The Efficacy of Tacrolimus Combined with Platelet Rich Plasma in Sjogren's Syndrome's Severe Dry Eye: A Randomized-Controlled Trial

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Abstract

Purpose: Dry eye in Sjogren's ends up with ulcerations, infections, and even corneal perforations. Present treatments are mainly conservative. Due to the immunosuppressive effects of Tacrolimus drop and regenerative properties of platelet-rich plasma (PRP), this study aimed to evaluate the simultaneous use of these products in dry eye management.

Methods: 20 cases of Sjogren's syndrome were included in this study. Patients were divided into three groups, the 'artificial tear drop,' Tacrolimus drops,' and 'Tacrolimus, and PRP drops.' The Schirmer's and TUBT tests and corneal fluorescein staining were assessed in each case following the determination of refractive errors and intraocular pressure, one week, one month, and three months after the initiation of therapy.

Results: The majority of our cases were females, making up approximately 80%. Significant differences were found when assessing the level of irritation, and the results of the TUBT as well as fluorescein staining tests between the group treated with artificial teardrops and both of the other groups three months after treatment started. (P-values of 0.0005, 0.002 and 0.01, respectively) Schirmer's test, however, did not reveal significant levels (P-value = 0.5) when comparing the three treatment groups.

Conclusion: Tacrolimus drop is a suitable and effective agent in severe cases of dry eye in Sjogren's syndrome, showing even more therapeutic benefits when given with PRP based on the results of this study. Owing to this combination's increased anti-inflammatory and regenerative effects and its accelerating effects on the resolution of clinical symptoms, it can be considered superior to conventional therapies.

Introduction

Sjogren's syndrome (SS) is a chronic multiglandular inflammatory disorder characterized by the disruption in the function of exocrine glands due to lymphocytic infiltration. [1]. Categorized into primary and secondary (with other autoimmune disorders present in the latter), primary SS is the second most common autoimmune disease with an approximate prevalence of 0.6% in the general population. [2, 3] Clinical manifestations vary noticeably depending on the affected site. Exocrine glands' involvement subsequently leads to the dryness of the eyes (i.e., keratoconjunctivitis sicca [KCS]) and mouth (xerostomia). Foreign body sensation, itching, increased sensitivity to light, tear production inability, heaviness in the eyelids, burning sensation, erythema, and ophthalmalgia are the most frequent complaints due to dryness. [4–6] In addition, debilitating fatigue deteriorates the quality of life and productivity [7]. Based on current guidelines, the treatment strategy is primarily palliative[8].

The Center for Evidence-based Medicine in Oxford has determined an approach to managing patients with primary Sjögren's syndrome[9]. Due to the immune-mediated pathophysiology of the disorder, they have recommended topical immunosuppressive medications, including Cyclosporine, as the authorized agents[9]. Another immunosuppressive agent is Tacrolimus(FK506), a calcineurin inhibitor. A Hydrophobic macrolide immunosuppressant, Tacrolimus, has been successfully tested in treating corneal transplant rejection, anterior scleritis, and vernal keratoconjunctivitis[10–12].

As the targeting by inflammatory cytokines decreases the function of lacrimal glands, which was due to the atrophy of acinar cells and gland fibrosis, some have suggested using regenerative agents to combat the ongoing loss[8]. One of the mentioned agents is the platelet-rich plasma(PRP), which has been proven helpful in managing ocular surface epithelial wound defects[13].

There are multiple factors involved in dry eye pathology. Combining both immunomodulators and regenerative agents which could provide us with an untold promise. We, indeed, tried to implement this idea in clinical research by utilizing topical Tacrolimus and PRP to manage primary SS.

Methods

We conducted a prospective, randomized, interventional double-blind placebo-controlled trial study on all available cases in the region's center for eye clinic diagnosed with Sjogren's syndrome from April to December 2019. The inclusion criteria for the study included all those aged 18 or above with a confirmation by corneal staining, those with Schirmer's test result of fewer than five millimeters during five minutes, and those whose tear breakup time test (TBUT) came to a result in less than 10 seconds. Those pregnant, breastfeeding, with a history of glaucoma, eye trauma, prior ocular intervention, or those using contact lenses or reported using any unconventional eye drops (except artificial teardrops) in the last month were excluded from the study.
Participants were randomly assigned to treatment or placebo (control) groups based on a 1:1:1 ratio (PRP: PRP and tacrolimus: artificial tear drops) within the randomization strata using permuted blocks. An interactive response technology was used to facilitate participant randomization accounting for the stratification factors.

