

Lo que aprendimos en el año 2021: Colirio de insulina en el tratamiento de los DEP

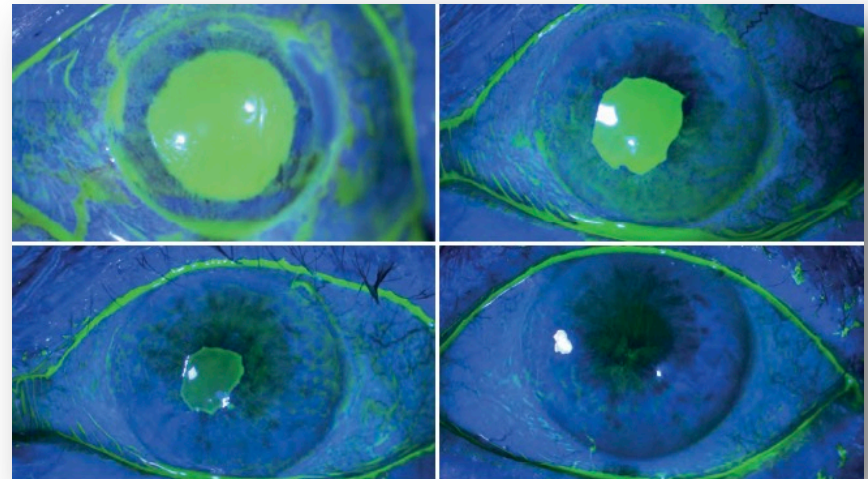
JA Gegúndez, David Díaz Valle, Bárbara Burgos Blasco, Daniela Rego, Virginia Puebla

Unidad de Superficie Ocular. Hospital Clínico San Carlos. Madrid,

Defectos epiteliales persistentes (DEP)

- **Defecto epitelial que persiste más de 2 semanas tras tto estándar^{1,2}**
 - Lubricación intensiva sin conservantes
 - Eliminación medicación epiteliotóxica
 - Antibióticos profilácticos
 - LDC-T / oclusión
- **Múltiples etiologías**
 - SOS, SIL, exposición
 - SECR, neurotróficas
 - Trauma, infección, toxicidad

Post-CXL. Regeneración epitelial 72 h



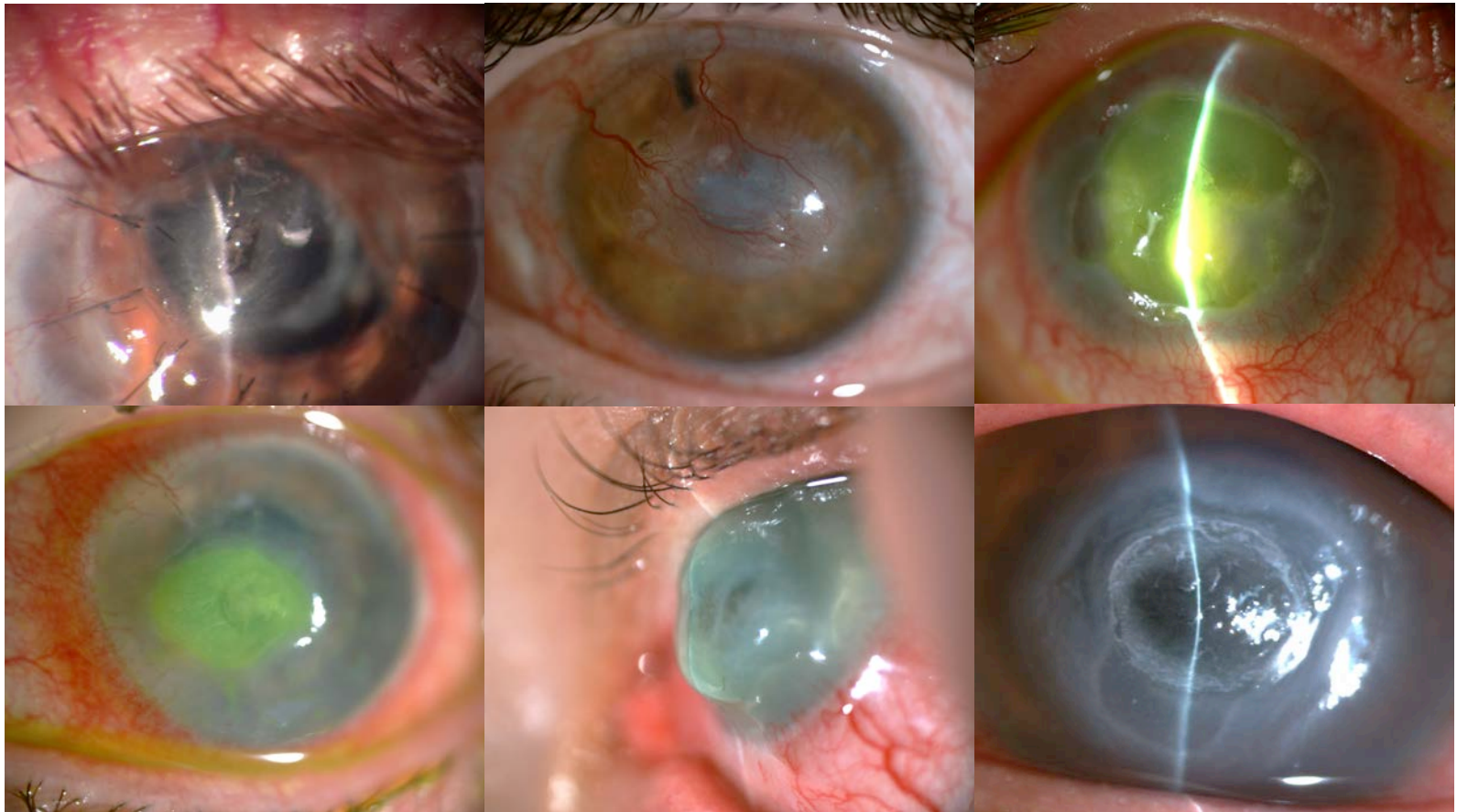
1. Dhillon HV et al. A comparative study): 29-33

