• Clinical Research •

Pilot study on topical insulin-enriched autologous serum to accelerate healing of persistent corneal epithelial defects

Rhizlane Abdi

Department of Ophthalmology, Regional Hospital Center of Beni Mellal, Faculty of Medicine, Sultan Moulay Slimane University, Beni Mellal 23000, Morocco

Correspondence to: Rhizlane Abdi. Department of Ophthalmology, Regional Hospital Center of Beni Mellal, Faculty of Medicine, Sultan Moulay Slimane University, Beni Mellal 23000, Morocco. rhizlane_a@hotmail.com

Received: 2025-11-30 Accepted: 2026-07-27

Abstract

● **AIM:** To evaluate the efficacy and safety of autologous serum enriched with topical insulin compared with topical insulin alone and autologous serum alone in patients with persistent corneal epithelial defects (PEDs) unresponsive to standard therapy.

● **METHODS:** This study included 45 eyes of 45 patients with PEDs persisting for more than 14d despite conventional treatment. Patients were randomized into 3 equal groups (all, *n*=15): autologous serum enriched with insulin 1 IU/mL (Group A, 8 males), autologous serum 20% (Group B, 7 males), and insulin 1 IU/mL (Group C, 9 males). Treatments were administered six times daily until complete epithelial closure. The primary outcome was time to full epithelial healing. Secondary outcomes included best-corrected visual acuity (BCVA), epithelial thickness on anterior segment optical coherence tomography (AS-OCT), recurrence, and tolerance.

● **RESULTS:** The mean ages in Groups A, B, and C were 58.4±12.1y, 59.7±11.4y, and 57.9±13.0y, respectively (*P*=0.92). Complete epithelial healing was 100%, 86.7%, and 93.3% of eyes in Groups A, B, and C, respectively (*P*=0.76). Mean healing time among healed eyes (*n*=15, 13, and 14) differed significantly across groups [one-way analysis of variance (ANOVA), *P*=0.007]; post-hoc Tukey analysis showed that Group A (9.5±2.8d) healed significantly faster than Group B (14.3±4.5d; *P*=0.005), with a non-significant difference versus Group C (11.8±3.9d; *P*=0.24). BCVA improved in all groups, with the greatest gain in Group A (0.89 to 0.52 logMAR). Optical coherence tomography (OCT) demonstrated earlier epithelial thickening and homogeneity in Group A. Recurrence within 1mo among healed eyes was low (6.7%–15.4%) with no significant difference among the 3 groups. All treatments were well tolerated without adverse events.

● **CONCLUSION:** In this pilot study, insulin-enriched autologous serum is associated with significantly faster epithelial healing than autologous serum alone. A numerically shorter healing time is observed compared with topical insulin alone, but this difference is not statistically significant. The combination is well tolerated over the study period. Given the small sample size, these preliminary findings should be interpreted with caution and require confirmation in larger, multicenter, adequately powered randomized controlled trials.

● **KEYWORDS:** corneal epithelial defect; autologous serum; topical insulin; neurotrophic keratopathy; corneal healing

DOI:10.18240/ijo.2026.12.10

Citation: Abdi R. Pilot study on topical insulin-enriched autologous serum to accelerate healing of persistent corneal epithelial defects. *Int J Ophthalmol* 2026;19(12):2400-2406

INTRODUCTION

The corneal epithelium plays a fundamental role in preserving ocular surface integrity and maintaining optimal vision. Disruption of epithelial homeostasis can lead to persistent epithelial defects (PEDs), typically defined as any corneal epithelial lesion that fails to heal within 10–14d despite standard therapy[1-2]. PEDs represent a therapeutic challenge, often arising from neurotrophic keratopathy, post-surgical complications, metabolic disorders, inflammatory disease, or drug toxicity. If inadequately managed, they may progress to stromal ulceration, melting, infection, or perforation[3].

Conventional treatment strategies focus on restoring a stable epithelial environment through preservative-free lubrication, therapeutic contact lenses, autologous serum, punctal occlusion, and correction of eyelid abnormalities[2-3]. When

these measures fail, more invasive or costly interventions, such as amniotic membrane transplantation (AMT), tarsorrhaphy, or biological agents, may be required[4-6]. Many of these advanced therapies remain inaccessible in low- and middle-income countries[7].