The researchers used a checklist to collect the variables data. The checklist included: age, sex, occupation status, pre-existing refractory disorders of the eyes, intraocular pressure, patients’ irritation levels, Fluorescein eye stain test, TUBT, and Schirmer’s test results.

**Treatment protocol:**

A unique code based on the patient’s group was then given to receive the medicine. The first group of patients received artificial tear drops; Tacrolimus drops were given to the second group. Blood samples were taken from the third group to prepare autologous PRP and were placed on Anticoagulant Citrate Dextrose (ACD) Solution. The samples were then centrifuged, and PRP was extracted. Moreover, after preparing the PRP drop with tacrolimus, it was given to the mentioned group. The tacrolimus-PRP mixture drop was prepared by combining 0.02% tacrolimus eye drops with an equal volume of autologous PRP. Ultimately, each group applied the given drop three times per day, with necessary information regarding the application method provided to each case.

**Follow-up Sessions:**

All three groups’ eyes were examined on three different follow-up sessions. The first one was carried out after one week, the second one after one month, and the third three months after the treatment initiation. Schirmer’s, corneal staining, and TBUT tests were performed on all sessions mentioned.

**Statistical analysis:**

The categorical variables were described by frequency and percentage. The continuous variables have been measured by the mean and standard deviation (SD). The ANOVA test was used to compare the means between three study groups for the Schirmer’s, corneal staining, and TUBT tests. The Bonferroni test as the post hoc test was used if there was a significant difference between groups. The Kruskal-Wallis test was used for the variables that did not have a normal distribution. The P-value < 0.05 was considered as the significance level for all analyses. The 14th edition of the Stata software was used for all statistical analyses.

**Ethical Statement:**

Written consent was obtained from all the participants. They were informed about the objectives and treatment procedures of the study. Furthermore, the Local Ethics Committee, as well as the Iranian Registry of Clinical Trials (IRCT) as well as the reviewed and approved the study protocol.

**Results**

A total of 20 cases with Sjogren’s syndrome were included. The participants were then randomly assigned to three groups of 7 (though it has to be noted that one participant in the placebo group did not complete the follow-up routines and, therefore, was excluded). 80% of our cases were females, of whom 50% were not occupied outdoors. In addition, none of the included cases had pre-existing refractory disorders (except for Sjogren’s syndrome). (Table 1)

The differences between the three groups regarding demographic data including age (P-value = 0.25), sex (P-value = 0.77), occupation (P-value = 0.57) and also the intraocular pressure (P-value = 0.34) as a confounding factor were not statistically significant. (Table 1)

At the baseline, the three groups revealed no statistical significance in the difference between the results of the level of irritation (P-value = 0.94), Corneal staining (fluorescein) (P-value = 0.32), Schirmer’s (P-value = 0.21), and TBUT (P-value = 0.31) tests. These findings represent the homogenous distribution of the mentioned characteristics across the included groups on bias and objectively. (Table 2)
Data on irritation levels, fluorescein, Schirmer’s, and TBUT tests obtained on the first, fourth, and 12th weeks after the initiation of each method were compared to that of the baseline and analyzed. Table 2 demonstrates the details about the results of each of the therapeutic methods.

None of the tests mentioned above in the artificial teardrop group showed statistical significance in any follow-up sessions. Additionally, except for Schirmer’s test results on the first and fourth week and the TBUT test results on the first-week follow-up sessions, all other results demonstrated statistical significance in the tacrolimus group. Furthermore, bar the Schirmer’s test results on the first and fourth-week follow-up sessions, the data from the tacrolimus-PRP group revealed statistical significance.

After analytically demonstrating the changes occurring in each group, the measured variables from the two treatment groups were then compared to the control group (Table 2).

**Irritation levels:**

On the first-week follow-up session, the differences between the groups were not statistically significant (P-value = 0.36). However, the examinations on the fourth week revealed statistical significance (P-value = 0.009). The Bonferroni post hoc test confirmed this result for the tacrolimus (P-value = 0.009) and the tacrolimus-PRP group (P-value = 0.002) compared to the control group. On the contrary, when comparing the results of the two treatment groups, the differences between them were not statistically significant (P-value = 1).

In the final examination performed three months after the intervention, the difference in results, similar to the second follow-up session, were statistically significant (P-value = 0.002). The post hoc test results revealed that the two treatment groups were significantly different from the control group (P-value = 0.028 for the tacrolimus group; P-value = 0.002 for tacrolimus-PRP). In contrast, the results of the two treatment groups were not significantly different statistically (P-value = 0.64). (Table 2, and Figure 1).