2. Ziaei M, Greene C, Green CR. Wound healing in the eye: Therapeutic prospects. *Adv Drug Deliv Rev.* 2018;126:162-176.

DEP

Complicaciones potenciales graves

Ulceración estromal-perforación, neovascularización, infección, cicatrización, pérdida visual permanente



DEP

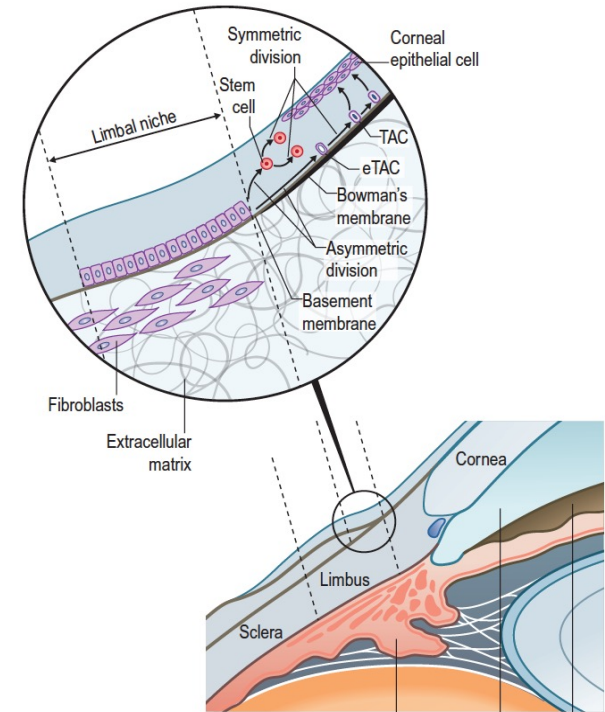
Tratamientos actuales

- Tratamiento convencional de 1º línea
- 2º línea: Hemoderivados (Suero autólogo, PRP, PRGF)
- Otras opciones escasamente accesibles
 - Carboximetilglucosa (Cacicol®). No disponible
 - rNGF (Cenegermin®)
 - rEGF (Easyef®, Corea)
- Tratamientos quirúrgicos
 - Desbridamiento epitelial + parche de Membrana Amniótica
 - Nuevo procedimiento: Neurotización corneal

Colirio de Insulina

Una nueva alternativa terapéutica en los DEP

- Cierre DEP a partir células madre limbares
- Factores de crecimiento y citoquinas:
 - NGF, EGF
 - Fibronectina
 - Sustancia P
 - Insuline-Growth Factor (IGF)
- IGF esencial en diferenciación, crecimiento y proliferación cels. epiteliales. Eficaz en DEP neurotróficos¹
- Cels epiteliales expresan receptores IGF e insulina
- Insulina: hormona anabolizante relacionada con IGF que favorece proliferación y regeneración epitelial²



1. N. Yamada, R. Matsuda, N. Morishige, R. Yanai, T.I. Chikama, T. Nishida, T. Ishimitsu, A. Kamiya, Open clinical study of eye-drops containing tetrapeptides derived from substance P and insulin-like growth factor-1 for treatment of persistent corneal epithelial defects associated with neurotrophic keratopathy, Br. J. Ophthalmol. 92 (2008) 896–900.


2. Trosan P, Javorkova E, Zajicova A, et al. The Supportive Role of Insulin-Like Growth Factor-1 in the Differentiation of Murine Mesenchymal Stem Cells into Corneal-Like Cells. Stem Cells Dev. 2016;25(11):874-881.

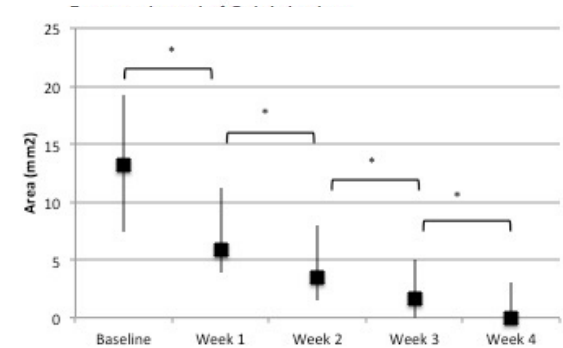
Colirio Insulina

- Farmacia Hospitalaria
- Concentración 1 UI/ml ^{1,2}
- Solución de insulina regular (100 UI/ml) diluida en una base de PEG + propilenglicol / suero salino
- Conservación en nevera. Uso 1 mes tras preparación
- Coste aprox 15 €/ mes
- Pauta 1 gota / 6h

1. Wang AL, Weinlander E, Metcalf BM, et al. The use of topical insulin to treat refractory neurotrophic corneal ulcers. *Cornea*. 2017;36(11):1426-1428.
2. Galvis V, Niño CA, Tello A, Grice JM, Gómez MA. Topical insulin in neurotrophic keratopathy after resection of acoustic neuroma. *Arch Soc Esp Ophthalmol*. 2019;94(2):100-104.

Topical insulin for refractory persistent corneal epithelial defects

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Jose A Gegundez-Fernandez¹, Sara Garcia-Caride¹,
Virginia Puebla-Garcia², Pilar Peña-Urbina¹
and Jose M Benitez-del-Castillo¹



Abstract

Purpose: To evaluate insulin eye drops for persistent epithelial defects (PEDs) that are refractory to usual treatment in clinical practice and to analyze how it may improve epithelization.

