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Short communication

The use of orthokine therapy for the treatment of post refractive surgery corneal ulcer, a case report

Kamran Mansouri [a], Gelavizh Rostaminasab [b], Touraj Ahmadi Jouybari [b], Masood Bagheri [b,c,*]

[a] Medical Biology Research Center, Health Technology Institute ,Kermanshah university of medical sciences, Kermanshah, Iran
[b] Clinical Research Development Center, Imam Khomeini and Mohammad Kermanshahi and Farabi Hospitals, Kermanshah University of Medical Sciences, Kermanshah, Iran
[c] Department of Ophthalmology, Imam Khomeini Eye Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

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ABSTRACT

Post refractive corneal ulcers is a disastrous complication, can affect healthy individuals, is cumbersome to treat, and sometimes has a poor prognosis with corneal scarring. Accurate diagnosis and prompt treatment of corneal infection is very important; however, until now, there has been no specific protocol for the management of this common eye disease and severe cases may require a corneal transplant.

The patient is a 42-year-old male who suffered a corneal ulcer after photo refractive keratectomy (PRK) surgery in which the cornea was completely destroyed. None of the routine treatments were effective and, due to the progression of corneal melting, the patient became a candidate for tectonic corneal transplant. As a last option, topical orthokine treatment was prescribed for this patient which had a dramatic improvement in the clinical course with the control of inflammation.

In this study, a new method of orthokine therapy was performed for a severe corneal ulcer and recovery was clearly evident in the patient follow-up. This is the first case report of treatment of a corneal wound infection with this method of orthokine therapy. It is suggested for consideration as a new treatment for such infectious disease.

1. Introduction

Corneal infection is a common and serious condition, considered as a silent epidemic in developing countries, that can cause the human eye to become inflamed or red [1]. With the passage of time without follow-up, this condition can cause blindness [2]. Corneal ulcers can occur with the entry of a foreign object into the cornea that introduces microorganisms into the eye that cause infection. Another common reason is the introduction of fungi or bacteria into the eye from contaminated contact lenses [3]. Infectious keratitis after laser refractive surgery remains an uncommon complication but known as a disastrous complication, can affect healthy individuals, is cumbersome to treat, and sometimes has a poor prognosis with corneal scarring. [4]. Symptoms of corneal infection include redness of the eye and blurred vision, decreased visual acuity, discharge from the eye, tearing and blepharospasm [3]. As a rule, the longer period of corneal infection and the deeper are more difficult to treat.

In the pathophysiology of corneal ulcer, there are two arms, inflammatory and infectious, and conventional treatments focus on controlling the infected arm with antibiotic prescribing [5]. If there is deterioration of the cornea, surgery will be required [6]. In the case study, none of the routine treatments were effective for improving the condition and there was no procedure or protocol available for the management of the corneal infection [3,5]. Quick and accurate diagnosis and timely treatment are key to improving the clinical and visual outcomes of corneal wound infection [6], however if only the infectious arm is treated, the inflammatory component may cause disease progression. Therefore, the options for controlling the inflammatory component, especially those with minimal side effects, should be considered at the same time.

Abbreviations: IRAP, Interleukin-1 receptor antagonist protein; IL-1, Interleukin-1; PRK, Photo refractive keratectomy; BCVA, Best corrected visual acuity; BCL, Bandage contact lens; B-scan, Brightness scan; ACS, Autologous conditioned serum.

* Corresponding author at: Clinical Research Development Center, Imam Khomeini and Mohammad Kermanshahi and Farabi Hospitals, Kermanshah University of Medical Sciences, Kermanshah, Iran.
E-mail address: Bagheri.m1368@gmail.com (M. Bagheri).

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In this study, the use of the new method of orthokine therapy was recommended. Orthokine therapy is a new biological technique, modern and reliable, which is an effective and comprehensive treatment that has been approved for use in Germany [7–8]. It is used to prevent the progression of inflammation. In this method, anti-inflammatory agents are removed from the patient's blood and administered to the affected area [9].

The primary anti-inflammatory agent is called Interleukin-1 receptor antagonist protein (IRAP) [10]. This compound is obtained by incubating serum that has been taken from the blood of the patient. Interleukin-1 (IL-1) is a cytokine that causes inflammation and the antagonist is an agent that prevents the effect of IL-1. Therefore, interleukin-1 receptor agonist prevents inflammation [11].

Orthokine-containing serum IRAP, an anti-inflammatory protein, at up to 10 thousand times the normal concentration [7]. IRAP inhibits its inflammatory counterpart (IL-1). In general, it relies on the body's natural ability to repair and regenerate damaged tissue and is considered a minimally invasive method [12].

