The long-term effects of platelet-rich plasma in diabetic dry eye: a series of cases

Os efeitos a longo prazo do uso de concentrado de plaquetas em olho seco diabético: uma série de casos

Marina Moura Rezende Ribeiro¹  https://orcid.org/0000-0001-7626-2806
Fabiano Timbó¹  https://orcid.org/0000-0001-6630-0629
Eurica Ribeiro¹  https://orcid.org/0000-0001-7983-7521
Luiz Eduardo Ribeiro²  https://orcid.org/0000-0002-6639-5928

ABSTRACT

Objective: To evaluate the long-term efficacy of autologous platelet-rich plasma (PRP) in the symptomatic dry eye of diabetic patients after 6 months of treatment suspension. Methods: A single intervention group, prospective study, series of cases; ten diabetic patients with refractory dry eye disease who used PRP and were reassessed 6 months after discontinuation of treatment. At the initial stage 221 diabetic patients were evaluated for dry eye; of these 12 were submitted to CPC, and evaluated for symptoms, Ocular Surface Disease Index (OSDI), TFBUT (Tear Film Break Up Time) and Schirmer's Test. At this stage of the study, patients were recruited after 6 months of CCP suspension, and the OSDI, TFBUT and Schirmer test scores were reviewed. Results: There was a statistically significant difference in the OSDI and TFBUT scores between the baseline (before PRP treatment) and after 1 month of PRP use; between the baseline and after 6 months of PRP use, and between the values after 1 month of use and after 6 months of non-use (p = 0.005, p = 0.010 and p = 0.028, p = 0.04, p = 0.03 and p = 0.02, respectively). Schirmer test values had no significant difference in any of the comparisons (p = 0.09, p = 0.26, p = 0.47 respectively). Conclusions: PRP after 6 months of use presents evidence that it would still be effective even with suspension of eye drops.

Keywords: Dry eye syndromes; Platelet-rich plasma; Diabetes mellitus, surface disease; Follow up

RESUMO

Objetivo: Avaliar a eficácia a longo prazo após 6 meses de uso do colírio de concentrado de plaquetas (CCP) autólogo no olho seco sintomático de pacientes diabéticos. Métodos: Um estudo de intervenção com único grupo prospectivo tipo série de casos; dez pacientes diabéticos com doença do olho seco refratário que usaram o CCP e foram reavaliados 6 meses após suspensão do tratamento. Na etapa inicial 221 pacientes diabéticos foram avaliados quanto a olho seco, destes 12 foram submetidos ao CPC, e avaliados para sintomas, escore de OSDI (Ocular Surface Disease Index), TFBUT (Tear Film Break Up Time) e Teste de Schirmer. Nesta etapa do estudo os pacientes foram reconvocados após 6 meses de suspensão do CCP, e o escore de OSDI, TFBUT e teste de Schirmer foram revistos. Resultados: Houve diferença estatisticamente significante nos escores de OSDI e TFBUT entre o basal (antes do tratamento com CCP) e após 1 mês do uso do CCP; entre o basal e após 6 meses de suspensão do uso do CCP, e entre os valores após 1 mês de uso e após 6 meses sem uso (p = 0.005, p = 0.010 e p = 0.028, p = 0.04, p = 0.03 e p = 0.02, respectivamente). Nos resultados do Teste de Schirmer não houve diferença significativa em nenhuma das comparações (p = 0.09, p = 0.26, p = 0.47 respectivamente). Conclusões: O CCP após 6 meses de uso apresenta evidências de que ainda seria eficaz mesmo com a suspensão do colírio.

Descritores: Síndromes do olho seco; Plasma rico em plaquetas; Diabetes mellitus; Doença de superfície; Seguimento

¹ Universidade Federal de Alagoas, AL, Brazil.
² Instituto de Olhos de Maceió

The authors declare no conflicts of interests.

Received for publication 08/10/2018 - Accepted for publication 13/12/2018.


The periodical Revista Brasileira de Oftalmologia is licensed under a Creative Commons CC-BY License
INTRODUCTION

According to recent literature, dry eye is a multifactorial disease caused by homeostatic tear imbalance. Its etiology is rooted in the instability of the tear film, the hyperosmolarity, the inflammation of the ocular surface as well as in sensorineural changes. All of these changes cause symptoms that lead to eye discomfort and reduced quality of life.(1)

The prevalence of dry eye ranges from 5% to 34% of the population, and its complications can lead to blindness due to lesions on the ocular surface in the most severe cases.(3)

Diabetes is a disease that affects more than 10 million people in Brazil and is a probable cause of dry eye. The pathophysiology involves metabolic, neuropathic, and vascular lesions caused by hyperglycemia, which lead to inflammation and functional degeneration of the ocular surface. Dry eye affects between 8.4% and 54.3% of diabetic patients.(4,7)

