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Clinical and Anatomical Outcomes of Platelet-Rich Plasma Therapy in Refractory Corneal Ulcers

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Abstract **Original Research Article**

Autologous platelet-rich plasma (PRP) has emerged as a promising regenerative therapy for refractory corneal ulcers. This prospective, non-randomized interventional study evaluated 21 corneal ulcers in 16 patients unresponsive to at least 15 days of conventional therapy, including vitamin A ointment, preservative-free lubricants, and occlusive patching. Patients received topical autologous PRP (1 drop, four times daily) in combination with supportive therapy. Clinical outcomes assessed included ulcer dimensions, visual acuity, and ocular symptom improvement. Median treatment duration was 21 days (range 15–60). Complete re-epithelialization was achieved in 71.4% of ulcers, with mean ulcer height and width decreasing by 86.2% and 83.0%, respectively ($p < 0.01$). Visual acuity improved by three lines in 31.25% and by two lines in 25% of patients. Significant reductions were observed in pain ($p < 0.05$), redness ($p < 0.01$), visual impairment ($p < 0.01$), and photophobia ($p = 0.01$). One patient developed corneal neovascularization. These results demonstrate that autologous PRP is a safe and effective therapy for promoting corneal healing, reducing ulcer size, and improving visual function and ocular comfort in refractory cases. Further standardization of PRP preparation and dosing protocols is warranted to optimize clinical outcomes and facilitate broader adoption in ophthalmic practice.

Keywords: Platelet-Rich Plasma; Ocular Surface Disease; Refractory Corneal Ulcer; Regenerative Therapy.

INTRODUCTION

Corneal ulceration is a major ocular surface disorder, characterized by epithelial loss and stromal involvement that can lead to corneal perforation if inadequately treated. Owing to its diverse etiologies and potential for severe visual impairment, it remains a major therapeutic challenge in ophthalmic practice. In recent years, the application of platelet-rich plasma (PRP) has emerged as a promising regenerative strategy for corneal surface disorders, due to its high concentration of growth factors, that stimulate epithelial regeneration [1]. However, despite progress in understanding its mechanisms of action, it remains necessary to clarify its true clinical efficacy. The present study was designed to evaluate the clinical and anatomical outcomes of autologous PRP therapy in patients with treatment-resistant corneal ulcers.

PATIENTS AND METHODS

A prospective, non-randomized interventional study was conducted in the Ophthalmology Department of Oued Eddahab Military Hospital (Agadir, Morocco) over a 10-month period (November 2022 – June 2023). The study included 21 non-infected corneal ulcers in 16 patients who were refractory to conventional therapy after a minimum of 15 days of adherence. Prior treatment comprised topical vitamin A ointment, preservative-free lubricants, and occlusive eye patching. All patients received topical autologous platelet-rich plasma (PRP) instilled at a dosage of 1 drop, 4 times daily, in combination with preservative-free lubricants (4 times daily), vitamin A ointment (twice daily), and occlusive dressing. PRP was prepared from 40 ml of peripheral venous blood collected in sodium citrate tubes and centrifuged at 1500 rpm for 10 minutes. The plasma is then collected using a pipette and transferred into sterile bottles. Patients were instructed to store these bottles in the freezer at 20° C until required. The bottle in use should be kept in refrigerated conditions at 4° C and should be used for no longer than 1 week.

Epidemiological (age, sex, general pathological antecedents, ophthalmological antecedents); clinical data (chief complaint, clinical signs, ophthalmologic findings); etiological, and treatment outcome data were systematically collected.

Quantitative variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), and qualitative variables as counts and percentages. Paired comparisons for quantitative variables were performed using the Wilcoxon signed-rank test, and categorical variables were analyzed with McNemar's test. A two-tailed p-value < 0.05 was considered statistically significant.

RESULTS

In our study, we included 21 ulcers occurring in 16 patients. The mean age of the patients was 53.4 ± 11.2 years, with an age range of 23 to 71 years. The sex ratio (f/m) was 1.29 with 9 females (56%) to 7 males (44%). The corneal ulcer was unilateral in 11 patients (68.75%) and bilateral in 5 patients (31.25%). General medical conditions were found in 12 cases (75%): 6 patients had diabetes, 4 had Sjögren's syndrome, 1 had hyperthyroidism, and 1 had severe rheumatoid arthritis. We found at least one prior ophthalmological antecedent in 14 patients, representing 87.5% of our series: 6 cases of corneal de-epithelialization during posterior segment surgery, 1 case of cataract surgery in a patient with rheumatoid arthritis, 4 cases of severe dry eye syndrome, 1 case of allergic keratoconjunctivitis, 1 case of ocular pemphigoid, and 1 case of neurotrophic keratitis. The clinical data collected after interview and ophthalmological examination are reported in the table 1.

