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CLINICAL STUDY

# The use of autologous serum tears in persistent corneal epithelial defects

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**Abstract**

***Purpose*** **Persistent corneal epithelial defects (PED) present a very challenging problem to anterior segment surgeons. Autologous serum tears had been demonstrated to be beneficial in the treatment of PED. The current study was conducted to review the local spectrum of indications and to examine the outcome of autologous serum tear usage.**

***Methods*** **All cases of PED treated with autologous serum tears at a tertiary referral centre for the period August 1999 – July 2001 were identified and reviewed.**

***Results*** **A total of 10 eyes from 10 patients were identified (5OD : 5OS). The gender ratio was 7M : 3F and the mean age was 36.8 (range 17–73) years old. The mean duration of PED before the usage of autologous serum tears was 22.4 $\pm$ 69.6 days. Six eyes healed within 2 weeks, but two eyes failed to heal after 1 month of treatment and two patients defaulted follow-up. No adverse effects were observed with the addition of autoserum tears.**

***Conclusions*** **The results of the current study correlated well with previous reported studies. Autologous serum tears may be considered as a valuable adjunct in the management of recalcitrant cases of PED.**

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*Keywords:* autologous serum tears; persistent epithelial defects; limbal stem cell deficiency

## Introduction

Persistent corneal epithelial defects (PED) are one of the difficult conditions encountered by ophthalmologists. They are associated with significant clinical morbidity in patients, resulting in discomfort or visual loss.[1] The causes of PED are diverse, with several definite aetiologies including dry eyes, limbal stem cell deficiency, diabetes mellitus, and neurotrophic problems.[1,2] A variety of treatment modalities have been described for PED. The elimination of predisposing-associated risks remains a key factor in the management process.[1] Conventional treatment includes ocular surface lubrication with frequent instillation of artificial tears, protective glasses, and punctal occlusion.[3] Essential tears component, such as epidermal growth factor (EGF), vitamin A, transforming growth factor $\beta$ (TGF$\beta$), are, however, lacking in artificial tears, as the key constituents of these are water and electrolytes. These essential components can contribute to healing in cases of PED usually associated with an already compromised ocular surface.

Serum has been shown to contain essential tears components in comparable concentrations to natural tears.[4] Studies have demonstrated that despite the lack of natural tears, the ocular surface epithelium can maintain its phenotype by application of serum alone. An elegant study conducted by Poon *et al*[5] also showed that corneal epithelial cells preserved their cell membrane integrity better (less reduction in cellular viability as measured by ATP assay) when incubated with serum drops in comparison to unpreserved hypromellose. This suggests that serum contains components present in natural tears, and may be used as an adjunct or 'aletrnative'.[6,7]

The use of autologous serum tears has previously been demonstrated to have a beneficial effect in the treatment of PED.[2,4,5] Apart from its usage in treating PED, autologous serum tears may also be used in ocular surface reconstruction and dry eyes from different causes.[2,5,8-11] Factors present in serum can induce proper proliferation and differentiation of corneal epithelium.[12]

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The current study was conducted to review the local spectrum of indications and to examine the outcome of autologous serum tears usage.

## Materials and methods

The design of the study was a retrospective noncomparative case series. Authors have employed various definitions of PED.[2,13–17] In this study, we adopted the one by Pfister — 'a defect with cells failing to show the expected rate of healing for the time course involved'.[17]

All patients treated with autologous serum tears at the Prince of Wales Hospital, Hong Kong (a tertiary referral centre), from the period August 1999 to July 2001 were reviewed. The underlying diagnoses, duration of PED, additional treatment, indications, frequency, and duration of autologous serum tears usage were documented. The main outcome measures were PED healing time after the initiation of autologous serum tears and if any adverse effects were experienced.

Autologous serum teardrops were prepared by taking 20 ml of peripheral blood from the patient under aseptic technique. The blood was then centrifuged for 5 min at 1500 revolutions/min. The serum was separated and was diluted to 20% with sterile saline. The solution was then put into a bottle with ultraviolet light protective coating on surface. The patients were instructed to store the eye drops in the freezer compartment of domestic refrigerator for no more than 1 month. Previous study reported that the concentrations of vitamin A, EGF and TGF$\beta$ stored at 4 and $-20^{\circ}$C could remain stable for 1 and 3 months, respectively.[2]

We adopted the grading system developed by Tsubota *et al*[2] in determining the efficacy of autologous serum tears in the treatment of PED. Autologous serum treatment was considered to be effective if the epithelial defect healed within 2 weeks, partially effective if there was a tendency to heal within 2 weeks and healing achieved in 1 month, and ineffective if healing was not achieved in 1 month.