Two major challenges in the management of dry eye are: diagnosis, in which tests often do not correlate with clinical practice, and treatment, mainly because conventional artificial tear therapy is not sufficient in moderate to severe cases of dry eye.(8,9)

In order to discover a treatment that is more similar to a human tear, with more advantages and less disadvantages in terms of conventional lubricants, Fox et al., Koffler and Tsutbota et al. began to study the effects of the autologous serum, which is rich in growth factors, immunoglobulins, in addition to not containing preservatives, and was then successfully used in keratoconjunctivitis sicca.(10-12)

The use of platelet-rich plasma (PRP) in ophthalmology was more recent and is superior to the autologous plasma due to its richer growth factors such as the epithelial growth factor and vitamin A, aside from not containing inflammatory cytokines present in the plasma, which makes it safer.(13,14)

There have been few studies evaluating the efficacy of platelet-rich plasma in dry eye, but all have demonstrated good efficacy of platelet-rich plasma (PRP) eye drops in treated patients.(15-19)

Another scarce topic in the literature is the long-term effect after the use of PRP in dry eye. Thus, the question would be whether even after discontinuing the use of this treatment, the results would be maintained.

One of the studies, carried out by Ribeiro et al., evaluated the effectiveness of PRP in diabetic patients with dry eye after one month of use and observed promising results.(16) Therefore, the objective of this study will be to evaluate the effectiveness of PRP after 6 months of suspension in the same diabetic patients with symptomatic dry eye.

METHODS

A prospective, non-randomized study of the series-of-cases type was conducted at the University Hospital of Alagoas, Dr. Alberto Antunes, in its Ophthalmology Sector. In the first stage, in 2015 Ribeiro et al. evaluated 221 diabetic patients, 12 of them with moderate to severe dry eye classified by severity according to DEWS (Dry Eye Workshop)(9) and refractory to conventional artificial tears therapy patients were selected for treatment with PRP. The inclusion criteria for the treatment of PRP was the diagnosis of diabetes according to the criteria of the American Diabetes Association,(20) absence of response or unsatisfactory response to conventional treatment, having at least one frequent or constant dry eye symptom, and a Schirmer test less than 15mm or for less than 10 seconds. Exclusion criteria were patients with keratopathy, use of eye drops for glaucoma and previous diagnosis of rheumatic disease. We also excluded patients who had contraindicated conditions for autologous donation (history of heart failure, severe aortic stenosis, heart attack or stroke in the last 6 months, angina, cyanotic disease, infection or use of antibiotics. (Further details for inclusion and exclusion criteria are described in the first study).(16)

In this first stage, according to the published article, the recommendations of the Declaration of Helsinki were followed, the patients signed a free and informed consent form, and the research was submitted and approved by the Ethics and National Research Committee and the Brazilian Registry of Clinical Trials under number RBR- 96463.

PRP was manufactured and preserved as described in the first article by Ribeiro et al., through a technique similar to that of Alio et al.(16,17)

In the second phase, which consists of the current study, the same 12 patients included and treated with PRP,(16) were reviewed, as well as the following variables: the OSDI score (Ocular Surface Disease Index-Allergan), (21) TRFL / TFBUT (tear film rupture time/ Tear Film Break Up Time), Schirmer test (assessment of lacrimal secretion rate), which were evaluated before treatment one month after the use of PRP, and in this study after 6 months of the suspension of the use of PRP, in July 2016.

The OSDI score consists of scoring based on dry eye symptoms, ranging from 0 to 12, considered normal eye or absence of dry eye, 13 to 22 light dry eye, 23 to 32 moderate dry eye, and 33 to 100 severe dry eye.(21)

TRFL / TFBUT consists of dripping fluorescein into the patient’s eye, and marking the time between the last blink and the appearance of the first spot related to tear film breakage. Normality is within 10 seconds or longer.(22)

The Schirmer test was conducted without anesthetic eye drops (Schirmer-Ophthalmos S.A Test), which consists in a strip of filter paper being inserted into the lower eyelid of both eyes, and requesting patients to close them lightly for 5 minutes. After this time, the paper was removed and the examiner evaluated where the moisture was located, 5mm being considered severe dry eye, 6 to 10 mm moderate dry eye and 10 to 15 mm light dry eye.(23)

The variables were analyzed in the first stage before PRP treatment, and after one month of use. Patients were told to stop PRP after 30 days and continue to use only artificial tears of their choice. It was clarified that they could return to the consultation at any time if any dry eye symptoms arose or worsened. After 6 months of PRP suspension, the patients were recalled by telephone and examined.

