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Assessment of Autologous (Platelet-Rich-Plasma) as A Monotherapy for Treatment of Dry Eye Disease

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ABSTRACT

Background: treatment of dry eye disease (DED) depends on minimizing inflammation and improving various components of the tear film. Artificial tears remain an important part of patient comfort, with many lipid- and gel-based formulations for a healthy ocular surface. **Objective:** the work aimed to evaluate the role of autologous platelet-rich plasma (PRP) as a monotherapy for treatment of dry eye disease, versus artificial tears use.

Patients and Methods: a prospective comparative study. The study included 55 eyes of 30 patients with moderate to severe dry eye disease. The study was performed at Ophthalmology Department in Alazhar University Hospitals.

Results: in our study PRP group of patients all are improved in all parameters and all of them were statistically significant. Symptoms OSDI score decreased indicating improvement in 86.6% of patients. TBUT improved in 66.6% of cases. CFS improved up to disappearance of staining in 33% of cases and fair improvement in 53.3%, total improvement was 86.6%. Schirmer test improved in 40% of cases. BCVA improved in 26.6% of patients, improvement was not more than one line. **Conclusion:** PRP is very effective in treatment of moderate and severe cases of DED at the level of subjective symptoms, TBUT, CFS, BCVA, and Schirmer test.

Keywords: Platelet-Rich-Plasma, Dry Eye Disease.

INTRODUCTION

Dry eye disease (DED) is one of the most popular ocular morbidities. Twenty-five percent of patients who come to Ophthalmic clinics report symptoms of dry eye, making it a growing public health problem and one of the most common conditions seen by ophthalmologists [(1)].

Many and different causes of dry eye disease as perimenopausal stages in women, increasing age, hormonal diseases, and certain drugs are just a few risk factors that can result in dryness on the ocular surface. Other causes include long-term contact lens wearing, smoking, and laser refractive eye surgery. Activities like watching television, extended computer use, and reading can trigger and/or aggravate dry eye symptoms. Low relative humidity, such as an office environment and air-conditioned places, can be detrimental to the tear film. Allergies, coexisting autoimmune diseases, or rosacea also can contribute to symptoms related to dry eye [(2)].

The standard treatment for dry eye is topical use of artificial tears, although the expected results are not satisfying and often ineffective. This has led to the use of other therapeutic methods based on blood derivatives. Autologous serum (AS) has been suggested to be a more efficient treatment for severe DED rather than preservative-free artificial molecules, with varying success rates [(3)].

Platelet rich plasma (PRP) and plasma rich in growth factors (PRGF) have also been reported as successful therapies for moderate to severe dry eye, with advantages over AS due to its higher concentration of anti-inflammatory cytokines, growth factors and other platelet derivatives, which could be with high benefit for the required ocular surface restoration in cases of moderate and severe dry eye [(4, 5)].

AIM OF THE WORK

The work aims to evaluate the role of autologous PRP as a monotherapy for treatment of dry eye disease versus artificial tears use.

PATIENTS AND METHODS

The study included 55 eyes of 30 patients with moderate to severe dry eye disease.

- **Study design:** A prospective comparative study.
- **Setting of study:** The study was performed at Ophthalmology Department in Alazhar University Hospitals. This study period from October 2018 to May 2019.
- **Inclusion criteria:** Moderate to severe dry eye disease.
- **Exclusion criteria:**
  - Pterygium.
  - Corneal ulcers.
  - Facial palsy.
  - Ectropion.

Methods

Each patient was subjected to the following:

1- Ethical approval and written informed consent: An approval of the study was obtained from Al-Azhar University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

2- Dry eye severity was determined by the Dry Eye Workshop (DEWS) severity scheme,

History taking:

Including:

- Demographic data: name, age and gender.

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- History of previous ocular or systemic disease.
- History of previous ocular surgery as LASIK surgery.

Ophthalmic examination including:

- Slit lamp examination, evaluation of tear meniscus.
- Schirmer test with anesthesia using a filter paper strip inside the lower eyelid of the two eyes that were tested at the same time.
- The patient was asked to close his eyes gently for five minutes. After five minutes, the doctor removes the paper and measures how many millimeters moistened.
- Tear film break up time (TBUT) using fluorescein stain to the cornea and calculating the time between the last blink and the appearance of the first area of break up.
- Corneal fluorescein staining (CFS) measured by application of fluorescein strips to the lower eye lids then examined by slit lamp blue filter and the corneal and conjunctival staining were evaluated using the modified oxford score
- Best spectacle corrected visual acuity (BCVA) measured by Snellen charts and expressed in decimal.
- A self assessed questionnaire of Ocular Surface Disease Index (OSDI) at the beginning of application of PRP or Artificial tears and one day after completing it.