Autologous serum eye drops are rich in growth factors, fibronectin, and vitamins structurally similar to natural tears and have demonstrated clinical benefit in neurotrophic and refractory epithelial defects[8-10]. Separately, topical insulin has emerged as a promising agent for enhancing corneal epithelial proliferation and migration. Insulin receptors are widely expressed on the ocular surface, and insulin stimulates mitogenic pathways analogous to insulin-like growth factor 1 (IGF-1)[11-12].

Given the complementary mechanisms of action, combining insulin with autologous serum may potentiate epithelial regeneration. To date, no comparative clinical study has evaluated the efficacy of insulin-enriched autologous serum versus insulin alone and serum alone. This pilot study aims to assess the feasibility, safety, and therapeutic benefit of this combination in the management of refractory PEDs.

PARTICIPANTS AND METHODS

Ethical Approval The study adhered to the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of Sultan Moulay Slimane University, Beni Mellal, Morocco (approval number: 512/24; date of approval: 02/01/2024). All participants provided written informed consent prior to enrollment.

Study Design and Setting This was a prospective, randomized, interventional pilot study conducted at the Department of Ophthalmology, Regional Hospital Center of Beni Mellal, Faculty of Medicine, Sultan Moulay Slimane University, Beni Mellal, Morocco, between January 2024 and June 2025.

Participants Eligible patients were adults diagnosed with PED defined as an epithelial defect persisting for more than 14d despite standard medical therapy.

Inclusion criteria: 1) age≥18y; 2) PED lasting>14d despite failure of conventional treatment (lubricants, therapeutic contact lens, punctal occlusion, discontinuation of toxic medications); 3) ability to comply with the follow-up schedule.

Exclusion criteria: 1) active microbial keratitis; 2) concurrent use of blood-derived products or growth factors; 3) severe stromal thinning (residual stromal thickness<20%) or perforation requiring urgent surgery; 4) ocular surface conditions precluding evaluation; 5) epithelial defect resolving with standard therapy before enrollment; 6) incomplete follow-up.

Randomization and Treatment Allocation Patients were randomly assigned (1:1:1) to one of the three treatment groups using a computer-generated randomization list with variable block sizes generated by an investigator not involved in patient enrolment or assessment. Group allocation was concealed in sealed opaque sequentially numbered envelopes opened sequentially at enrollment. Outcome assessment, including grading of fluorescein staining and interpretation of anterior segment optical coherence tomography (AS-OCT) images, was performed by an examiner who was independent of the treating physicians and masked to treatment allocation. Because the three formulations differed in preparation and appearance, masking of patients and of the physicians administering treatment was not feasible.

The three study arms were: 1) Group A: autologous serum 20% enriched with insulin 1 IU/mL; 2) Group B: autologous serum 20%; 3) Group C: topical insulin 1 IU/mL. Treatments were administered six times daily until complete epithelial closure. All patients received the same prophylactic topical antibiotic, preservative-free moxifloxacin 0.5% twice daily, across the three groups to standardize co-treatment and minimize the risk of epithelial toxicity.

Preparation of Autologous Serum and Insulin Formulations

Autologous serum 20% A 20 mL venous blood sample was collected under sterile conditions and allowed to clot for 2h at room temperature. Samples were centrifuged at 3000 rpm for 10min. The serum supernatant was aspirated, diluted to 20% with balanced salt solution (BSS), filtered through a 0.22-μm sterile filter, aliquoted, and stored at 4℃ for up to 7d.

Insulin-enriched autologous serum Regular human insulin was added to the prepared 20% serum solution to obtain a final concentration of 1 IU/mL. The solution was mixed under sterile laminar flow conditions and stored identically to autologous serum.

Topical insulin Regular human insulin was diluted with sterile BSS to a final concentration of 1 IU/mL and prepared fresh weekly.

Clinical Evaluation and Follow-up Patients were examined at baseline and at days 3, 7, 14, and 30. At each visit, the following parameters were assessed: 1) best-corrected visual acuity [BCVA; logarithm of the minimum angle of resolution (logMAR)]; 2) ulcer size (mm^2) and depth; 3) epithelial integrity using fluorescein staining; 4) patient tolerance and symptoms; 5) AS-OCT epithelial thickness and reflectivity; 6) recurrence within 1mo after closure.

