Topical insulin for neurotrophic corneal ulcers

Neurotrophic keratitis (NK) is a degenerative corneal epithelial disease characterized by decreased corneal innervation, causing epithelial breakdown and poor wound healing.[1−3] NK may be a result of ocular infections or disorders, or secondary to systemic disorders.[1,2,4] Affected corneas range from mild (persistent epithelial defects and irregularities) to severe disease (corneal melt and perforation).[2] Neurotrophic ulcers might be considered refractory when they are unresponsive to conventional treatments. These include conservative measures, such as aggressive topical lubrication (nonpreserved artificial tears, ointments, or autologous serum drops), punctal plugs, or use of a bandage contact lens, and surgical measures, such as amniotic membrane graft, tarsorrhaphy, or penetrating or lamellar keratoplasty in the setting of corneal perforation.[2] Many options, including amniotic membrane grafts, autologous serum drops, and recombinant human nerve growth factor (rhNGF), have significant costs to patients and the health care system.[2] Few case series describe using topical insulin, which may be an effective and affordable option for patients with refractory NK. In this report, we describe a case of bilateral NK that was successfully treated with topical insulin and review the existing literature on the topic. The purpose of this discussion is to explore the utility of topical insulin in the armamentarium for treatment of NK where conventional methods have failed.

A 55-year-old poorly controlled patient with diabetes presented with bilateral corneal ulcers and severe hypoesthesia. He was treated with topical nonpreserved artificial tears every hour, moxifloxacin drops 3 times daily, oral valacyclovir 500 mg twice daily, and a tapering dose of topical prednisolone 1% drops, as he was thought to have previously had herpetic keratitis. Bandage contact lenses were placed in both eyes several times. They repeatedly fell out and did not promote epithelial healing. Finally, a temporary tarsorrhaphy was placed in both eyes, with no improvement in the neurotrophic ulcers.

Before initiating topical insulin therapy, epithelial defects were 7.5 mm × 4.5 mm in the right eye (OD) and 5 mm × 3 mm in the left eye (OS) with rolled edges (Fig. 1). Corneal neovascularization extended from the inferior limbus to the inferior edges of the epithelial defects. Visual acuity was 20/150 OD and 20/200 OS. Intraocular pressure was 18 OD and 19 OS. There was no evidence of diabetic retinopathy in either eye. Insulin drops were compounded by a local pharmacy using sterile technique (25 IU/mL). The patient received insulin drops 6 times per day in each eye. Within 1 week, the neurotrophic ulcers had dramatically re-epithelialized, resulting in improved patient comfort (Fig. 2). Visual acuity was 20/70 OD and 20/200 OS. Central corneal haze was noted in the left greater than the right (Fig. 2). Intraocular pressure was 22 OD and 18 OS.

Few cases report the use of topical insulin for NK. Wang et al.[3] described sterile, refractory neurotrophic ulcers from various pathologies (diabetic keratitis, herpetic keratitis, and postsurgical cranial nerve injury) that re-epithelialized less than 25 days after starting topical insulin drops (1 IU/mL) 2−3 times daily.[3] Galvis et al.[4] discussed a case of exposure keratopathy that progressed to an infected, neurotrophic ulcer after acoustic neuroma resection. Topical insulin (1 IU/mL) was used as an adjuvant therapy to topical antibiotics, steroids, autologous serum drops, and bandage contact lens.[4] It may be difficult to ascertain how much this case benefited from insulin drops, compared with the other simultaneous interventions. Bastion and Ling[5] and Fai et al.[6] described higher concentrations of topical insulin drops to help improve epithelial defect wound healing in patients with diabetes who were not at risk of NK after vitreoretinal surgery. Bastion and Ling[5] suggested that 50 IU/mL topical insulin might improve the rate of epithelial wound healing, whereas Fai et al.[6] found that dilutions of 25 IU/mL was associated with better healing. As discussed by Wang et al.,[3] it is likely that insulin drops may benefit patients with NK of heterogeneous etiologies, other than diabetic neuropathy.

To our knowledge, this is the only reported case of proven bilateral NK that responded to topical insulin 25 IU/mL. Several other interventions were first proven unsuccessful before insulin drops were trialled. All other therapies were stopped before insulin drops were applied. It is clear in this case that topical insulin was able to promote re-epithelialization where conventional interventions had failed.