## Results

A total of 10 eyes in 10 patients were identified. The mean age of the patients was 36.8 (range 17–73) years, with a sex ratio of 7M : 3F (5OD:5OS). All the patients failed conventional treatment including general measures such as artificial tears, punctal occlusion, and tarsorrhaphy.

The diagnoses yielding limbal stem cell deficiency included Steven Johnson syndrome (one patient), ectodermal dysplasia (one patient), alkaline burns (two patients), sacrificing eye from previous radiation therapy for nasopharyngeal carcinoma (one patient), and postsuperficial keratectomy for pterygium covering the whole cornea (one patient). The remaining diagnoses were neurotrophic ulcers (three patients) and PED after penetrating keratoplasty (one patient). (Table 1).

The mean duration of PED before the commencement of autologous serum tears was $22.4 \pm 69.6$ days (range 1–92 days). In view of the past history of severe recurrent PED and limbal stem cell deficiency in ectodermal dysplasia, patient 3 started autologous serum tears only 1 day after lamellar keratoplasty (Table 1).

The frequency of autologous serum tears ranged from 6 to 14 times per day. In addition, all patients were prescribed preservative artificial tears and preservative-free antibiotics. Other general treatment measures included bandage contact lens in one patient, lateral tarsorrhaphy in three patients, and amniotic membrane transplantation in five patients.

Six eyes healed within 2 weeks and autologous serum tears therapy was considered to be effective. In this 'effective' group, all healed within 1 week after the initiation of autologous serum tears. Two eyes failed to heal within 1 month and autologous serum tears therapy was considered to be ineffective in these patients. No adverse effects (eg induced vascularisation, infection or discomfort) were observed with the application of autologous serum tears (Table 2).

Two patients, however, defaulted follow-up. One patient was lost to follow-up 5 days after the initiation of serum tears. The epithelium was not healed at the last follow-up examination. The second patient self-discontinued autologous serum tears after 13 days usage, because he declined further blood taking. The PED was healing with good progress while applying autologous serum tears, but the defect became static after discontinuation of drops. The PED eventually healed after receiving 'conventional' treatment of 2 months.

## Discussion

PED may lead to severe morbidity with potential serious complications.[1,2] The strategies of treatment for PED include removal of any identifiable aetiologies and promotion of epithelial healing. Any lid abnormalities present such as lagophthalmos, entropion, trichiasis, or chronic blepharitis should be corrected accordingly. Dry eyes should be treated with frequent application of preservative-free medications. Punctal occlusion can preserve natural tears. In addition to their benefit of preventing surface desiccation, essential tears components are also present to promote healing.[4] In diabetic corneal epitheliopathy, the use of aldose reductase inhibitor has been reported to improve nerve function and corneal sensation, and hence promote

**Table 1** Summary of clinical details of patients

| *Patient* | *Diagnosis* | *Duration of PED (days)* | *Autologous serum tears* | *Other treatment measures* | *Outcome (healing/days)* |
|---|---|---|---|---|---|
| 1 | Steven Johnson syndrome (limbal stem cell deficiency) | 14 days recurrent PED 2 days AMT | Freq: 6x/days Duration: >5 days | Ocular lubricants with artificial tears and gel Topical antibiotics | Lost to follow-up |
| 2 | Neurotrophic ulcer, postherpetic | 29 | Freq: q2h Duration: 14 days | As per Case 1 + ateral tarsorrhaphy + punctal occlusion | 6 |
| 3 | Ectodermal dysplasia (limbal stem cell deficiency) | 1 | Freq: 6x/days Duration: 19 days | As per Case 1 + topical steroids | 5 |
| 4 | Alkaline burn, post-AMT | 3 | Freq: q6h Duration: 4 days | As per Case 3 + oral doxycycline + AMT + lateral tarsorrhaphy | 4 |
| 5 | Postpenetrating keratoplasty | 12 | Freq: q2h Duration: 8 days | As per Case 3 | 8 |
| 6 | Neurotrophic ulcer (postherpetic) | 17 | Freq: 14x/d Duration: >5 days | As per Case 1 + topical acyclovir ointment + punctal occlusion | 7 |
| 7 | Total pterygium excision (limbal stem cell deficiency) | 9 | Freq: 6x/days Duration: 8 days | As per Case 3 + punctal occlusion | 7 |
| 8 | Nasopharyngeal carcinoma with sacrificing radiation therapy | 20 | Freq: q2h Duration: 13 days, then refused | As per Case 1 + punctal occlusion + BCL + limbal autograft | Reduced in size while in use of tears. Healed in 2 months |
| 9 | Alkaline burn | 39 | Freq: 6x/days Duration: 28 days | As per Case 3 + punctal occlusion + BCL + AMT + lateral tarsorrhaphy + oral steroid + oral doxycycline + Vitamin C | 64 |
| 10 | Neurotrophic ulcer | 92 | Freq: 6x/days Duration: 43 days | As per Case 1 + patching + punctal occlusion + conjunctival flap + AMT | 43 No recurrence |

BCL = bandage contact lens; AMT = amniotic membrane transplant.