Statistical analysis

The means and standard deviation of the variables age, OSDI score value, and Schirmer test values (in millimeters) were calculated. The mean of the TFBUT values (in seconds) was also calculated. The median and interquartile range were also calculated using the Biostat 5.3 software. These values of the variables pre, post treatment and after 6 months of treatment discontinuation were compared using the Wilcoxon 5% alpha signed test. As the same test was used several times, it was necessary to use the Bonferroni correction (CB), with a corrected alpha of 0.016.

**RESULTS**

Of the 12 patients treated with PRP and called by phone for a new consultation, one had died and another was not found. Everyone who came to the consultation had been told that after the end of the PRP they could re-use the lubricant of their preferences. However, all of them were using the artificial tears, but without regular frequency. None of the patients reported any complaints before being called. The average age of the patients was 57.9 years (± 9.45 (SD)). Only one patient was male among the ten (patient G). The results of each patient, in relation to the OSDI, TFBUT / TRFL and Schirmer’s test, are shown in Tables 1, 2, 3.

OSDI had a baseline mean of 51.91 (dp 17.37), and median (interquartile range) of 51.17 (40.59-68). The mean value after 1 month of PRP use was 14.24 (SD 11.93), and the median (interquartile range) was 18.7 (13.52 - 40.34). The mean of 6 months after PRP suspension was 25.46 (dp 16.83) and the median (interquartile range) of 12.5 (5.83 - 21.25). There was a statistically significant difference in OSDI scores between the baseline (before PRP treatment) and 1 month after PRP; between the baseline and after 6 months of PRP use, and between the values after 1 month of use and after 6 months of non-use (p = 0.005, p = 0.010 and p = 0.028, respectively).

TFBUT / TRFL was assessed by averaging the values in seconds between the two eyes. The baseline mean was 8.8 (dp 0.42), the median (interquartile range) was 9 (8.75 - 9). The mean after 1 month was 10 (dp 1.56), and the median (interquartile range) was 10 (9-11); the mean after 6 months of PRP suspension was 6.6 (dp 2.48) and the median (interquartile range) of 6 (4.62 - 8.75). There were statistically significant differences between baseline values and 1 month after treatment, between baseline and 6 months without treatment, and also between 1 month of treatment and 6 months without CPB (p = 0.04, p = 0.03 and p = 0.02 respectively).

The Schirmer’s test values were also obtained through the mean values between the two eyes. The baseline mean was 7.25 (dp 3.64), and the median (interquartile range) was 6.5 (4.76 - 10). The 1 month mean was 9.3 (dp 4.89) and the median (interquartile range) of 8.5 (5.12 - 12.7). The 6 months mean after PRP suspension was 10.6 (dp 7.29) and the median (interquartile range) of 9.5 (4.25 - 17.62). There was no statistically significant difference between the baseline values and after 1 month of treatment, between the baseline and 6 months, nor after one month of treatment and after 6 months (p = 0.09, p = 0.26; p = 0.47 respectively).

**DISCUSSION**

The treatment of dry eye presents difficulties because of the multifactorial nature of the condition, and the fact that the treatment with artificial lubricants and habitual therapy has disadvantages, as none of them presents the properties of the human tear.(16-24)

Therefore, the PRP has shown promising results in dry eye, with the advantage of being superior to the autologous serum in its properties, being rich in growth factors, promoting corneal reepithelialization, being free of preservatives, and being acquired from human blood itself. When the techniques are satisfactory the risk of infection is almost null.(16, 17, 25-27) Promising results, especially in relation to symptoms after one month of PRP use, have already been observed in the few published studies, such as Lopez-Plandonlit et al., Ribeiro et al. and Alio et al. (15-17)

However, due to its anti-inflammatory and re-epithelializing effects, the intention of this study was to evaluate whether these results would be maintained in the long term, even after PRP suspension, something which has never been evaluated. The safety and efficacy of prolonged use of autologous serum is known, as Lee and Chen have evaluated 23 patients for 18 months with improved fluorescein spotting and symptoms in approximately 75% of patients. However, it is also known that there are drawbacks to collecting blood every 3 months due to the invasive nature of...