**Corneal staining (Fluorescein test):**

When comparing the results of the Fluorescein tests, the study groups did not differ significantly on the first session (P-value = 0.76). However, there was a significant difference between the groups on the second and third follow-up sessions (P-value = 0.006 and P-value = 0.001, respectively). Therefore, the Bonferroni post hoc test was carried out.

This statistical test demonstrated that compared to the control group, on both the second and third follow-up sessions, the changes in fluorescein test results in the tacrolimus treatment group were not statistically significant (P-value = 1 for both sessions). Yet, the results regarding the tacrolimus-PRP group improved significantly (P-value = 0.007 and P-value = 0.002 for the 2nd and third sessions, respectively). These differences also existed when comparing the results of the two treatment groups on the mentioned two sessions (P-value = 0.03 and P-value = 0.009 for the 2nd and 3rd sessions, respectively). (Table 2, and Figure 2)

**Schirmer’s Test:**

When comparing the test results, none was statistically significant in any of the first, second, and third follow-up sessions (P-value = 0.21, P-value = 0.22, and P-value = 0.53, respectively). (Table 2, and Figure 3)

**TBUT:**

There was no significant difference between the groups in the test results in the first follow-up session (P-value = 0.16), but after one month and then on the last follow-up session, the difference was statistically significant (P-value = 0.0002 and P-value = 0.0005, respectively). Consequently, the Bonferroni post hoc test was used to determine if the differences between the groups were significant. When comparing the second follow-up session’s results, the differences between the control and treatment groups were significant (P-value = 0.041 and P-value = 0.0001 for the tacrolimus and the tacrolimus-PRP groups, respectively). By contrast, on the third session, the significance level between the control and tacrolimus groups vanished (P-value = 0.063), whereas the level between the control and tacrolimus-PRP group persisted (P-value = 0.0001). In addition, when comparing the results of the two treatment groups from the 2nd and 3rd sessions, the tacrolimus-PRP group results improved significantly (P-value = 0.028 and P-value = 0.037, respectively). (Table 2, and Figure 4)
Discussion

The present study results showed that the three treatments of artificial tears, tacrolimus drops, and concomitant use of tacrolimus drops and PRP have different effects on dry eye in patients and treatment with tacrolimus drops. We could demonstrate that a therapy regimen consisting of only artificial teardrops would not significantly help those suffering from eye dryness, neither short nor long term. However, when applying tacrolimus alone or in combination with PRP, the results would remarkably improve on most of the available assessment methods. Besides, we found that the combination therapy of tacrolimus and PRP is far more effective than tacrolimus alone or artificial teardrops. In other words, it can be said that the use of PRP as an adjunct to treatment with tacrolimus can have a beneficial effect on the treatment of severe dry eye in patients with Sjogren's.

Contrasting with ours, a study by Moscovici et al. found that, although the Schirmer's test did not improve dramatically in the first month, it did after continuous use of the tacrolimus drops for three months[14]. In our study, the Schirmer's test for both treatment groups did not show statistical significance in the follow-up sessions.

According to our study, the controls in our study had no significant improvement in the level of irritation in any of the follow-up sessions, pointing towards the ineffectiveness of this method in mitigating symptoms. Even though the two treatment groups showed desirable results in alleviating the symptoms, we believe that adherence to the therapy should be maintained by informing the patients about the therapy's required duration to be adequately effective. Both treatment groups took some time to demonstrate considerable and profound effects. Though, it must be noted that the tacrolimus-PRP group was significantly faster in that regard.

Another finding of Moscovici et al.'s study was the significant changes in fluorescein tests as statistical significance was noted in all follow-up examinations compared to baseline[14]. In our study, however, significant fluorescein changes were observed only from the second session onward compared to the control group. We think that the short period between the intervention and first follow-up session might be the culprit for the statistical insignificance, while in Moscovici et al.'s study, the first examination was performed two weeks after the initiation of treatment[14]. Thus, we can conclude that fluorescein changes also take time.

Nevertheless, it is noteworthy that fluorescein changes in cases receiving tacrolimus-PRP drops were significantly different from the first week after starting treatment, suggesting that concomitant use of tacrolimus and PRP accelerates the recovery of patients.

Similar conditions were observed for TBUT in the same study[14]. However, no significant changes were observed in the first two weeks of treatment. Afterwards, statistical significance was found in the examinations performed at one and three-month follow-up sessions, consistent with our study. In our study, the changes in the results of TBUT in the group taking tacrolimus-PRP at all follow-up periods were statistically significant since the first week, which confirms the acceleration of treatment improvement in this group.