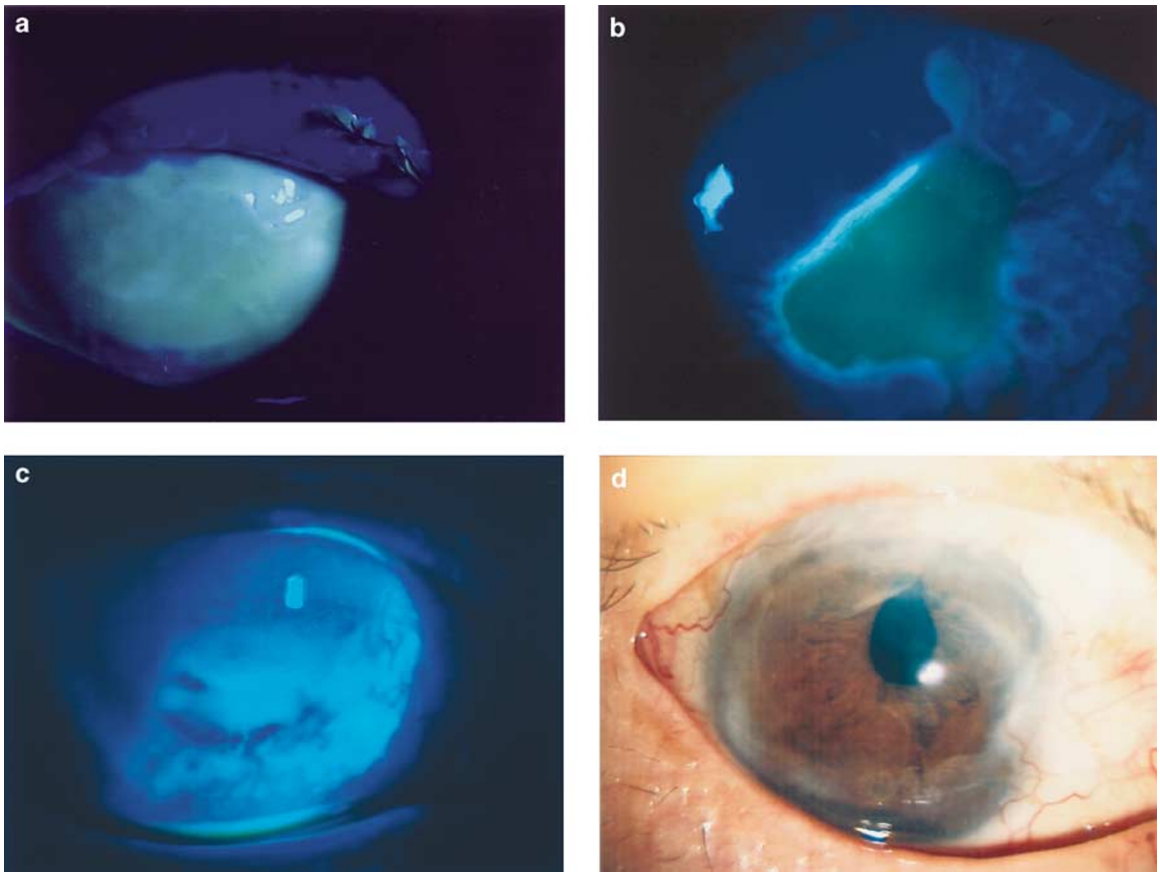


**Figure 1** Pre- and post-treatment status of Patent 8. (a) — Subtotal persistent corneal defect after limbal autograft. (b) — After 2 weeks treatment of autologous serum tears. (c) — totally healed defect post-treatment. (d) — taken after 3 years with reasonably stable smooth surface.