Autologous platelet-rich plasma (PRP) instillations were administered 4 times daily to all patients after the failure of conventional wound-healing therapy and ocular occlusion maintained for at least 15 days. The median duration of administration was 21 days, with a range from 15 to 60 days. In addition to PRP, all patients received preservative-free wetting agents at a dose of one drop 4 times daily, and a vitamin A ointment morning and evening with ocular occlusion. In our series, two patients received rituximab as etiological treatment after conjunctival biopsy revealed fibrosing conjunctivitis.

The clinical and anatomical evolution under PRP treatment in our patients was favorable, as shown in table 1. Nevertheless, we noted the presence of corneal opacities in 3 eyes. Furthermore, we observed persistent bilateral ulcers in 2 patients, representing 19.04% of all ulcers, without any evidence of worsening. We recorded complications in only one patient, consisting of corneal neovascularization in both eyes. Comparative statistical analysis of ulcer characteristics before and after PRP treatment, revealed a statistically significant difference, demonstrating the effect of PRP in reducing ulcer size ($p < 0.01$).

Table 1: Clinical data before and after PRP therapy from our series

Variable	Before PRP	After PRP	Interpretation
Functional signs (n=16)			
Eye Pain	16/16 (100 %)	Disappeared: 7/16 (43,75%) Improved: 7/16 (43,75%) Unchanged: 2/16 (12,5 %)	87,5% improvement in eye pain (n =16)
Eye Redness	13/16 (81,25 %)	Disappeared: 6/16 (37,5%) Improved: 4/16 (25 %) Unchanged: 2/16 (12,5%) Aggravated: 1/16 (6,25 %)	76,9 % improvement in eye redness (n=13)
Decreased Visual Acuity (DVA)	12/16 (75 %)	3 ligne gain: 5/16 (31,25%) 2 ligne gain: 4/16 (25%) Unchanged: 2/16 (12,5%) Aggravated: 1/16 (6,25%)	75% improvement in Visual acuity (n =12)
Photophobia	11/16 (68,75 %)	Disappeared: 7/16 (43,75%) Persistance: 4/16 (25%)	63,6% improvement in photophobia (n=11)
Tearing	10/16 (62,5%)	Disappeared: 7/16 (43,75%) Persistance: 3/16 (18,75%)	70% improvement in tearing (n = 10)
Blépharospasm	3/16 (18,75%)	Disappeared: 2/16 (12,5%) Persistance: 1/16 (6,25%)	66,6% improvement in blepharospasm (n=3)
Examination data (n =16 patients)			
Conjunctival hyperemia	13/16 (81,25%)	Disappeared: 6/16 (37,5%) Improved: 4/16(25%) Unchanged: 2/16(12,5%) Aggravated: 1/16 (6,25%)	76,9 % improvement in conjunctival hyperemia (n=13)
Eye dryness (break up time =BUT)	Severe (25%) (25%). BUT < 5s Moderate (12,5%) (2/16). BUT 5-10 s	—	—
Site of the ulcer	Central: 10	—	—

(n = 21)	Paracentral: 8 Peripheral: 3		
Size of the ulcer (n = 21)			
Average height	2,76 mm (1-6mm)	0,381 mm (0–2 mm)	Average decrease of 86,2 %
Average width	2,81mm (1-7mm)	0,476 mm (0–3 mm)	Average decrease of de 83,04 %
Reepithélialization	0/21 (0 %)	15/21 (71,4 %)	71,4 % improvement

Table 2: Therapeutic protocols in our and other studies

Author	Frequency of administration	Average duration of administration
Our series	4 Times Daily	21 Days (15- 60 days)
López-Plandolit *et al.,* [12]	12 Times Daily	10,9 week (2-39 week)
Wu *et al.,* [13]	12 Times Daily	17 - 35 Days
Sanchez-Avila *et al.,* [14]	4 Times Daily	6-12 Week
Alio *et al.,* [15]	6 Times Daily	6 Week
Wróbel Dudzińska *et al.,* [16]	5 Times Daily	12 Week (Maximum)
Ronci *et al.,* [17]	3 Times Daily	14 – 21 Days
Filtriana *et al.,* [18]	6 Times Daily	7 Days