Epithelial defect size was assessed at each visit on slit-lamp photographs taken after fluorescein staining; the horizontal and vertical diameters and the defect area (mm^2) were quantified using image-analysis software (ImageJ, NIH, Bethesda, USA) by a masked observer. AS-OCT was performed using a Cirrus

Table 1 Baseline characteristics of the study population mean±SD or *n* (%)

Variable	Group A: serum+insulin (*n*=15)	Group B: autologous serum 20% (*n*=15)	Group C: insulin 1 IU/mL (*n*=15)	*P*
Age (y)	58.4±12.1	59.7±11.4	57.9±13.0	0.92
Sex (M/F)	8/7	7/8	9/6	0.77
Initial ulcer size (mm²)	10.6±4.2	11.1±4.6	10.9±3.9	0.95
Baseline BCVA (logMAR)	0.89±0.31	0.91±0.34	0.87±0.29	0.94
Etiology–neurotrophic	6/15 (40)	6/15 (40)	6/15 (40)	1.00
Etiology–post-surgical	3/15 (20)	4/15 (26.7)	3/15 (20)	0.89
Etiology–metabolic	3/15 (20)	2/15 (13.3)	3/15 (20)	0.87
Etiology–drug toxicity	1/15 (6.7)	1/15 (6.7)	1/15 (6.7)	1.00
Etiology–autoimmune	1/15 (6.7)	1/15 (6.7)	1/15 (6.7)	1.00
Etiology–idiopathic	1/15 (6.7)	1/15 (6.7)	1/15 (6.7)	1.00

P values: One-way ANOVA for continuous variables; Chi-square test for categorical variables. BCVA: Best-corrected visual acuity; logMAR: Logarithm of the minimum angle of resolution; SD: Standard deviation; ANOVA: Analysis of variance.

HD-OCT 5000 (Carl Zeiss Meditec, Dublin, CA, USA); central epithelial thickness over the defect was measured with the device's automated software, and epithelial/stromal reflectivity was graded as low, moderate, or high reflectivity, with "stromal recovery" defined as normalization of reflectivity compared to adjacent unaffected stroma. Adherence to the prescribed instillation schedule was monitored at each visit by patient diary review and bottle-return count.

Primary outcome Time to complete epithelial healing defined as the interval (days) from treatment initiation to the first scheduled visit at which no fluorescein staining was observed, provided that absence of staining was confirmed at the next scheduled visit.

Secondary outcomes 1) Rate of complete epithelial closure; 2) BCVA improvement; 3) OCT epithelial thickness and homogeneity; 4) recurrence rate; 5) safety and tolerability.

Statistical Analysis Because this was a pilot study, no formal sample size calculation was performed prior to enrollment; the sample size of 15 eyes per group was determined pragmatically based on feasibility. Statistical analyses were performed using SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean±standard deviation (SD) and compared using one-way analysis of variance (ANOVA) with Tukey post-hoc tests, which adjust for multiple pairwise comparisons. Categorical variables were compared using the Chi-square test or Fisher's exact test (Fisher–Freeman–Halton extension for 2×3 tables), as appropriate. Time-to-healing distributions were evaluated using Kaplan–Meier survival analysis with log-rank testing. Comparisons of mean healing time were restricted to eyes that achieved complete closure (*n*=15, 13, and 14 in Groups A, B, and C, respectively). All 45 eyes were included in the Kaplan–Meier analysis, in which eyes without complete closure were censored at their last follow-up visit (day 30). A *P*-value<0.05 was considered statistically significant.

RESULTS

Baseline Characteristics Forty-five eyes of 45 patients were included. Baseline demographic and clinical characteristics were comparable across the three groups (Table 1), with no significant differences in age, sex, ulcer size, BCVA, or etiology (all *P*>0.05).

Etiological distribution (*n*=45): 1) neurotrophic: 40%; 2) post-surgical: 22%; 3) metabolic: 18%; 4) drug-induced toxicity: 7%; 5) autoimmune/inflammatory: 7%; 6) idiopathic: 7%.

Epithelial Healing Complete epithelial closure occurred in: Group A: 15/15 (100%); Group B: 13/15 (86.7%); Group C: 14/15 (93.3%). The differences were not statistically significant (Fisher–Freeman–Halton exact test, *P*=0.76; Figure 1).