Group (A): Artificial tears of Hyaluronic acid (Hyfresh) was used for treatment of dry eye disease in 27 eyes of 15 patients, for 6 weeks 4 times daily.

Group (B): Nine ml venous blood was taken under complete aseptic conditions, the PRP extracted was put in a sterile plastic bottle with eye dropper, the PRP was extracted weekly, and used as eye drops for 6 weeks 4 times daily in 28 eyes of 15 patients.

The bottle used should be kept at +4–8 °C for one week.

The patients were asked not to touch the eye dropper by their hands or eyes.

After the period of treatment we asked about subjective symptoms (OSDI), the tear meniscus, Schirmer test, tear film break up time (TBUT), and the best corrected visual acuity (BCVA) were evaluated.

The patients were asked not to use any type of eye drops during the 6 weeks, and to stop the PRP and Artificial tears at least 24 hours before the first and second assessment.

PRP preparation:

Using a 10 ml sterile plastic syringe with a wide pore needle, 9 ml of fresh blood was extracted, to a sterile glass tube containing 1ml of sodium citrate as an anticoagulant, autologous PRP was extracted by single spin method, whole blood was centrifuged at 2500 RPM for 3 minutes, the supernatant PRP withdrawn to a sterile plastic eye dropper that was used as eye drops.

Using a centrifuge (Eppendorf 5804) and hemocytometer (Diagon D-cell 60) the whole blood and supernatant PRP.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:
- Probability (P-value):
- P-value <0.05 was considered significant.
- P-value <0.001 was considered as highly significant.
- P-value >0.05 was considered insignificant.

RESULTS

This study was held on 55 eyes of 30 patients with moderate and severe dry eye disease.

Five eyes of 5 patients were excluded (3 pterygium, 2 ectropion).

- Average age was (50.5±14.5) range from 23 years to 74 years.
- They were 22 females (73.3%) and 8 males (26.7%).
- Type of DED was distributed as 6 cases of ADDED (20%) and 24 cases EDED (80%).

Table (1): Demographic data of studied patients No.=30

	Variable	Studied patients No.=30
Age (years):	Mean ±SD Rang Median	50.5±14.5 23-74 52.5
Sex:	Male Female	**No. (%)** 8(26.7%) 22(73.3%)
Type of eye dryness:	ADDED EDED	6(20%) 24(80%)

Table (2): Distribution of type of dryness in studied patients' groups

	PRP group No.=15	hyaluronic acid No=15
Type of eye dryness ADDED EDED	4(26.6%) 11(73.4%)	2(13.3%) 13(86.7%)

The patients were divided into two groups:

- Group A: 28 eyes of 15 patients treated with PRP eye drops 4 times a day for 6 weeks. 2 eyes of 2 patients were excluded according to exclusion criteria.
- Group B: 27 eyes of 15 patients treated with artificial tears containing sodium hyaluronate 4 times per day for 6 weeks. 3 eyes of 3 patients were excluded according to exclusion criteria.

We found that in PRP group A:

Regarding to symptoms of DED evaluated by OSDI questionnaire there is a great decrease in the score of OSDI, indicating a decrease in dry eye symptoms from (64.9±21.1) pretreatment to (40.1±19.5) post treatment (P value =0.001) which is statistically significant,. Figure **1**.

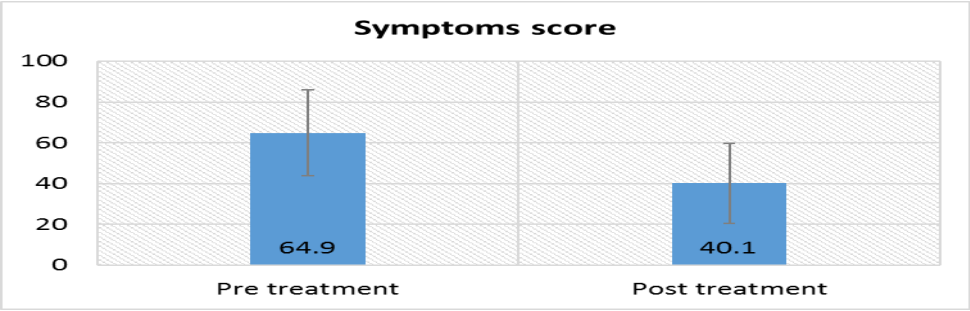

Figure (1): Pre and post comparison in patients received PRP regard Symptoms score