Table 3: Evolution of visual acuity under PRP therapy in our series and other series

Author	Gain in lines of visual acuity (After PRP therapy)	Percentage Improvement in Visual Acuity
Our Study (n=12)	3 lignes gain: 5/12 (41,66%) 2 lignes gain: 4/12 (33,33 %) Unchanged: 2/12 (16,66%) Agravated; 1/12 (8,33%)	75 % Improvement
Alio and all (15) (Study in 2018) (n=44)	1 ligne gain: 29/44 (65,9%) Stable; 9/44 (20,5%) Agravated; 6/44 (13,6%)	65,9 % Improvement
Alio and all (19) (Study in 2007) (n=40)	6 ≥ lines gain: 10,5 % 4 to 5 lines gain: 16 % 1 to 3 lines gain: 34 % Unchanged: 39,5 %	60,5 % Improvement
Sanchez-Avila and al (14) (n=38)	not specified by the author	52,8 % Improvement

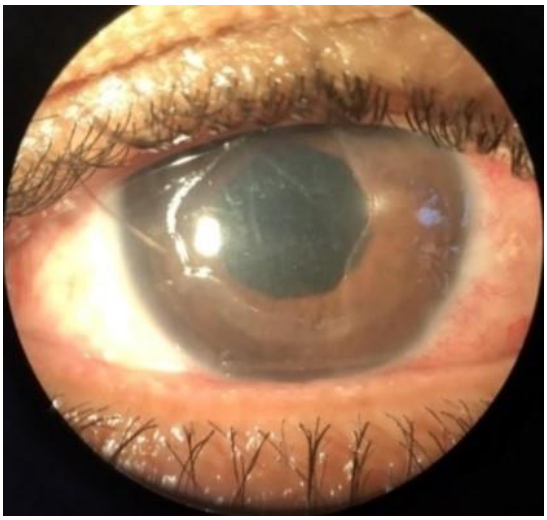

Figure1 : Central ulcer before PRP therapy

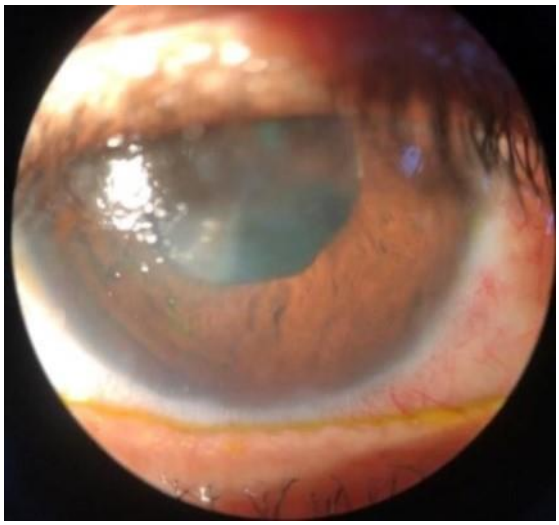

Figure 2 : appearance after PRP therapy

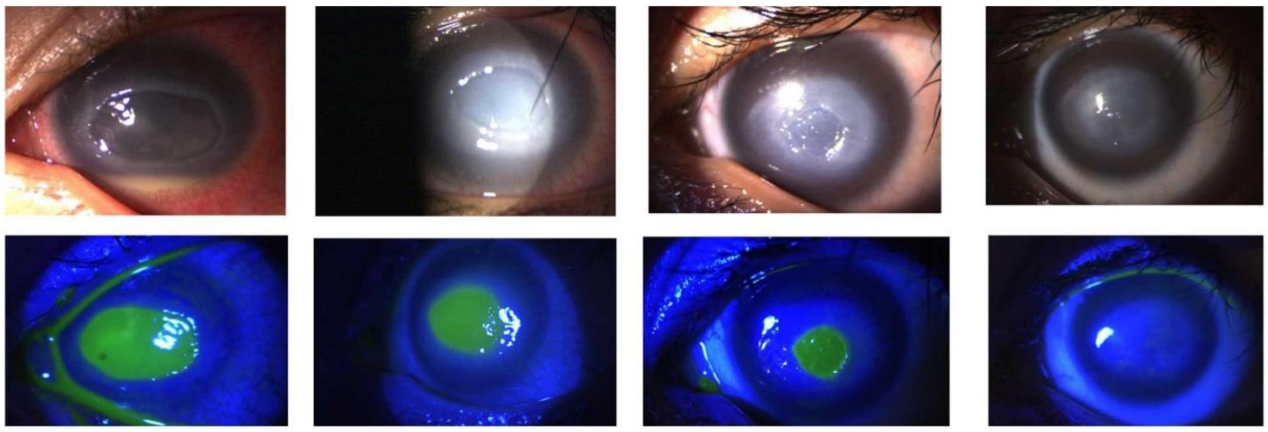

Figure 3: Anatomical evolution after PRP therapy

DISCUSSION

Autologous platelet-rich plasma (PRP) is a plasma fraction obtained from the patient's own blood via centrifugation, in which platelets are concentrated to a level higher than that in the initially collected whole blood [2]. Platelets release multiple bioactive growth factors, including basically: PDGF (Platelet-derived growth factor), TGF-β (Transforming growth factor β), FGF (Fibroblast growth factor), HGF (hepatocyte growth factor), EGF (Epithelial growth factor), VEGF (Vascular endothelial growth factor), and NGF (Nerve Growth Factor) [2,3-8], which collectively promote epithelial regeneration, and stromal repair. PRP has therefore emerged as a promising regenerative therapy for persistent corneal ulcers [9].

PRP preparation involves centrifugation of venous blood to separate its different components [10]. While several preparation techniques exist, no standardized protocol has yet been established [11]. Methods can be broadly categorized into simple kit-free methods based on the centrifugation of the blood collected in citrate tubes, then the plasma was recovered; and commercial kits-based methods allowing for a higher concentration of platelets. In our study, conventional epithelial healing therapy was first administered for 15 days. PRP treatment was initiated immediately if the ulcer persisted. Patients received 4 instillations daily for a median of 21 days (range 15–60 days). The diversity of protocols is evident in the literature (table 2). This variability underscores the absence of consensus on optimal dosing and highlights the importance of tailoring treatment to ulcer characteristics and patient factors.