Methods: A prospective non-randomized hospital-based study was performed. Patients with PEDs that were refractory to conventional treatment were treated with insulin eye drops four times a day. Patients' demographics, PED etiology, concomitant treatments, and comorbidities were reviewed. The rate of PED closure and epithelial healing time were considered the primary outcome measures.

Results: 21 patients were treated with insulin drops (12 females and 9 males; mean age 72.2 years). Mean PED area before treatment was $17.6 \pm 16.5 \text{ mm}^2$ (median 13.2; range 3.9–70.6). PED comorbidities included seven eyes with infectious keratitis (33%), five eyes with calcium keratopathy (24%), ocular surgery on three eyes (14%), three eyes with lagophthalmos (14%), two eyes with bullous keratopathy (10%), and one patient with herpetic eye disease (5%). The eyes of 17 patients (81%) with refractory PEDs had reepithelized and four patients (19%) had still presented an epithelial defect by the end of the study follow-up period, although it had decreased in size. In patients where PED closure was achieved, mean time until reepithelization was 34.8 ± 29.9 days (median 23; range 7–114). In the remaining patients, a mean area reduction of 91.5% was achieved for the PEDs.

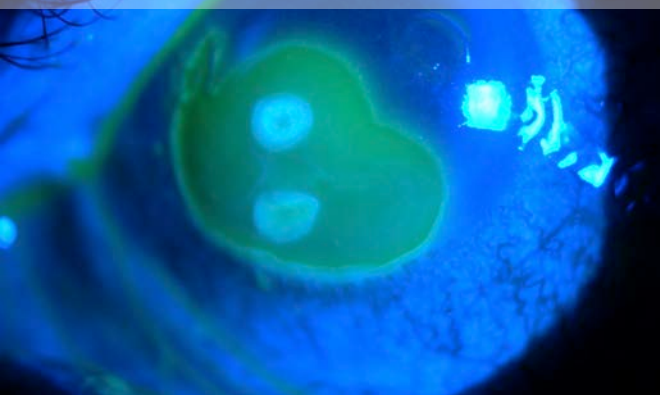
Conclusion: Topical insulin can promote and accelerate corneal reepithelization of refractory PEDs. It also offers many other advantages, including excellent tolerance, availability, and cost-effectiveness.

Keywords

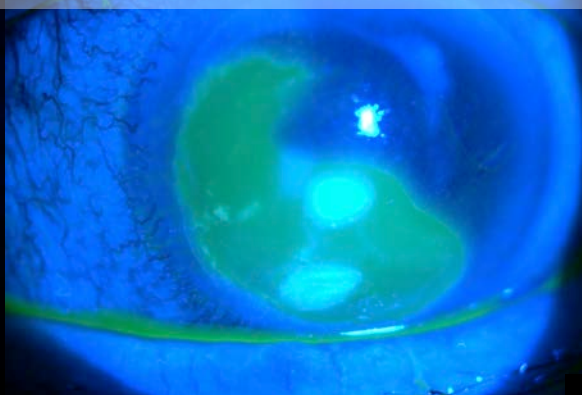
Corneal epithelium, persistent epithelial defect, corneal ulcer, insulin

Lagofthalmos parolítico (LA + SA + ATB profilático + oclusión nocturna)