Time to Healing Among eyes that achieved complete closure (*n*=15, 13, and 14 in Groups A, B, and C, respectively), mean healing time differed significantly across groups (one-way ANOVA, *P*=0.007): Group A: 9.5±2.8d; Group B: 14.3±4.5d; Group C: 11.8±3.9d (Figure 2). Post-hoc analysis (Tukey HSD) showed that Group A healed significantly faster than Group B (*P*=0.005). The difference between Group A and Group C did not reach statistical significance (*P*=0.24), nor did that between Group B and Group C (*P*=0.21). Kaplan–Meier cumulative healing rates significantly differed among groups (log-rank test, *P*=0.012).

Visual Acuity BCVA improved in all groups: Group A: 0.89±0.31 to 0.52±0.28; Group B: 0.91±0.34 to 0.63±0.30; Group C: 0.87±0.29 to 0.58±0.27 (Figure 3). Inter-group comparison of BCVA gain did not reach statistical significance (*P*=0.06).

OCT Findings AS-OCT revealed: 1) Earlier epithelial thickening and homogeneity in Group A (from day 7); 2) Delayed normalization in Groups B and C; 3) Comparable epithelial thickness across groups by 1mo (Figures 4, 5). Group A showed earlier restoration of epithelial thickness and normalization of stromal reflectivity.

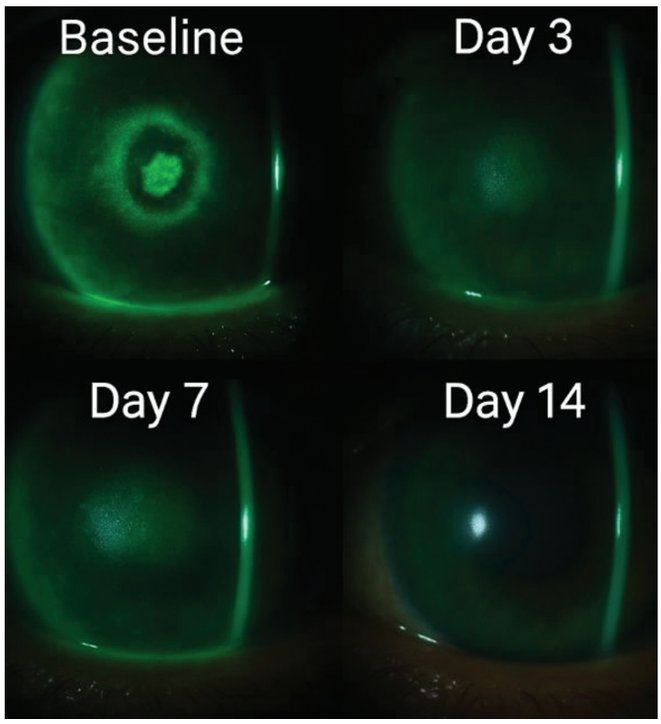


Figure 1 Representative slit-lamp photographs with fluorescein staining demonstrating progressive epithelial closure in Group A (insulin-enriched autologous serum) at baseline, day 3, day 7, and day 14.

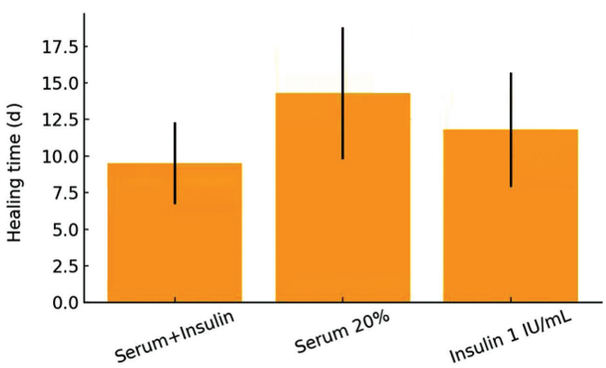


Figure 2 Mean healing time in eyes that achieved complete closure in the three treatment groups (*n*=15, 13, and 14; mean±SD) Group A: Insulin-enriched autologous serum; Group B: Autologous serum 20%; Group C: Topical insulin 1 IU/mL. SD: Standard deviation.