**Table 2** PED healing time comparison

| *Healing within* | *Current series* (n = *10*) | *Tsubota*[2] (n = *16*) |
|---|---|---|
| 2 Weeks (effective) | 6 (60%) | 7 (43.8%) |
| 1 Month (partially effective) | 0 (0%) | 3 (18.8%) |
| >1 Month (ineffective) | 2 (20%) | 6 (37.5%) |
| Defaulted | 2 (20%) | 0 (0%) |
| Side effects documented | 0 (0%) | 0 (0%) |

healing of PED.[18] Limbal stem cell transplantation has been established as the treatment of choice for limbal stem cell deficiency.[19,20] Other mechanical aids to facilitate epithelial healing include bandage contact lens (BCL) and tarsorrhaphy.[21] Both can reduce the mechanical stress of blinking and desquamation of the corneal epithelium. The prolonged contact of the ocular surface to natural tears with its essential components for wound healing has been associated with a significantly faster resolution of PED.[15] In recent years, amniotic membrane transplantation has also been shown to be useful in the treatment of refractory PED.[22,23]

The exact mechanism of action of autologous serum tears in the promotion of epithelial healing is unknown. It is postulated that essential growth factors for epithelial healing are present. These factors include EGF, vitamin A, TGF $\beta$, and fibronectin.[2] In addition, neuropeptides such as substance P and insulin-like growth factors are present in the serum.[2] This may contribute to the relative deficiency of neuropeptides from natural innervation in cases of neurotrophic ulcers. Serum has been shown to accelerate the migration of corneal epithelial cells *in vitro*, with upregulation of mucin expression.[8] The presence of serum antiprotease such as $\alpha$2-macroglobulin, which may inhibit collagenase, may be beneficial in cases with alkaline burn. These findings may account for the beneficial effect from autologous serum tears in the treatment of PED (Figure 1).

The mean duration of PED before starting autologous serum tears was $11.8 \pm 17.2$ days (range 1–29 days) for six patients in the 'effective' group (Table 1). Two patients (patients 9 and 10) failed to heal within 1 month, and treatment was considered to be 'ineffective'. The time for the PED to heal in these two patients were 64 and 43

days, respectively. The mean duration of PED of these two patients before starting serum tears was 65.5±26.5 days (39 and 92 days), which was longer than that of the 'effective group'. It is not known if the delayed commencement of autologous serum tears contributed to the apparent treatment 'ineffectiveness'. As with Tsubota's series, we also observed the tendency of poorer healing when the onset of autologous serum tears treatment was delayed. In comparing our results with the study by Tsubota *et al*,[2] our series revealed a larger number of patients in the 'effective' group (43.8 *vs* 60%) (Table 2). This may be related to the shorter duration of PED before initiation of serum tears in our group of patients. When both effective and partially effective criteria were included, 62.6% of the patients healed in Tsubota's group. No adverse effects or toxicities were observed in any of the patients (Tables 3 and 4).

Poon *et al*[5] (in a prospective cohort case study) demonstrated a success rate in nine out of 15 eyes (60%) of PED treated with autologous serum tears. The mean duration of healing was 29 days (ranged 3–60 days). However, the definition of success used was different from the one adopted in this series. Successful treatment was defined as closure of epithelial defect, including defects that healed beyond 1 month. If the duration of time in healing was examined, seven eyes healed within 1 month (46.7%), corresponding to the effective and partially effective groups, as defined in the current study and by Tsubota *et al*. Unfortunately, three patients developed microbial infections that necessitated the stoppage of the autologous serum drops. All the three patients had risk factors that may have contributed to the infections.[5] No other significant complications were reported with the use of autologous serum tears.[5]

In conclusion, the use of autologous serum tears appears to be a safe and useful adjunctive therapy in resistant cases of PED. The results of the current study correlated well with previous reports. The delayed onset of treatment with autologous serum tears may delay healing.

**Table 3** Comparison of response rate in various underlying pathologies

| *Effective & partially effective* | *Current series (healed/total)* | *Tsubota*[2] *(healed / total)* |
|---|---|---|
| LSCD | 2/3 | 4/6 |
| Post PK | 1/1 | 3/4 |
| Neurotrophic | 2/3 | 2/3 |
| Post-irradiation | 0/1 | 0/1 |
| Alkaline burn | 1/2 | N/A |
| GVHD | N/A | 1/2 |
| Total | 6/10 | 10/16 |

**Table 4** Mean duration (days) for healing after initiation of autologous serum tears

| *Diagnosis* | *Current series (n = 10)* | *Tsubota*[2] *(n = 16)* |
|---|---|---|
| Limbal stem cells deficiency | 6±1 | 42.7±53.3 |
| Post penetrating keratoplasty | 8 | 37.0±46.4 |
| Neurotrophic corneal PED | 18.7±24.3 | 37.0±46.3 |
| Postirradiation therapy | 60[a] | 60 |
| Alkaline burn | 34±30 | N/A |
| Graft-versus-host disease | N/A | 24.5±14.8 |

[a]Only one patient in this group.

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