In a study conducted by Kharbanda et al. to treat severe and chronic dry eye, it was noted that patients' irritation levels improved significantly after one month. Fluorescein changes and Schirmer's test also improved significantly, yet no significant difference was found in the first month concerning TBUT[15]. These results have similarities and differences with our study in that the level of patient irritation significantly improved. Nonetheless, with the fluorescein and Schirmer's test, our study's results differ. Though, after three months, the results from both studies are comparable in their data significance levels. In terms of TUBT, the combination therapy of tacrolimus-PRP revealed statistical significance even in the first week, pointing towards improved efficacy.

In a randomized clinical trial study conducted by Moscivici et al. to compare the effects of tacrolimus drops and almond oil in the treatment of severe dry eye in patients with Sjogren's syndrome, patients were treated with tacrolimus drops or almond oil for three months after random allocation in two groups[16]. Fluorescein changes in tacrolimus cases showed statistical significance in the first week, and in three months, the changes on physical examinations were still visible[16]. However, no statistical significance regarding the fluorescein change was noted in the group treated with almond oil in the meantime[16]. In comparison with our study, the above-mentioned results are similar. Concerning TBUT, the results of the two studies are consistent when comparing the tacrolimus group. However, regarding Schirmer's test, contrasting results are observed, as in the study by Moscivici et al.[16], Schirmer's test results
improved considerably after four weeks, but in our study, it did only after the last follow-up session. Furthermore, the same conditions also applied to the group using tacrolimus and PRP, with no statistical significance in the first month, which may probably be attributed to the group’s poor adherence.

A study by Tsubota et al. reported statistical significance regarding the fluorescein changes after two and four weeks when treating severe dry eye in patients with Sjogren’s syndrome with autologous serum[17]. Our study showed statistical significance in those treated with tacrolimus-PRP. However, in the study by Tsubota et al., no statistical significance was noted regarding TBUT. In our study, though, statistical significance became noticeable one month after the tacrolimus initiation, which points towards relative resolution.

On the other hand, it is essential to note that patients who used tacrolimus drops and PRP showed statistical significance in TBUT since the first week after the initiation of treatment. Overall, even though a therapy regimen consisting of tacrolimus alone has demonstrated significant efficacy, combination therapy of tacrolimus-PRP has shown to be a more effective and faster method in managing Sjogren’s cases with dry eye, as evident by comparing our study with those of Tsubota et al.[17], Moscivici et al.[14, 16], and Kharbanda et al. [15].

Conclusions

Our study indicates that the treatment with artificial tear drops for patients with Sjogren’s syndrome suffering from the severe dry eye has been neither appropriate nor effective and, at best, can only prevent the progression of the disease. Tacrolimus drops for the treatment of severe dry eye are suitable and sufficient. However, according to our study, tacrolimus drops with PRP are much more effective and a lot faster.

One of the core treatment issues is the necessary duration that could lead to significant outcomes. Hence, simultaneous utilization of tacrolimus and PRP has been proven to require less time than solo therapy with tacrolimus to demonstrate the desired effects.

Eventually, we have that the use of tacrolimus drops and PRP can be a highly beneficial and effective method for managing severe dry eye in Sjogren’s syndrome, and due to their enhanced and accelerated effects, we strongly recommend that further trials be undertaken to clarify the merits and demerits further.

Declarations

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Funding: No funding or sponsorship was received for the conduct of this study.

Authorship: All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Ethical Statement:

Written consent was obtained from all the participants. They were informed about the objectives and treatment procedures of the study. Furthermore, the Local Ethics Committee and the Iranian Registry of Clinical Trials (IRCT) reviewed and approved the study protocol. [IRCT20211011052725N1]

Availability of data and materials: The dataset supporting the conclusions of this article (i.e., data extracted from included studies) is available upon request to the corresponding author, Alireza Farsinejad.

Conflict of interests: The authors declare that no conflict of or competing interests existed or occurred in the conduction of this manuscript.
References

15. Kharbanda M, Walia S, Singh H, Singh I. Efficacy of Tacrolimus 0.03% Eye ointment in treatment of chronic ocular surface inflammation in severe dry eye.