Recurrence and Safety Recurrence within 1mo after closure, among healed eyes, was: Group A: 1/15 (6.7%); Group B: 2/13 (15.4%); Group C: 1/14 (7.1%). Overall recurrence across groups showed no statistically significant difference (*P*=0.72). Treatment adherence exceeded 90% in all three groups, as assessed by patient diary review and bottle return count. All treatments were well tolerated. No cases of infection, inflammation, allergy, or toxicity were observed. Because topical insulin was used, capillary blood glucose was monitored at each visit; no episodes of hypoglycaemia or other systemic adverse events attributable to treatment were recorded during follow-up.

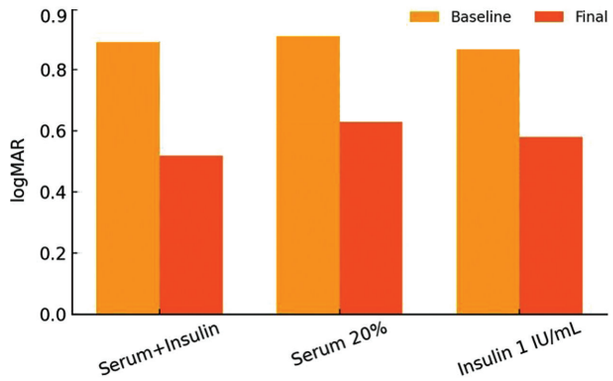


Figure 3 Best-corrected visual acuity (logMAR) at baseline and after treatment in the three groups Group A: Insulin-enriched autologous serum; Group B: Autologous serum 20%; Group C: Topical insulin 1 IU/mL. logMAR: Logarithm of the minimum angle of resolution.

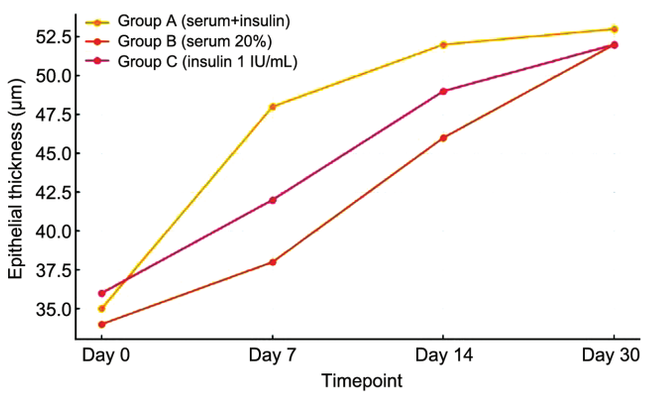


Figure 4 Anterior segment optical coherence tomography epithelial thickness evolution over time in the three treatment groups Group A: Insulin-enriched autologous serum; Group B: Autologous serum 20%; Group C: Topical insulin 1 IU/mL.

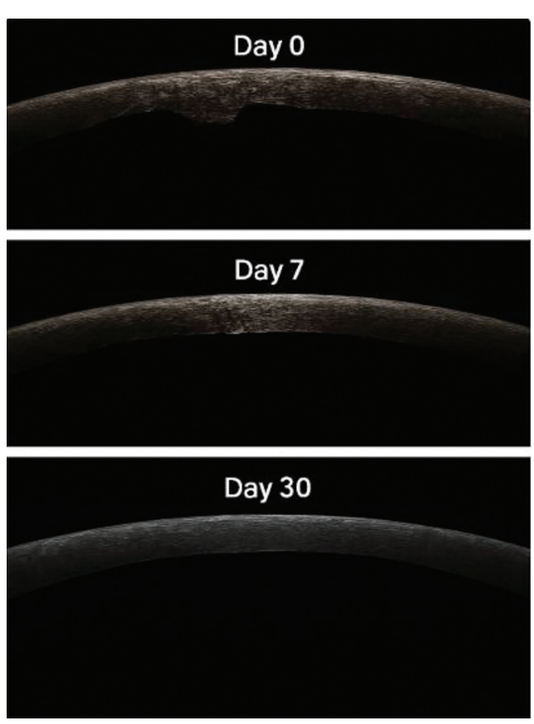


Figure 5 Representative anterior segment optical coherence tomography images demonstrating progressive epithelial regeneration during follow-up in Group A at day 0, day 7, and day 30.