Regarding to TBUT there was an improvement in break up time in seconds from (4.2±3.1) pretreatment to (6.3±2.7) post treatment, (P value=0.004) which is statistically significant. **Figure 2**

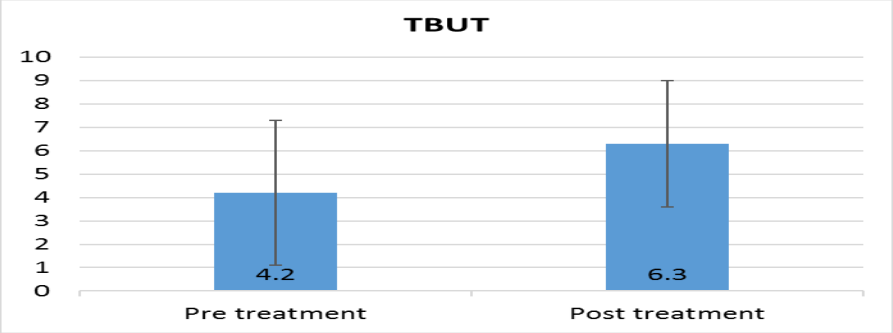

Figure 2: Pre and post comparison in patients received PRP regard TBUT.

Regarding to Schirmer test it also show an improvement from (10.2±4.8) to (12.6±3.5) P value = 0.01 which is statistically significant. **Figure 3**

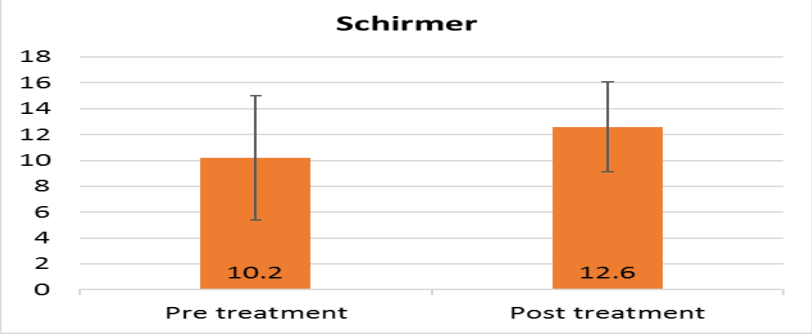

Figure 3 : Pre and post patients received PRP regard Schirmer

Regarding to CFS there was an improvement up to disappearance of staining from (2.1±0.97) to (0.60±0.63), P value = 0.001 which is statistically significant. **Figure 4**

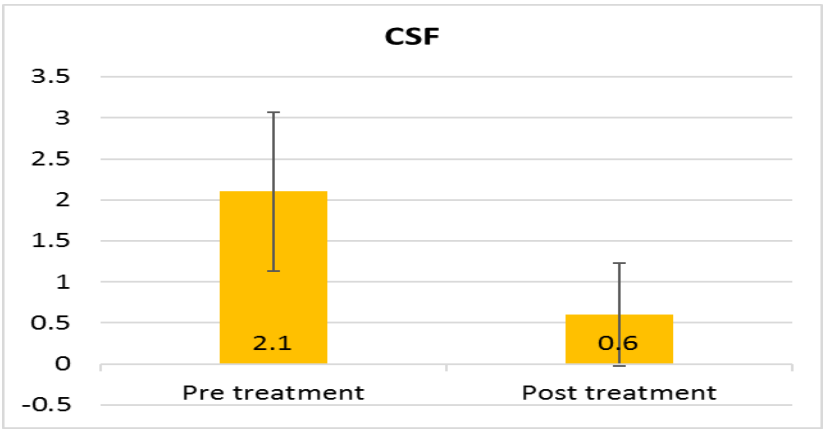

Figure 4 : Pre and post comparison in patients received PRP regard CFS

Regarding to BCVA there was an improvement from (0.50±0.17) to (0.60±0.24) P value=0.008 which is statistically significant. **Figure 5**