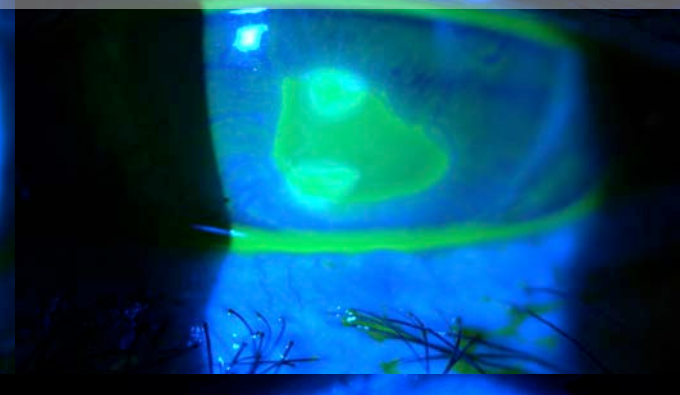
Basal



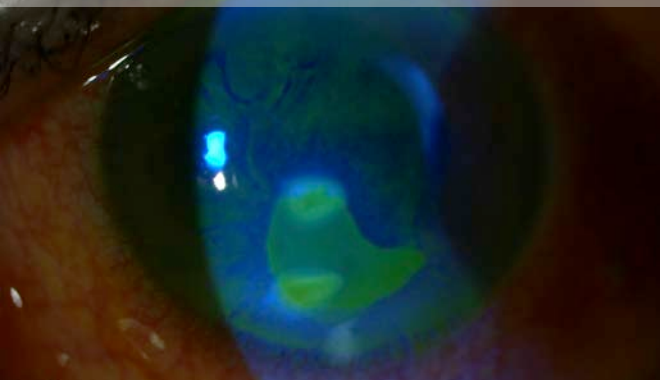
4 días



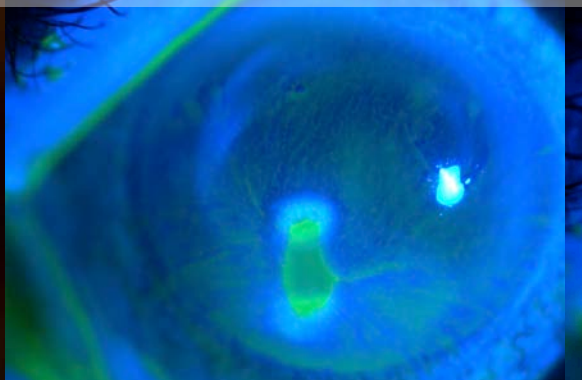
7 días



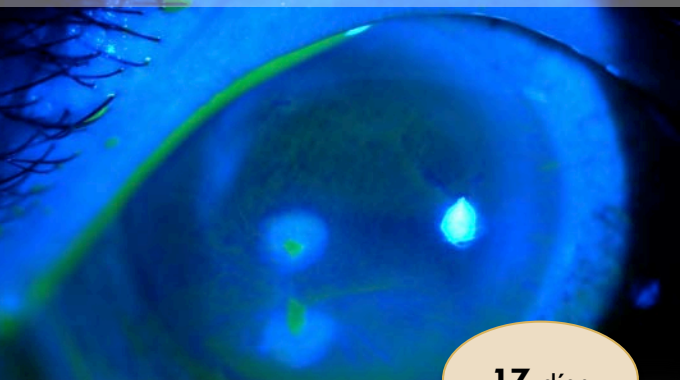
9 días



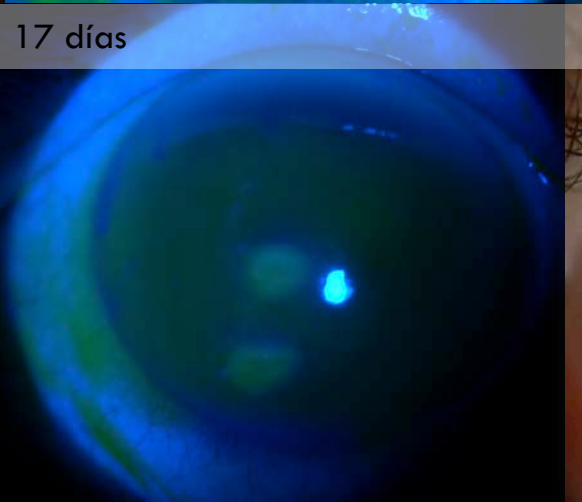
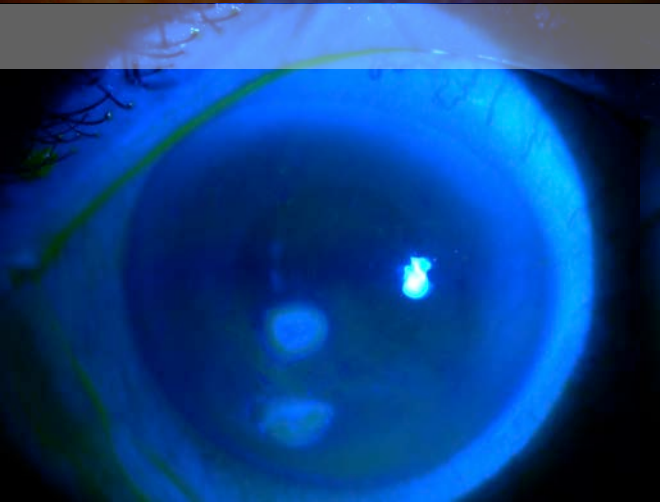
12 días

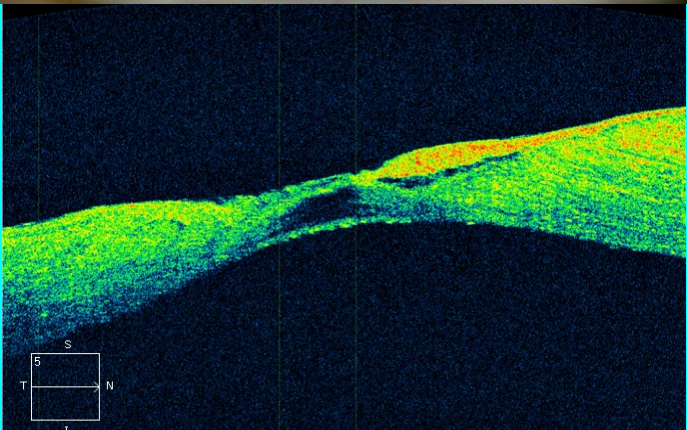
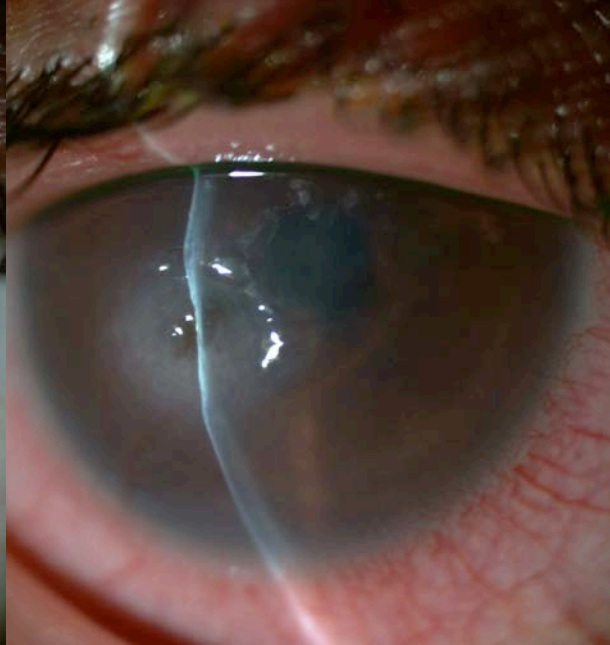