The mechanism by which topical insulin might improve corneal wound healing is not well understood. The presence of insulin receptors on the cornea and lacrimal gland, and increased prevalence of keratopathy in diabetic patients suggest that insulin may contribute to corneal wound healing.[7,8] Zagon et al.[9] used a rat model to show a marked improvement in corneal hypoesthesia after topical insulin exposure, suggesting that early hypoesthesia in type 1 diabetics may be reversible and contribute to improved epithelial wound healing.[9] A rabbit model showed that topical insulin might alter the ocular surface response, by increasing tensile strength in corneal wounds.[10] Finally, an in vitro model of immortalized corneal epithelial cells showed increased cell migration when exposed to insulin.[11]

No adverse events were noted with the use of topical insulin at concentrations up to 100 IU/mL in any of the published cases.[12]

Recently, rhNGF was approved as a safe and effective topical treatment.[2,13] A significant barrier to widespread adoption of rhNGF is its extremely high cost[2]. Insulin-like growth factor-1 and substance P also seem to improve

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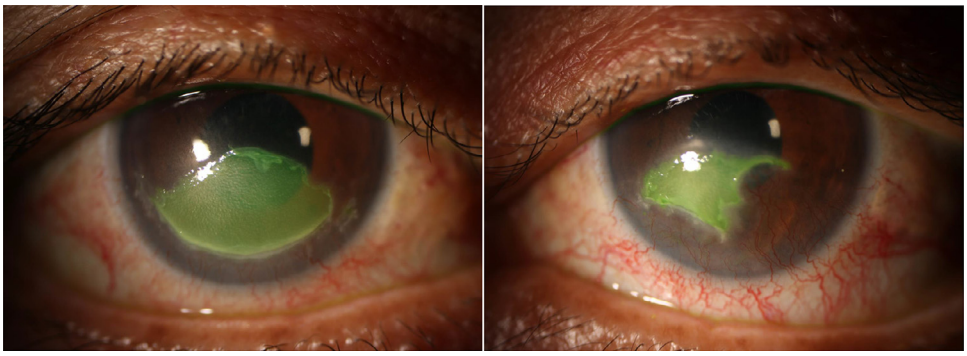

Fig. 1—Neurotrophic corneal ulcers in the right eye (A) and left eye (B) unresponsive to conventional treatments before starting topical insulin (25 IU/mL), with large persistent epithelial defects.

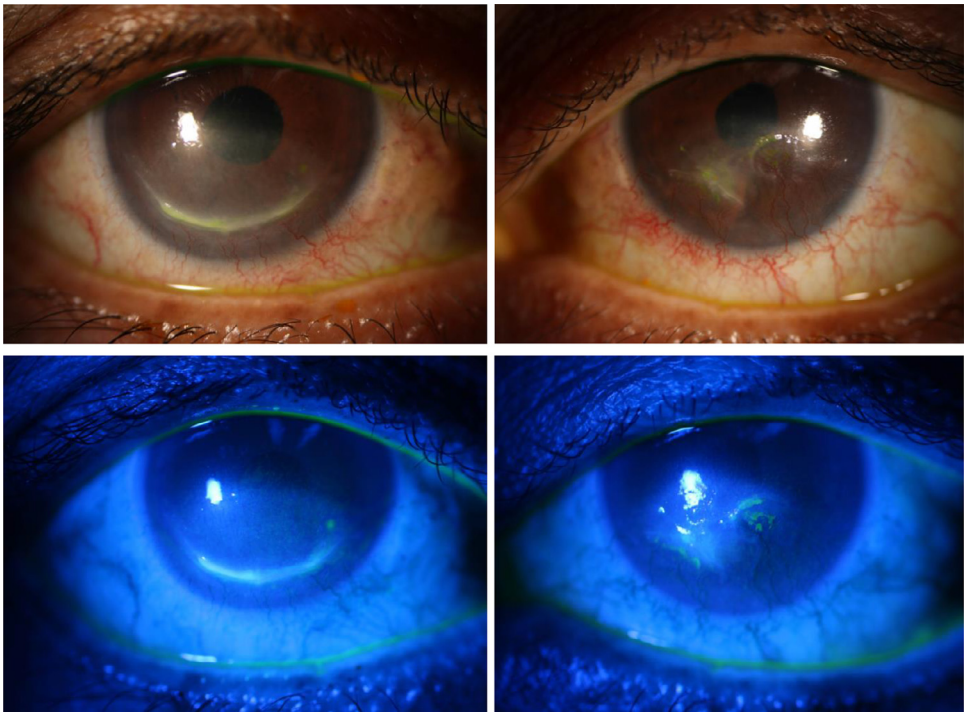

Fig. 2—Neurotrophic corneal ulcers in the right eye (A) and left eye (B) 1 week after topical insulin treatment, with almost complete re-epithelialization in both eyes, as demonstrated with fluorescein staining and cobalt blue light in the right eye (C) and left eye (D).

corneal healing in animal models.[14] Insulin-like growth factor-1 and substance P promote epithelial wound healing in NK by synergistically facilitating corneal epithelial migration, and promoting attachment of epithelial cells to the extracellular matrix.[14] Other experimental treatments for NK still under investigation include human growth hormone, regenerating matrix therapy agents, plasma with enriched growth factors, and thymosin beta 4.[2,15]

Topical insulin drops (25 IU/mL) can be used to successfully manage neurotrophic corneal ulcers unresponsive to conventional treatments. It may be an effective and affordable therapy for bilateral NK where conventional treatments have failed. Further studies are required to determine the ideal concentration of insulin drops, identify side effects, and further characterize the patients and underlying etiologies for NK that might benefit.

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Footnotes and Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this article.