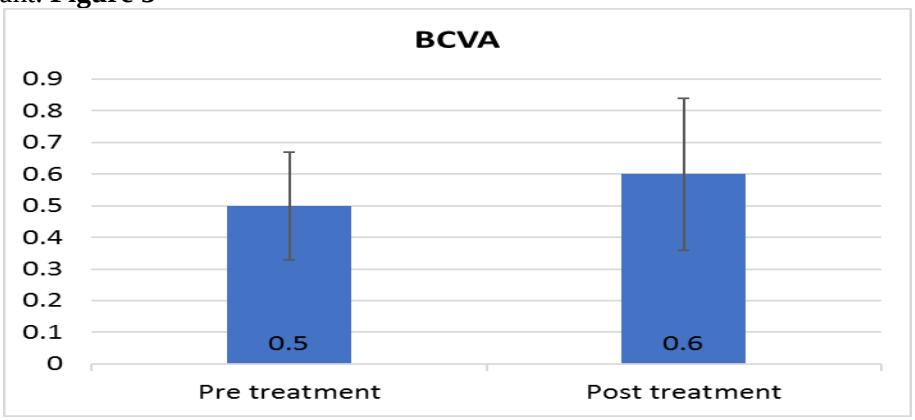

Figure 5 : Pre and post comparison in patients received PRP regard BCVA

In PRP group A:

There was an improvement in symptoms of DED in 86.6% of cases (13/15) and two cases not improved (2/15) 13.3%.

TBUT improved in 10 cases from 15 (66.6%) , 5 cases not improved (33.3%).

CFS improved up to disappearance of staining in 5 cases 33% of cases and fair improvement in 8 cases 53.3%, total cases improved 13 cases 86,6%, 2 cases not improved 13.3%.

Schirmer test improved in 6 cases (40%) of cases.

Regarding BCVA improvement of 4 cases (26.6%) improvement was not more than one line.

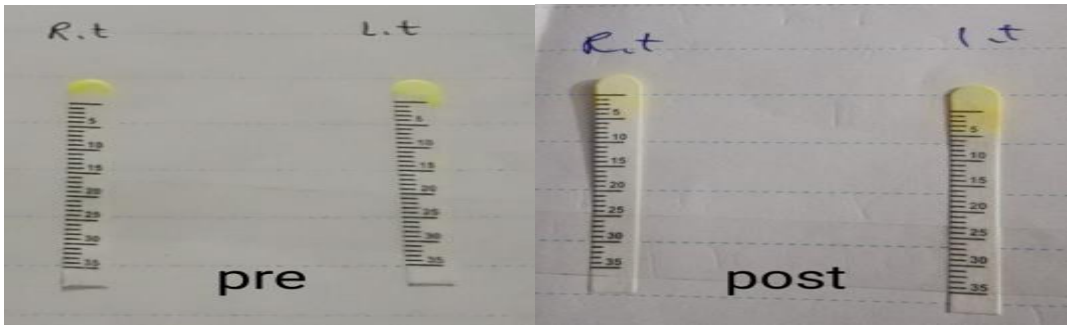

Figure 6: Showing Schirmer test before and after treatment by PRP in a case of severe ADDED.

Table (3): Pre and post comparison in patients received PRP regard symptom score, TBUT, Schirmer, CFS and BCVA

	Variables	Pre treatment	Post treatment	Test of sig. Wilcoxon test	P value
Symptoms score	Mean ± SD Rang Median	64.9±21.1 31.3-93.8 70.3	40.1±19.5 12.5-66 46.6	3.3	0.001 S
TBUT	Mean ± SD Rang Median	4.2±3.1 0-11 3.5	6.3±2.7 3-11 7	2.9	0.004 S
Schirmer	Mean ± SD Rang Median	10.2±4.8 0-14 12.5	12.6±3.5 4-16 14	2.24	0.01 S
CFS	Mean ± SD Rang Median	2.1±0.97 1-4 2	0.60±0.63 0-2 1	3.4	0.001 S
BCVA	Mean ± SD Rang Median	0.50±0.17 0.21-0.81 0.50	0.60±0.24 0.21-1 0.56	2.67	0.008 S

NS= non-significant (P-value >0.05), S= Significant (P-value <0.05), HS= highly significant (P-value ≤0.001).

Regarding to TBUT there was an improvement in break up time in seconds from (5.9±2.7) pretreatment to (6.5±2.5) post treatment, (P value=0.09) which is statistically non-significant.
Regarding to Schirmer test it also show no improvement from (10.2±2.8) to (10.9±3.1) P value = 0.06 which is statistically in significant.

Regarding to CFS there was an improvement from (2.1±1.08) to (0.51±0.19) , P value = 0.03 which is statistically significant. Regarding to BCVA there was no improvement from (0.48±0.19) to (0.50±0.19) P value= 0.31 which is statistically in significant.