14 días



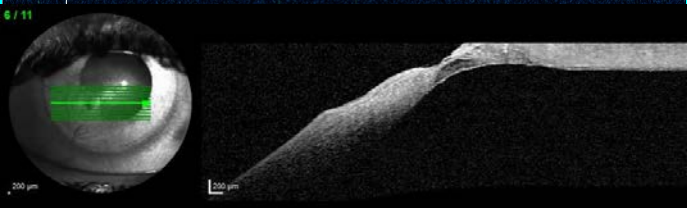
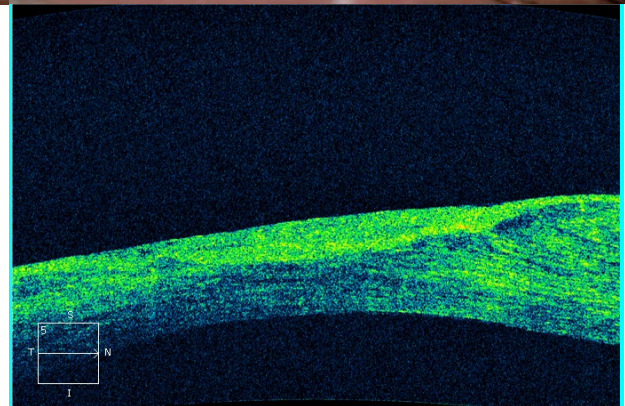
17 días



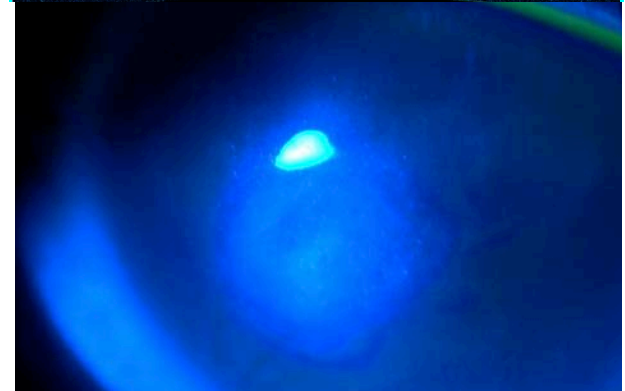


Descemetoccele post-QI
por *Pseudomonas*

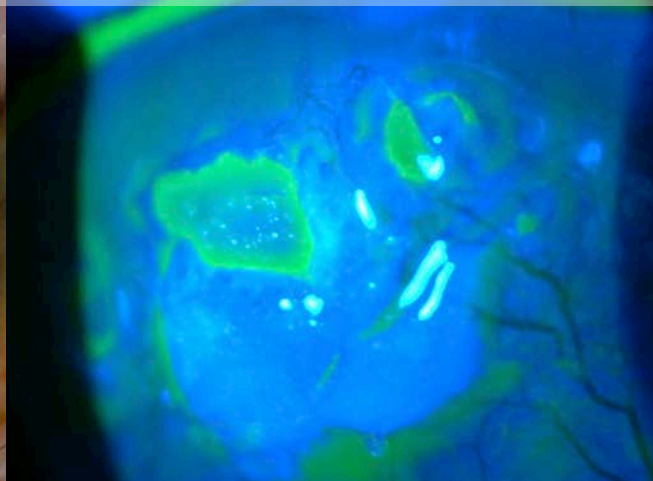
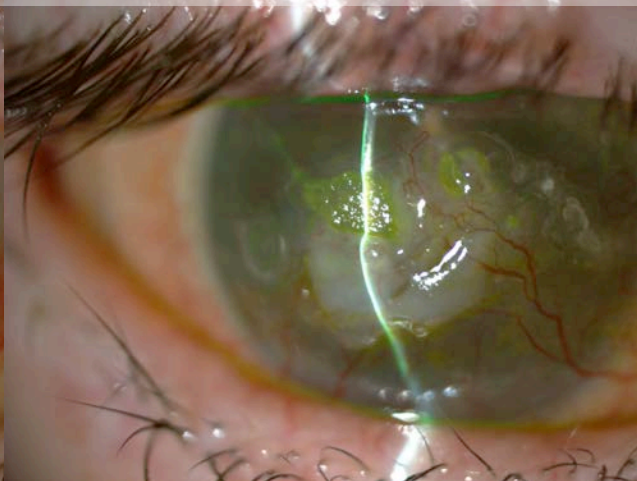
Cierre del DEP
Regeneración estromal



21 días



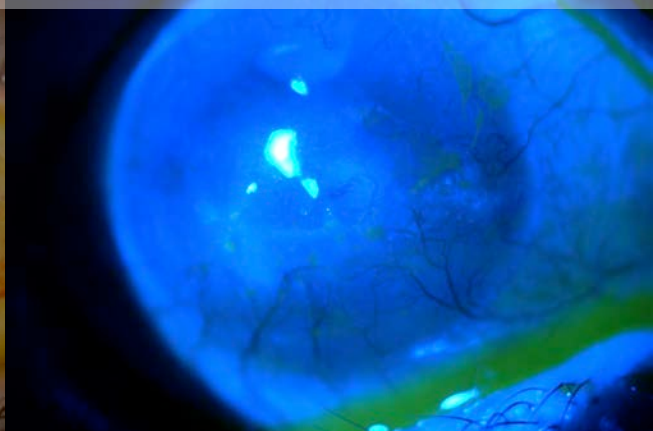
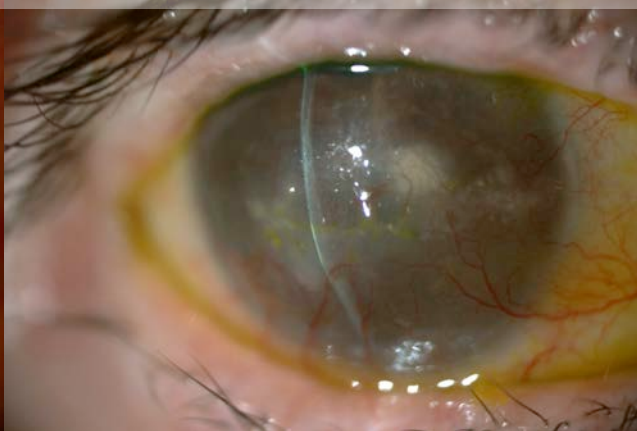
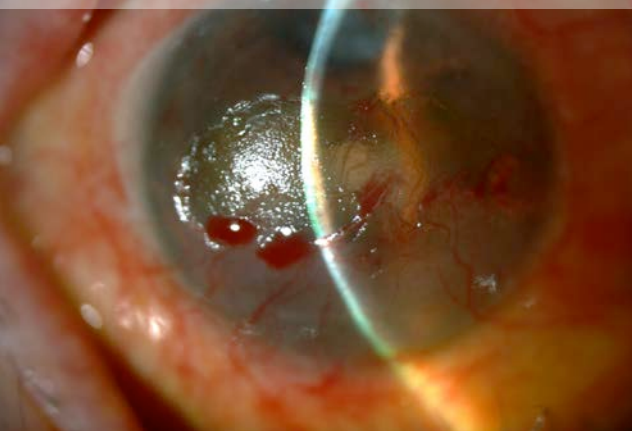
Ojo amaurotico. DEP + degeneración cálcica + hipertrofia epitelial (nódulos de Salzmann) + neovascularización corneal