DISCUSSION

Refractory corneal defects represent a serious condition threatening functional prognosis. They arise from local and systemic conditions that alter epithelial proliferation or adhesion. The most common causes are neurotrophic keratopathy, often associated with herpes infection, diabetes mellitus or trigeminal nerve damage; post-surgical epithelial defects following keratoplasty, refractive surgery, or retinal surgery; and metabolic or inflammatory disorders[2,7]. Systemic factors such as poor glycaemic control, autoimmune disease, and malnutrition can further compromise corneal healing[2,13].

Treatment of refractory ulcers is generally staged, beginning with stimulation of epithelial regeneration and management of underlying causes. First-line treatments include preservative-free lubricants, therapeutic contact lenses, autologous serum, correction of eyelid irregularities or tear film dysfunction[2-3]. Surgical procedures such as conjunctival flap grafting, tarsorrhaphy, or amniotic membrane grafting may be necessary when medical treatment fails[3-4]. As these interventions are invasive, costly, and not always accessible, simpler and more affordable alternatives remain important. A recent Meta-analysis confirms that autologous serum remains effective in ocular surface disease[14], and clinical studies support its benefit in persistent and traumatic corneal epithelial defects[10,15].

In this context, autologous serum enriched with insulin represents a promising, cost-effective, and accessible option. Beyond its metabolic role, insulin acts as a growth factor, promoting epithelial proliferation, migration, and differentiation *via* activation of insulin and IGF-1 receptors expressed on the ocular surface[11-12]. The clinical efficacy of topical insulin has been supported by a recent systematic review[16] and clinical studies[17]. Activation of these receptors engages phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase (MAPK) signalling cascades, which drive epithelial cell proliferation and directional migration during wound closure[18]. Insulin may also support focal adhesion and hemidesmosome assembly, potentially improving epithelial adhesion and reducing recurrence, and may additionally limit secondary stromal damage by dampening pro-inflammatory mediators at the ocular surface. When combined with autologous serum, which supplies fibronectin and native growth factors, these complementary trophic and anti-inflammatory effects provide a plausible biological basis for the faster and more uniform healing observed in the combined group.

Diaz-Valle *et al*[19] conducted a retrospective non-randomized comparison of topical insulin versus autologous serum in patients with PEDs and reported faster re-epithelialization with insulin. Our study extends this work prospectively by introducing a third arm—insulin-enriched serum—in a randomized design. To the best of our knowledge, no previous prospective randomized trial has directly compared insulin, autologous serum, and their combination as three separate arms, which constitutes the main novelty of the present work.

Experimental and clinical studies have reported the beneficial effects of topical insulin on corneal healing. Zagon *et al*[12] first showed that topical insulin normalised corneal epithelial regeneration in diabetic rat models. Clinical series subsequently reported faster re-epithelialization with topical insulin in refractory neurotrophic corneal ulcers[20] and in diabetic patients after corneal debridement during vitreoretinal surgery[21], and a randomized clinical trial by Dasrilsyah *et al*[13] showed faster healing of iatrogenic epithelial defects with topical insulin than with artificial tears in diabetic patients. Long-term results and case series across diverse etiologies, including chemical injury and dry eye disease, have further supported the safety and efficacy of this treatment[22-25]. In our series, the insulin-enriched serum group healed faster than the insulin-alone group (9.5±2.8d *vs* 11.8±3.9d); although this difference did not reach statistical significance, it suggests that combining insulin with autologous serum may offer an additional therapeutic benefit that warrants confirmation in larger trials.

This pilot study complements existing data by showing that insulin-enriched autologous serum achieves complete epithelial closure in 100% of eyes (15/15), compared with 93.3% (14/15) for insulin alone and 86.7% (13/15) for serum alone. Mean time to healing was significantly shorter in Group A (9.5±2.8d) than in Group B (14.3±4.5d; P=0.005). The difference versus Group C (11.8±3.9d) did not reach significance (P=0.24), and neither did that between Groups B and C (P=0.21).

Functionally, all three groups showed improvement in BCVA, with the greatest mean gain in Group A. AS-OCT revealed earlier restoration of epithelial homogeneity and resolution of hyperreflective areas in Group A, consistent with earlier structural corneal recovery. No ocular or systemic adverse events were recorded. These findings suggest that insulin-enriched autologous serum is associated with faster and more uniform epithelial healing than serum alone, possibly through the complementary trophic and anti-inflammatory effects of insulin on corneal epithelial proliferation and adhesion. A recent comprehensive review of emerging PED treatments further positions topical insulin as a valuable adjunct in refractory cases[26], supporting the biological rationale for the combination approach evaluated here.