In Na hyaluronate group:

There was an improvement in symptoms of DED in 60% of cases (9/15) and 6 cases not improved (6/15) 40%.

- TBUT slightly improved in 3 cases but not significant.
- CFS gave some improvement in 4 cases (26.6%).
- Schirmer test not improved in any of cases.
- Regarding BCVA not improved in any of cases.

Table (4): Pre and post comparison in patients received sodium hyaluronate regard symptom score, TBUT, Schirmer, CFS and BCVA

	Variables	Pre treatment	Post treatment	Test of sig. Wilcoxon test	P value
Symptoms score	Mean ± SD Rang Median	75.2±14.2 41.7-93.8 79.1	55.9±17.7 21.7-83.3 62.5	3.1	0.001 S
TBUT	Mean ± SD Rang Median	5.9±2.7 2-12 6.5	6.5±2.5 2-11 7	1.6	0.09 NS
Schirmer	Mean ± SD Rang Median	10.2±2.8 4-17 12	10.9±3.1 4-13 11	2.01	0.06 NS
CFS	Mean ± SD Rang Median	2.1±1.08 0-4 2	0.51±0.19 0-3 2	2.1	0.03 S
BCVA	Mean ± SD Rang Median	0.48±0.19 0.25-0.81 0.50	0.50±0.19 0.25-1 0.50	1.01	0.31 NS

NS= non-significant (P-value >0.05) S= Significant (P-value <0.05) HS= highly significant (P-value ≤0.001).

In comparison of improvement between the two groups A,B regarding parameters improved in the two groups:

Symptoms score improvement in PRP was (40.04±19.1) and improvement in Na hyaluronate was (25.01±20.07) p value 0.01 which is statistically significant. **Figure 7**

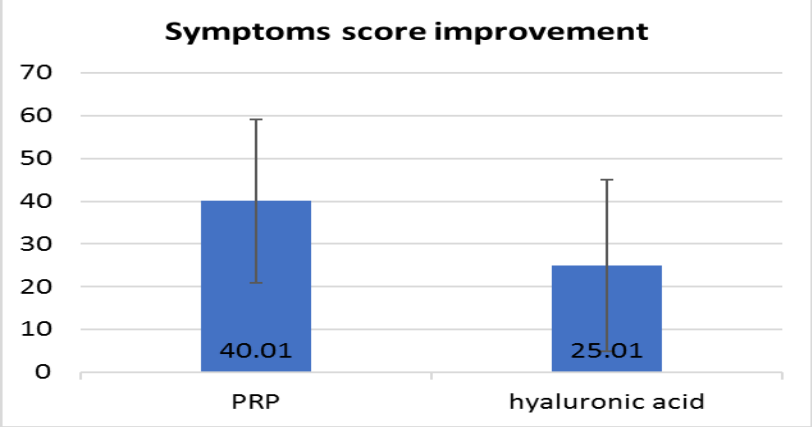

Figure (7): comparison of improvement between PRP and hyaluronic acid post treatment regard symptom score

CFS improvement in PRP was (77.3±25.2) and in Na hyaluronate group (44.3±41.5) p value =0.02 which is statistically significant. **Figure 8**

In Schirmer test, TBUT and BCVA there is no significant improvement in Na hyaluronate group but improved in PRP group significantly.

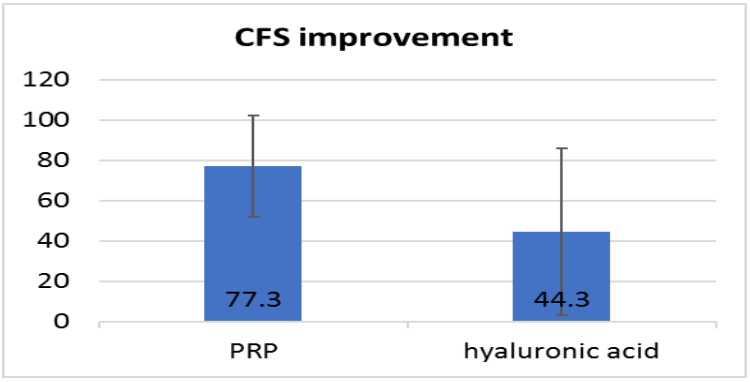

Figure (8): comparison of improvement between PRP and hyaluronic acid post treatment regard CFS

DISCUSSION

In our study PRP was prepared by centrifugation of citrated blood at 2500 rpm for 3 minutes and the enrichment was =1.90. At the same study PRP was prepared by centrifugation of 100 ml of blood and put in bottles one in use put at +4ºC and the remaining was stored at -20ºC.