Tras eliminación calcio y nódulos con fresa de diamante

7 días

15 días. Córnea epitelizada. Asintomática



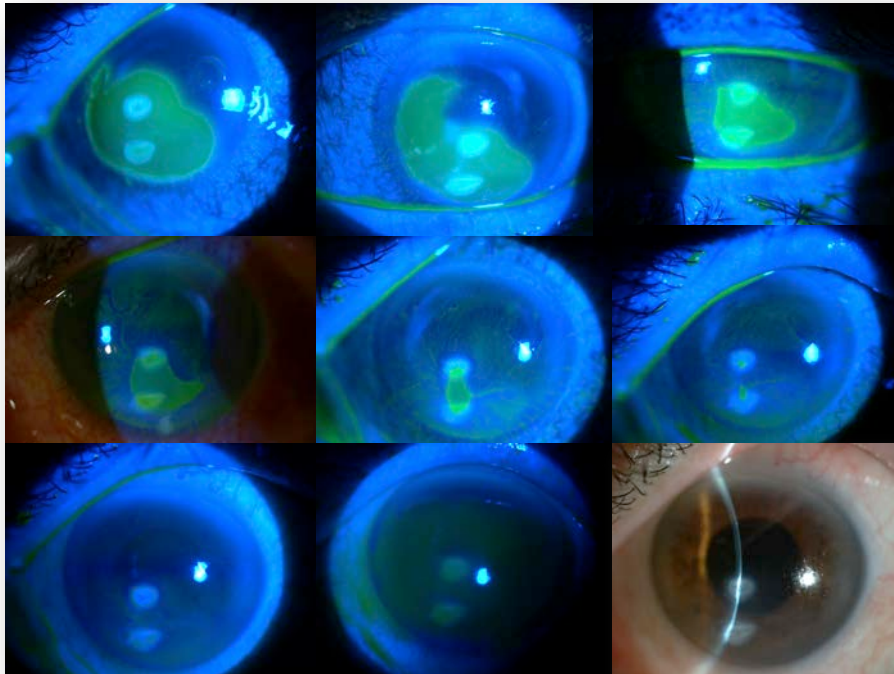
Comparison of the efficacy of topical insulin with autologous serum eye drops in persistent epithelial defects of the cornea

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ABSTRACT.

Purpose: To investigate the effect of topical insulin on epithelization in persistent epithelial defects (PED) refractory to usual treatment compared to autologous serum.

Design: Retrospective, consecutive case-control series.

Methods: The charts of 61 consecutive patients with PED treated with topical insulin (case group) and 23 treated with autologous serum (control group) were reviewed. Primary efficacy end points were the percentage of patients in which epithelization was achieved, as well as the rate and time until epithelization. Secondary efficacy point was need for amniotic membrane transplantation (AMT) or other surgeries.

Results: Mean time between PED diagnosis and start of topical insulin was 22.7 ± 18.5 days (range 13–115) and the mean area was 14.8 ± 16.2 mm² (range 1.1–70.6). In the control group, mean time was 27.9 ± 16.8 days, mean epithelial defect area being 18.6 ± 15.0 mm² (range 1.7–52.9). No differences in baseline characteristics were found between groups ($p > 0.05$). Epithelization was achieved in 51 patients (84%) on insulin and 11 patients (48%) on autologous serum ($p = 0.002$). In those patients, mean time until reepithelization was 32.6 ± 28.3 days (range 4–124) in the insulin group and 82.6 ± 82.4 days (range 13–231) in the autologous serum group ($p = 0.011$). The need for AMT was significantly lower in the insulin group ($p = 0.005$). PED recurrence was higher in patients treated on autologous serum (43%) compared with insulin (11%) ($p = 0.002$).

Conclusions: Topical insulin is an effective treatment and safely promotes healing of PED. In our series, topical insulin presented better epithelization outcomes than autologous serum and could thus be considered as a first-line treatment.

Key words: autologous serum – corneal epithelial defect – insulin

DD-V and BB-B contributed equally.