Tables

Table 1 - Demographic and Intraocular Pressure Measurements Data
<table>
<thead>
<tr>
<th>Variable</th>
<th>Artificial teardrop</th>
<th>Tacrolimus drops</th>
<th>Tacrolimus drops and PRP</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N(%)</td>
<td>Mean(SD)</td>
<td>N(%)</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>5(88.33%)</td>
<td>5(71.43)</td>
<td>6(85.71)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>1(16.67%)</td>
<td>2(28.57)</td>
<td>1(14.29)</td>
</tr>
<tr>
<td>Occupation</td>
<td>Self employed</td>
<td>1(16.67%)</td>
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<td>0</td>
</tr>
<tr>
<td></td>
<td>House wife</td>
<td>3(50%)</td>
<td>4(57.14)</td>
<td>3(42.86)</td>
</tr>
<tr>
<td></td>
<td>employee</td>
<td>2(33.33%)</td>
<td>3(42.86)</td>
<td>4(57.14)</td>
</tr>
<tr>
<td>Age</td>
<td>48.33(8.26%)</td>
<td>46.71 (6.67)</td>
<td>42.28 (4.82)</td>
<td>0.25</td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td>14.66(1.75%)</td>
<td>13.57 (2.22)</td>
<td>13.28 (0.95)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Abbreviations: N, Number; SD, Standard Deviation; PRP, Platelet Rich Plasma

Table 2 - Treatment and Control Groups' Test Results Data
<table>
<thead>
<tr>
<th>Test</th>
<th>Group</th>
<th>Artificial teardrop Mean(SD)</th>
<th>P-Value (Compared to Baseline)</th>
<th>Tacrolimus drops Mean(SD)</th>
<th>P-Value (Compared to Baseline)</th>
<th>Tacrolimus and PRP drops Mean(SD)</th>
<th>P-Value (Compared to Baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follow-Up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>level of irritation</strong></td>
<td>Baseline</td>
<td>4 ± 0.89</td>
<td>4 ± 0.89</td>
<td>4 ± 0.81</td>
<td>0.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>One week</td>
<td>4 ± 0.89</td>
<td>3.57 ± 0.97</td>
<td>3.28 ± 0.75</td>
<td>0.008</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>One month</td>
<td>3.8 ± 0.44</td>
<td>2.57 ± 0.78</td>
<td>2.83 ± 0.4</td>
<td>0.001</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Three months</td>
<td>3.5 ± 1</td>
<td>2.2 ± 0.44</td>
<td>1.71 ± 0.48</td>
<td>0.0007</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td><strong>Fluorescein</strong></td>
<td>Baseline</td>
<td>4.16 ± 1.33</td>
<td>5 ± 0.81</td>
<td>4.85 ± 0.9</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>One week</td>
<td>4.16 ± 1.33</td>
<td>4.28 ± 1.11</td>
<td>3.85 ± 0.9</td>
<td>0.0007</td>
<td>0.76</td>
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<tr>
<td></td>
<td>One month</td>
<td>4.2 ± 1.3</td>
<td>3.57 ± 1.27</td>
<td>1.83 ± 0.4</td>
<td>0.004</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Three months</td>
<td>3.5 ± 1</td>
<td>3 ± 1</td>
<td>1.28 ± 0.48</td>
<td>0.0001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Schirmer's</strong></td>
<td>Baseline</td>
<td>4.15 ± 0.4</td>
<td>3.78 ± 0.48</td>
<td>4.17 ± 0.41</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>One week</td>
<td>4.15 ± 0.4</td>
<td>3.78 ± 0.48</td>
<td>4.17 ± 0.41</td>
<td>1.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>One month</td>
<td>4.2 ± 0.47</td>
<td>3.85 ± 0.5</td>
<td>4.27 ± 0.36</td>
<td>0.08</td>
<td>0.22</td>
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<tr>
<td></td>
<td>Three months</td>
<td>4.12 ± 0.35</td>
<td>4.12 ± 0.51</td>
<td>4.38 ± 0.39</td>
<td>0.003</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td><strong>TBUT</strong></td>
<td>Baseline</td>
<td>4.5 ± 0.54</td>
<td>4.71 ± 0.48</td>
<td>4.71 ± 0.48</td>
<td>0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>One week</td>
<td>4.5 ± 0.54</td>
<td>5.14 ± 0.69</td>
<td>5.14 ± 0.69</td>
<td>0.016</td>
<td>0.16</td>
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</tr>
<tr>
<td></td>
<td>One month</td>
<td>4.4 ± 0.54</td>
<td>5.57 ± 0.97</td>
<td>5.57 ± 0.97</td>
<td>0.0002</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Three months</td>
<td>4.5 ± 0.57</td>
<td>6 ± 1.22</td>
<td>6 ± 1.22</td>
<td>0.0001</td>
<td>0.0005</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SD, Standard Deviation; PRP, Platelet Rich Plasma; TBUT, Tear Breakup Test

**Figures**
**Figure 1**

Level of irritation (means) across the three groups on intended follow-up sessions

**Figure 2**

Fluorescein test means across the three groups on intended follow-up sessions
**Figure 3**

Schirmer's test means across the three groups on intended follow-up sessions

**Figure 4**

TBUT test means across the three groups on intended follow-up sessions