In our study PRP was prepared just 10 ml weekly as a fresh not frozen PRP. In our study PRP group of patients all are improved in all parameters and all of them were statistically significant.

Symptoms OSDI score decreased indicating improvement in 86.6% of patients.

TBUT improved in 66.6% of cases. CFS improved up to disappearance of staining in 33% of cases and fair improvement in 53.3%, total improvement was 86.6%.

Schirmer test improved in (40%) of cases.

BCVA improved in (26.6%) of patients, improvement was not more than one line.

In a study by **Alio *et al.*[6]** on 368 cases of moderate and severe DED, 297(80.7%) patients were women, and 71 (19.3%) were men. 232(63%) patients had EDED, while136 (37%) had ADDED. After 6 weeks of monotherapy treatment with autologous PRP, Dry eye symptoms improved in 322 (87.5%) cases. a decrease of CFS was observed in 280 (76.1%) patients. 106(28.8%) patients improved at least 1 line of BCVA. The scores in the ocular Surface Disease Index and the

Oxford scale of corneal fluorescein staining decreased statistically after the treatment (p value <0.05). Results at this study were near our study, but CFS improved more in our study, may be due to the more enriched PRP (1.90) we used and the fresh plasma used as mentioned before.

Another study by **Alio *et al.*** [7] a prospective, nonrandomized, observational consecutive pilot study that included 36 eyes of 18 patients with moderate to severe dry eye disease. E-PRP was given topically as eye drops (4-6 times a day per eye) to patients suffering from moderate to severe dry eye symptoms. After 1 month of treatment with PRP eye drops 89% of the patients came with improvement of subjective symptoms. 28% of patients had at least 1 line or more of visual acuity improvement of CFS was found in 72% of the cases results were similar to our study but CFS still better in our study. BCVA improved in the 2 studies one line or more, but in our study just one line, may be due to insufficient PRP frequency (4 times per day).

In another study; **Ribeiro *et al.*** [8] on treatment of DED in diabetic patients, a prospective interventional study; 12 patients were treated with autologous PRP eye drops four times a day for a month. Resulted in**:** 100% of patients had symptomatic improvement regarding dryness, itching, burning and redness (p=0.002). Five patients, 41.66% (5/12) had improvement of 1 or more lines of visual acuity in both eyes, Schirmer test improved in 66.66% (8/12) of patients,25% (3/12) had no alteration in this test value and 8.33% (1/12) had a reduced value the value of BUT test 58.33% (7/12) had improvement in the test value and 41.66% (5/12) had no alteration in this test value (p=0.018) symptoms and Schirmer values improved in this study more than our study, may be due to using two spin methods of PRP preparation which give an enrichment more than one spin method but less plasma volume.

In a study **Conca *et al.*** [9] for treatment of hyposecretory dry eye disease using PRP and sodium hyalurinate that result in Significantly larger reduction in symptomatology (p <0.001), visual improvement (p <0.001), and corneal and conjunctival staining (p <0.001), increased Schirmer test outcome (p ≤0.005), in the PRP group in both eyes compared to SH group at 15 and 30 days of treatment. Strong and statistically significant correlations were found in the PRP group of the change achieved in visual acuity, hyperemia, osmolarity, and conjunctival and corneal staining with the baseline values of these variables (p <0.001). In Na hyalurinate there is significant improvement in subjective symptoms p = 0.001). Reduction of conjunctival staining in both eyes only at 15 days (p=0.020), and reduction of corneal staining in RE at 15 days (p=0.020).

In a study **Aragona *et al.*** [10] of sodium hyalurinate in ttt of dry eye and placebo in both treatment groups an improvement for all symptoms compared with baseline was observed. After 3 months of treatment the overall efficacy score was better in the hyaluronate group but this difference was not statistically significant.

CONCLUSION

We found that

- PRP is very effective in treatment of moderate and severe cases of DED at the level of subjective symptoms, TBUT, CFS, BCVA, and Schirmer test.
- All Cases of ADDED and EDED are responsive to treatment by PRP.
- Rather than the use of artificial tears, despite improving subjective symptoms, and CFS significantly (but less than the effect of PRP at the two levels of sodium hyalurinate), it had no significant effect on the level of TBUT, BCVA, and Schirmer test.
- I thought that the cases of ADDED cannot obtain a valuable benefit from SH at the level of aqueous deficiency represented by Schirmer test.
- Also PRP is safe, preservative free and affordable.

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