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Table 2. Epithelization results in patients treated with insulin and autologous serum

Epithelization results	Insulin (<i>n</i> = 61)	Autologous serum (<i>n</i> = 23)	<i>p</i>
Epithelization achieved. N (%)	51 (84%)	11 (48%)	0.002*
Qualified success. N (%)	16 (26%)	0	0.004*
Partial success. N (%)	17 (28%)	3 (13%)	0.250*
Time till epithelization (days)			
Mean ± SD	32.6 ± 28.3	82.6 ± 82.4	0.011[†]
Range	4–124	13–231	
Epithelization rate (mm ² /day)			
Mean ± SD	0.51 ± 0.55	0.33 ± 0.30	0.407 [†]
Range	0.04–2.33	0.03–0.99	
Epithelization failure			
AMT. N (%)	10 (16%)	11 (48%)	0.005*
Other surgeries. N (%)	1 (2%)	3 (13%)	0.061*
Recurrence. N (%)	7 (11%)	10 (43%)	0.002*
Follow-up (months)			
Mean ± SD	8.6 ± 5.4	23.0 ± 3.7	<0.001[†]
Range	2–17	18–30	

AMT = amniotic membrane transplantation, SD = standard deviation.

* Fisher test.

[†] Mann–Whitney *U* Test.

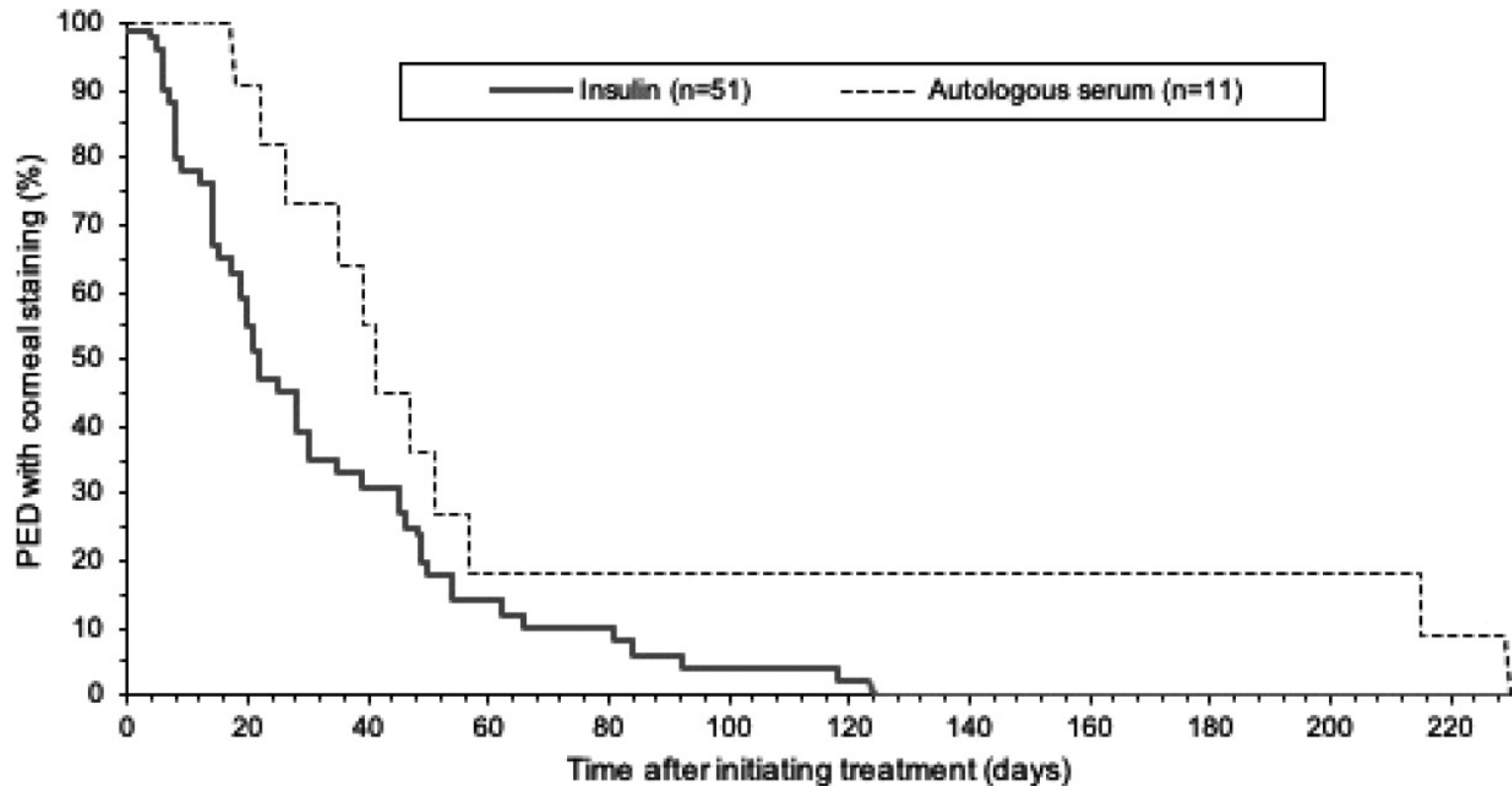
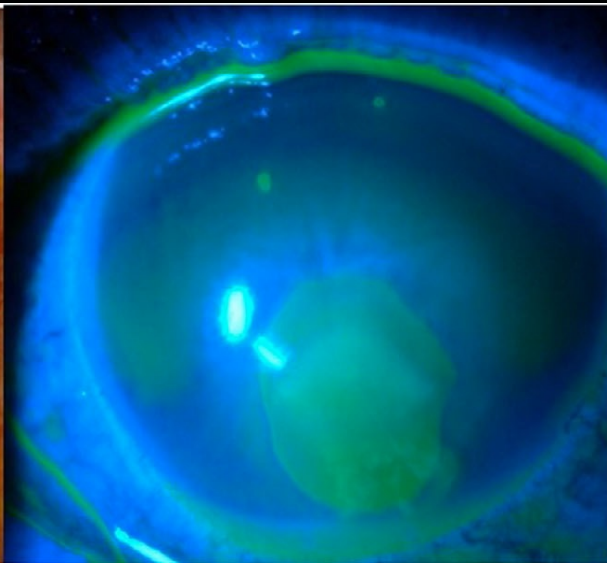