In our cohort, PRP therapy led to significant improvements in both symptoms and objective outcomes : Ocular pain (87,5%), redness (76,9%), decreased visual acuity (75%), and photophobia (63,3%), tearing (70%), blepharospasm (66,6%), all improved significantly ($P < 0.05$-0.01). In comparison with literature, Sanchez-Avila and al. [14] demonstrated an improvement in pain in 60% of the cases. Alio and al. [15] observed an improvement in symptoms in 90.9% of the patients. Wróbel Dudzińska and al. [16] reported an improvement in subjective symptoms without specifying the degree of each. These results suggest that PRP treatment is associated with significant improvements in major symptoms. Although inter-study differences likely reflect variations in PRP protocols, ulcer etiology, and baseline patient characteristics. Functionally, among the 12 patients in our series who presented with decreased visual acuity, 9 patients saw their visual acuity improve, representing an improvement in 75 % of cases. The comparison between our series and those in the literature is detailed in the table 3. These results suggest that PRP treatment is associated with significant improvement in visual acuity in the majority of patients.

Anatomical outcomes were equally favorable (figures 1,2,3). In our study mean corneal ulcer height decreased by 86.2% and mean width by 83.04%. Fitriana *et al.*, [18] documented a 42.4% reduction in ulcer area at the end of PRP therapy. Alio *et al.*, [15], in his series, he observed a significant reduction in ulcer size in 59,1% of cases without specifying the dimensions. Literature data on absolute ulcer dimensions are limited, most authors report a reduction or complete resolution of the ulcer without specifying the dimensions. In our study complete re-epithelialization was achieved in 71.4% of ulcers, comparable to Wróbel-Dudzińska and al. [16] and Alio and al. [19] who reported re-epithelialization rates of 80% and 53% respectively. Sánchez-Avila *et al.*, [14] reported a remarkable complete re-epithelialization rate of 97.4% of the patients.

Overall, these findings confirm that autologous PRP is an effective adjunctive therapy for corneal ulcers, promoting both symptomatic relief and structural healing. The lack of comparable statistical analysis data in several studies in the literature makes it difficult to compare the effects of PRP. Differences in therapeutic protocols, measurement criteria, and analysis methods can influence the variability of results between studies. Future randomized controlled trials are warranted to optimize PRP therapy and further elucidate its regenerative potential in ocular surface disease.

CONCLUSION

The use of autologous platelet-rich plasma (PRP) in the treatment of corneal ulcers represents a significant advancement in ophthalmology. Its demonstrated efficacy in promoting corneal healing establishes PRP as a highly promising regenerative therapy. However, there remains a critical need to define optimal administration protocols, which would enable the development of evidence-based guidelines to maximize its clinical effectiveness.

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