of BSS as a vitreous substitute (*odds ratio* 6.24). Although the exact explanation is still unknown, we believe that the higher incidence of fibrin formation associated with the use of BSS compared to gas or silicone oil may be related to the diffusion of inflammatory cells between the anterior and posterior chambers of the eye. It is possible that the presence of BSS in the vitreous chamber has facilitated the diffusion of fibrin-forming substances between the anterior and posterior segments. On the other hand, gas or silicone oil in the vitreous may have functioned as a more effective barrier to the diffusion of inflammatory agents and, therefore, accounted for the smaller incidence with those vitreous substitutes.

Of all the factors related to fibrin formation in the anterior chamber, the one that suggested the highest risk was the performance of phacoemulsification combined with vitreoretinal surgery (*odds ratio* 23.6). Williams et al.<sup>(6)</sup> in 1988, reported the presence of fibrinoid reaction after extensive vitrectomy in 3 aphakic eyes. Jaffe et al.<sup>(2)</sup> described the intense presence of fibrin in anterior chamber after vitrectomy in seven patients, also all aphakic. Therefore, the lens extraction combined with posterior vitrectomy seems to be a risk factor for development of fibrin in anterior chamber. In this study, 11 of 12 eyes presented with fibrinoid reaction had been submitted to phacoemulsification with intraocular lens implantation associated with posterior vitrectomy. Therefore, the association between anterior chamber fibrin formation, posterior vitrectomy and phacoemulsification seems to be a reasonable assumption.

This association can be justified, at least in part, by surgical manipulation of the anterior segment during

phacoemulsification, which usually precedes the vitrectomy, promoting a change in the blood-aqueous barrier, increasing vascular permeability, platelet activation, platelet derived growth factor secretion and increased levels of fibrinogen, which finally, will be converted into fibrin<sup>(3-5)</sup>. The case 12 (table 2) underwent vitrectomy for rhegmatogenous retinal detachment, and presented with fibrin in anterior chamber, but without the concomitant performance of phacoemulsification. This patient was already pseudophakic and had posterior capsule rupture. During the intraoperative period, in this case, it was necessary to approach the anterior segment because of the migration of gas to anterior chamber. The manipulation of the anterior segment could justify, in this case, the breaking of the blood-aqueous and fibrin formation.

In fact, all 185 study patients, who underwent to vitreoretinal surgery, no phakic patients showed fibrin in the anterior chamber. Therefore, it seems that the absence of surgical manipulation of anterior segment and the preservation of lens, may act as protective factors for the occurrence of anterior chamber fibrin formation in patients submitted to vitreoretinal surgery.

Prior surgical procedures could be a risk factor for fibrin formation, since we can assume that these cases are more complex and also because they have been previously surgically manipulated, thus these factors can contribute to fibrin formation. This is the case of patients who underwent silicone oil removal. In the present study, 7 eyes had silicone oil removal at the time of surgery and three of them developed fibrin formation. When we calculated the odds ratio in a univariate model it was 14.08 (CI 95%; 2,73 - 72,62;  $p=0.002$ ) suggesting that it might be an important factor. However, 6 of the 7 patients had also been submitted to simultaneous phacoemulsification including all three that developed fibrin formation. Therefore when we pursued in the statistical analysis using multivariate logistic regression analysis the odds ratio for silicone oil extraction dropped to 3.64 (not significant,  $p=0.17$ ). The fibrin formation in these cases was therefore probably related to both the phacoemulsification and use of BSS and not directly related to silicone oil removal.

All patients who developed fibrin in anterior chamber were treated with 25mcg/0.1mL of t-PA intracameral, with complete resolution and no relevant side effects. In fact, several previous studies, clinical and experimental, have shown that t-PA is a safe and effective form of treatment for fibrinoid reaction, both in patients undergoing phacoemulsification and vitreoretinal surgery<sup>(2,8,9,11-17)</sup>.

In accordance with the present study, the anterior chamber fibrin formation is a possible and unwanted complication after vitreoretinal surgery. Factors such as combined performance of phacoemulsification and the use of balanced salt solution as a vitreous substitute may predispose the occurrence of this complication. Surgeons should be warned about this complication and its related factors for it may have great influence in patients' visual outcome.

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