A recent article demonstrated the efficacy of small-diameter acellular porcine corneal stroma grafting for refractory peripheral corneal ulcerations[27], underscoring the continued clinical need for accessible alternatives to invasive surgical interventions. Unlike surgical approaches, which require

specialized infrastructure and carry procedural risks, the insulin-enriched autologous serum described in the present study offers a non-invasive, low-cost option that may be particularly relevant in resource-limited settings.

This study has several limitations. First, the sample size was small (15 eyes per arm) and was not based on a formal power calculation; the study was therefore underpowered to detect differences in the rate of complete closure (P=0.76) and BCVA improvement (P=0.06), which should be interpreted accordingly rather than as evidence of equivalence. Second, the single-centre design may limit generalizability. Third, masking was applied to outcome assessors only; patient and physician masking was not feasible given the differing appearances of the formulations, which may introduce performance bias. Fourth, one month of follow-up is insufficient to assess long-term recurrence and corneal stability. Fifth, the cohort included a heterogeneous PED population across six etiological categories: neurotrophic (40%), post-surgical (22%), metabolic (18%), drug-induced (7%), autoimmune/inflammatory (7%), and idiopathic (7%). Each subtype involves distinct pathophysiological mechanisms that may influence the magnitude and kinetics of treatment response—for example, impaired neuropeptide signalling in neurotrophic cases versus altered epithelial mitogenesis in metabolic PEDs. Although subgroup analyses were precluded by the small sample size, this heterogeneity may have introduced variability across groups, and future adequately powered trials should include etiology-stratified analyses. Sixth, because follow-up visits were scheduled at fixed time points (days 3, 7, 14, and 30), epithelial closure may have occurred between visits, leading to potential overestimation of healing times—a recognized interval-censoring effect that applies equally across all three groups and is therefore unlikely to have introduced differential bias. Neither the comparison of means nor the standard Kaplan–Meier analysis accounts specifically for interval censoring; future studies with more frequent assessments or interval-censored survival methods could estimate healing time more precisely.

In this pilot study, insulin-enriched autologous serum appeared well tolerated and was associated with significantly faster epithelial healing than autologous serum alone; a numerically shorter healing time compared with topical insulin alone did not reach statistical significance. These preliminary results suggest that it may be a promising, cost-effective option, particularly in resource-limited settings. However, the underpowered, single-centre design limits the conclusions that can be drawn, and confirmation in larger, multicentre, adequately powered randomized controlled trials with extended follow-up and etiology-stratified analyses is required before this combination can be recommended as standard practice.

ACKNOWLEDGEMENTS

Data Availability Statement: The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

AI Generated Content Disclosure: During the preparation of this manuscript, the author used ChatGPT (OpenAI) solely to correct the English language. The author reviewed and approved all language corrections and take full responsibility for the final content of the manuscript.

Conflicts of Interest: Abdi R, None.

REFERENCES

1 Dua HS, Gomes JA, Singh A. Corneal epithelial wound healing. *Br J Ophthalmol* 1994;78(5):401-408.

2 Vaidyanathan U, Hopping GC, Liu HY, *et al*. Persistent corneal epithelial defects: a review article. *Med Hypothesis Discov Innov Ophthalmol* 2019;8(3):163-176.

3 Katzman LR, Jeng BH. Management strategies for persistent epithelial defects of the cornea. *Saudi J Ophthalmol* 2014;28(3):168-172.

4 Lee SH, Tseng SCG. Amniotic membrane transplantation for persistent epithelial defects with ulceration. *Am J Ophthalmol* 1997;123(3):303-312.

5 Bonini S, Lambiase A, Rama P, *et al*. Topical treatment with nerve growth factor for neurotrophic keratitis. *Ophthalmology* 2000;107(7):1347-1351.

6 Bonini S, Lambiase A, Rama P, *et al*. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. *Ophthalmology* 2018;125(9):1332-1343.

7 Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol* 2014;8:571-579.