---

**Table 1**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>OSDI Previous</th>
<th>OSDI 1 month post PRP</th>
<th>OSDI 6 months no PRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>60</td>
<td>50</td>
<td>12.5</td>
<td>12.5</td>
</tr>
<tr>
<td>B</td>
<td>70</td>
<td>58.3</td>
<td>27.7</td>
<td>47.2</td>
</tr>
<tr>
<td>C</td>
<td>48</td>
<td>63.8</td>
<td>8.33</td>
<td>16.6</td>
</tr>
<tr>
<td>D</td>
<td>59</td>
<td>52.33</td>
<td>36.40</td>
<td>36.40</td>
</tr>
<tr>
<td>E</td>
<td>52</td>
<td>90</td>
<td>5</td>
<td>2.77</td>
</tr>
<tr>
<td>F</td>
<td>67</td>
<td>50</td>
<td>22.5</td>
<td>50</td>
</tr>
<tr>
<td>G</td>
<td>41</td>
<td>27.2</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>H</td>
<td>69</td>
<td>42.5</td>
<td>12.5</td>
<td>20</td>
</tr>
<tr>
<td>I</td>
<td>60</td>
<td>32.5</td>
<td>0</td>
<td>41.66</td>
</tr>
<tr>
<td>J</td>
<td>53</td>
<td>52.5</td>
<td>17.5</td>
<td>17.5</td>
</tr>
</tbody>
</table>

OSDI: Ocular Surface Disease Index. PRP: platelet-rich plasma eye drops.

---

**Table 2**

<table>
<thead>
<tr>
<th>Patient</th>
<th>TFBUT Previous</th>
<th>TFBUT 1 month post PRP</th>
<th>TFBUT 6 months no PRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>B</td>
<td>9</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>C</td>
<td>8</td>
<td>8</td>
<td>3.5</td>
</tr>
<tr>
<td>D</td>
<td>9</td>
<td>12</td>
<td>6.5</td>
</tr>
<tr>
<td>E</td>
<td>9</td>
<td>11</td>
<td>4.5</td>
</tr>
<tr>
<td>F</td>
<td>9</td>
<td>11</td>
<td>5.5</td>
</tr>
<tr>
<td>G</td>
<td>9</td>
<td>12</td>
<td>5.5</td>
</tr>
<tr>
<td>H</td>
<td>9</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>I</td>
<td>9</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>J</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

TFBUT: Tear Film Break Up Time. PRP: platelet-rich plasma eye drops.

---

**Table 3**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Schirmer Previous</th>
<th>Schirmer 1 month post PRP</th>
<th>Schirmer 6 months no PRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>B</td>
<td>9.5</td>
<td>10</td>
<td>3.5</td>
</tr>
<tr>
<td>C</td>
<td>5</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>D</td>
<td>10</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>E</td>
<td>10</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>F</td>
<td>5</td>
<td>5.5</td>
<td>5</td>
</tr>
<tr>
<td>G</td>
<td>14</td>
<td>17.5</td>
<td>18.5</td>
</tr>
<tr>
<td>H</td>
<td>8</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>I</td>
<td>5</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>J</td>
<td>4</td>
<td>4</td>
<td>9</td>
</tr>
</tbody>
</table>

PRP: platelet-rich plasma eye drops.
the venipuncture procedure, and in some patients with vascular problems such as diabetics, this procedure becomes even more difficult.\(^{(16)}\)

Therefore, what we observed in this study was that patients, although advised to return to the clinic in case of worsening or onset of dry eye symptoms, did not do so, which corroborates with the evidence that even after suspending the eye drops they remained well, which was the information collected from the majority. This can be evidenced by the OSDI and TFBUT scores, in which there was a statistically significant difference between baseline values (before treatment) and after 6 months without the use of eye drops, confirming that after 6 months these results were already better than before the PRP.

Regarding the Schirmer test, it was observed that comparing the values of this test after 1 month of treatment and after 6 months without PRP, there was no statistically significant change, which confirms that they did not worsen expressively even without treatment. The gross values had a significant variation, but probably occurred due to the small sample, as in this study of evaluation of evolution of the previously treated patients, only the ten patients who returned were observed, as in a case series report.

There were limitations in this study, which were obviously identical in the first stage and in the small sample because among the first 221 patients only 10 completed this last evaluation after 6 months. Another limitation that could occur in any dry eye study is that many systemic or ocular diseases that cause or worsen this condition may have been neglected or undiagnosed. Although our questionnaire includes questions for the diagnosis of other dry eye causes, such as iatrogenic, pharmacological, secondary, or systemic etiology causes, the patient is often unaware that he or she is taking specific medication or has a certain pathology.\(^{(16)}\)

In conclusion, there are few studies on the use of PRP in dry eye and none of them are randomized. Regarding the long-term effect of the PRP even after its suspension, there is yet no research on the subject. Therefore, new clinical trials are needed both to compare PRP with other treatments and to evaluate long-term outcomes, which may be of extreme relevance in reducing the morbidity of this disease in a more definitive manner.

References


Corresponding author:
Marina Viegas Moura Rezende Ribeiro
Rua Pref. Abdón Arroxeles, 251, Maceió, AL, Brazil
Phone: 5582-33132529
E-mail: dra.marinabrieiro@gmail.com.