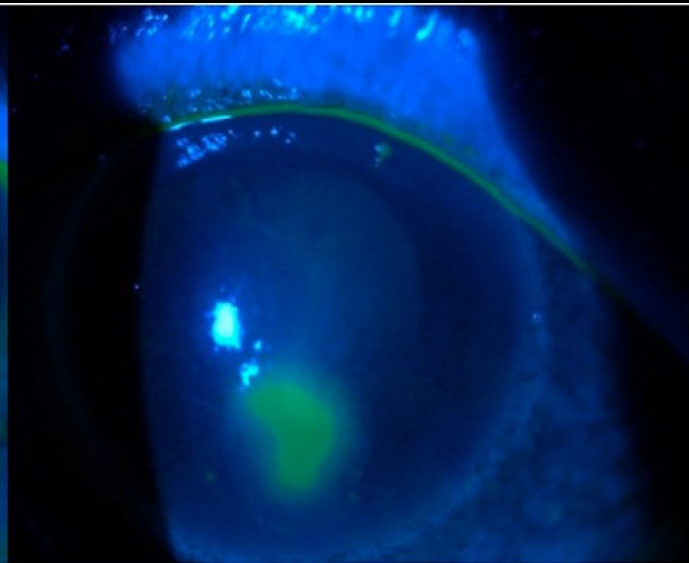
Fig. 1. Kaplan–Meier curves for days till epithelization in patients with persistent epithelial defects on topical insulin (solid line) and autologous serum (broken line). Only patients who achieved epithelization (defined as absence of corneal fluorescein staining) are included in this analysis.



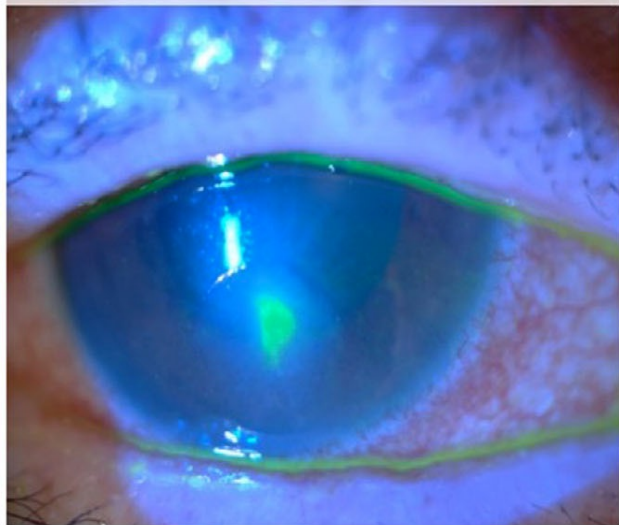
Baseline



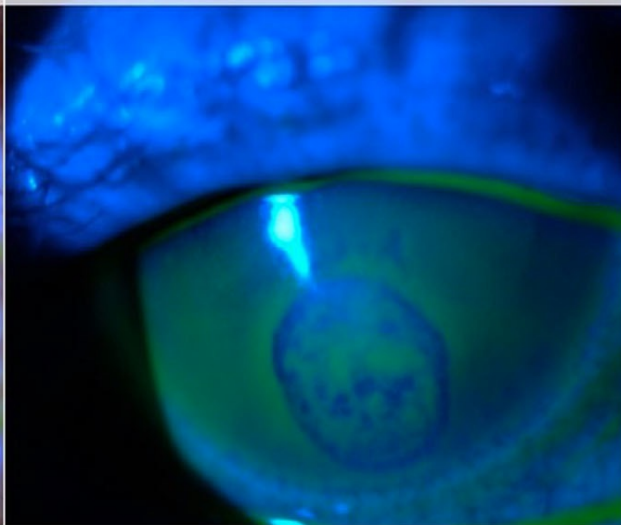
baseline



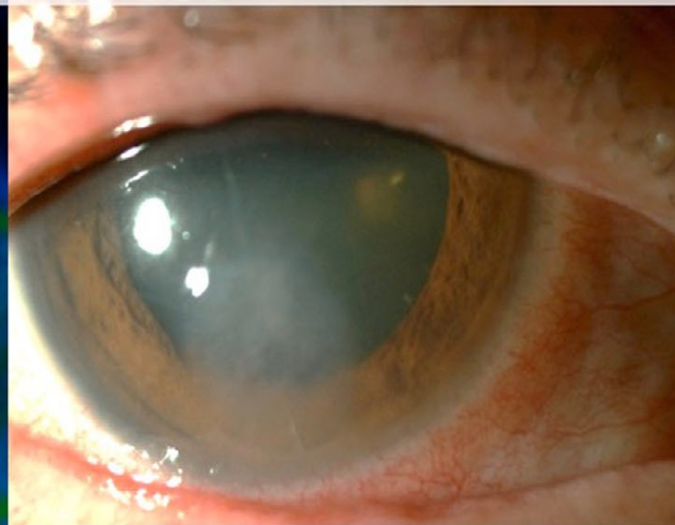
10 days



17 days



25 days



25 days

Insulina t3pica: Conclusiones

- Promueve de forma eficaz y segura la epitelizaci3n en DEP refractarios al tratamiento est3ndar.
- Excelente tolerancia, disponibilidad y coste-efectividad.
- En nuestra serie mejores tasas de reepitelizaci3n que el suero aut3logo, pudiendo considerarse un tratamiento de 1ª l3nea.