8 Geerling G, MacLennan S, Hartwig D. Autologous serum eye drops for ocular surface disorders. *Br J Ophthalmol* 2004;88(11):1467-1474.

9 Pan Q, Angelina A, Zambrano A, *et al*. Autologous serum eye drops for dry eye. *Cochrane Database Syst Rev* 2013;8(8):CD009327.

10 Tsubota K, Goto E, Shimmura S, *et al*. Treatment of persistent corneal epithelial defect by autologous serum application. *Ophthalmology* 1999;106(10):1984-1989.

11 Rocha EM, Cunha DA, Carneiro EM, *et al*. Identification of insulin in the tear film and insulin receptor and IGF-1 receptor on the human ocular surface. *Invest Ophthalmol Vis Sci* 2002;43(4):963-967.

12 Zagon IS, Klocek MS, Sassani JW, *et al*. Use of topical insulin to normalize corneal epithelial healing in diabetes mellitus. *Arch Ophthalmol* 2007;125(8):1082-1088.

13 Dasrilsyah AM, Wan Abdul Halim WH, Mustapha M, *et al*. Randomized clinical trial of topical insulin versus artificial tears for healing rates of iatrogenic corneal epithelial defects induced during vitreoretinal surgery in diabetics. *Cornea* 2023;42(11):1395-1403.

14 Pertiwi AN, Susiyanti M. Efficacy of different concentrations of autologous serum eye drops in the treatment of ocular surface diseases: a systematic review and meta-analysis. *J Curr Ophthalmol* 2025;37(2):159-171.

15 Doğan L, Özer Ö, Baysal Z, *et al*. The efficacy of autologous serum in corneal healing following metallic foreign body injuries. *Graefes Arch Clin Exp Ophthalmol* 2025;263(10):2835-2840.

16 Bievel Radulescu R, Ferrari S, Stanca HT, *et al*. Topical insulin as a novel treatment for persistent epithelial defects and other ocular surface disorders: a systematic review. *Graefes Arch Clin Exp Ophthalmol* 2025;263(9):2427-2445.

17 Abdi P, Ghaffari R, Azad N, *et al*. Topical insulin for refractory persistent corneal epithelial defects. *Sci Rep* 2024;14(1):12459.

18 Yu FS, Yin J, Xu KP, *et al*. Growth factors and corneal epithelial wound healing. *Brain Res Bull* 2010;81(2-3):229-235.

19 Diaz-Valle D, Burgos-Blasco B, Rego-Lorca D, *et al*. Comparison of the efficacy of topical insulin with autologous serum eye drops in persistent epithelial defects of the cornea. *Acta Ophthalmol* 2022;100(4):e912-e919.

20 Wang AL, Weinlander E, Metcalf BM, *et al*. Use of topical insulin to treat refractory neurotrophic corneal ulcers. *Cornea* 2017;36(11):1426-1428.

21 Bastion MLC, Ling KP. Topical insulin for healing of diabetic epithelial defects : a retrospective review of corneal debridement during vitreoretinal surgery in Malaysian patients. *Med J Malaysia* 2013;68(3):208-216.

22 Almeida J, Costa TR, Vivas M, *et al*. Long-term results of topical insulin treatment for persistent corneal epithelial defects. *J Ophthalmic Vis Res* 2024;19(4):397-404.

23 Mester A, Gabriel M, Boldin I, *et al*. The performance of topical insulin in persistent corneal epithelial defects and persistent corneal ulcers–a case series. *Curr Eye Res* 2025;50(5):477-480.

24 Balal S, Din N, Ashton C, *et al*. Healing of chemical injury-related persistent corneal epithelial defects with topical insulin. *Cornea* 2023;42(8):1000-1004.

25 Burgos-Blasco B, Diaz-Valle D, Rego-Lorca D, *et al*. Topical insulin, a novel corneal epithelial regeneration agent in dry eye disease. *Eur J Ophthalmol* 2024;34(3):719-725.

26 Kwon JE, Kang C, Moghtader A, *et al*. Emerging treatments for persistent corneal epithelial defects. *Vision* (*Basel*) 2025;9(2):26.

27 Liang T, Wang X, Wu J, *et al*. Small-diameter acellular porcine corneal stroma for peripheral corneal ulceration treatment. *Int J Ophthalmol* 2024;17(5):831-837.