Case. *The patient was a 42-year-old male who referred to the emergency room of Imam Khomeini Eye Center in Kermanshah with a complaint of pain in his left eye. He had a history of photo refractive keratectomy (PRK) refractive surgery six days previous. In the initial examination, periorbital edema, blepharospasm and abundant purulent discharge were evident along with severe redness of the left eye. The patient's best corrected visual acuity (BCVA) was 9/10 in the right eye and light perception in the left eye. In the slit lamp examination, bandage contact lenses (BCLs) were seen in both eyes. In the left eye, diffuse corneal edema and infiltration with severe corneal melting and thinning plus a 3-mm hypopyon were evident* (Fig. 1*a*). *Due to the severe pain, despite the use of a topical anesthetic (Anestocaine drops), the patient's cooperation during the clinical examination and photo-slit was poor. Because of the media opacity, it was not possible to evaluate the posterior segment, but the vitreous space and retina were reported to be normal in the ultrasound B-scan.*

Immediately after a diagnosis was made of corneal ulcer following refractive surgery, the patient was admitted and managed. The BCLs of both eyes were removed and sent to the laboratory for microbiology examination. After obtaining a culture and smear from the involved corneal tissue, the patient was admitted and treated topically with vancomycin and ceftazidime drops and systemic clarithromycin with follow-up visits every 8 h. In the follow-ups at 24 and 48 h, no treatment response was evident. The hypopyon had increased in size by 4 mm and due to the progress of corneal melting, he became a candidate for tectonic corneal transplant according to the consultation with the anterior segment service.

The patient was insistent on the use of conservative measures and refused consent for surgery; thus, after consultation with the regenerative medicine service, as the last hope topical orthokine drops were recommended. After obtaining blood from the patient and preparing it, orthokine drops were prescribed to the patient every 4 h.

Whole blood was taken 50 ml from the patient's vein using a special syringe with increased inner surface area (Orthogen, Dusseldorf, Germany). The blood was incubated at 37 degrees Celsius for about 6–9 h to stimulate the production of the anti-inflammatory protein interleukin-1 receptor (IL-1Ra). Then, using a centrifuge, the protein was separated from other components of the blood and the serum supernatant drawn into a filtered (0.22 μm; Millipore, Carrigtwohill, Co. Cork, Ireland) and aliquoted in 1 ml portions. The aliquots were frozen at −20 degrees Celsius and the part that was supposed to be used was taken out of the refrigerator.

Orthokine topical treatment was provided for a period of three days. In the follow-up examination at 24 h after day three of orthokine treatment, the progression of corneal thinning had stopped, the hypopyon had decreased in size by 2 mm, the purulent discharge had decreased and the patient reported a significant improvement in pain. The patient was candidated to receive the second course of orthokine therapy and on days four and five of orthokine treatment, improvement in the corneal melting was clinically evident and the patient's vision had increased to 1 m counting finger (1mCF). Because the patient did not agree to continue hospitalization, they were advised to continue treatment on an ambulatory basis. An additional blood sample was obtained they were treated with orthokine drops on an outpatient for an additional three days.

After 8 days, the culture results reported Pseudomonas aeruginosa resistance to Penicillin, Cephlexin, Cefazolin, Ciprofloxacin, and Amikacin but susceptible to Ceftazidime. Concurrently with the orthokine treatment, topical antibiotic treatment was continued with Vancomycin and Ceftazidime drops. Follow-up periods were scheduled daily initially and, with clinical improvement, were increased to every three days and then one week. In the last visit four weeks later, the corneal edema and infiltration had completely disappeared and only traces of corneal opacity were visible at the ulcer site (Fig. 1c) and vision had increased to 4/10. The patient did not return for further visits, but reported complete recovery during a telephone follow-up.

2. Discussion

Corneal wound infection can be caused by trauma, chemical stimuli and microorganisms [2–3]. It can also be caused by epithelial damage. Pathogen toxins released from damaged tissues will cause inflammation and necrosis, followed by corneal infection [5]. Corneal wound infection management includes planned medical and surgical treatments in accordance with the specific characteristics [3,5]. Delayed intervention can cause permanent corneal opacity and eventual blindness. This indicates that the treatment of corneal wound infection should begin as soon as possible [6,13]. But it should be considered that most of the current treatment protocols only cover the infectious part of the disease and inflammatory component can progress the disease process.

This study provides valuable findings regarding the management of inflammation in a patient with a treatment-resistant corneal wound infection. The administration of orthokine in the form of topical drops into the eyes of a patient with a corneal ulcer led to a significant decrease in the intensity of pain and purulent secretions. In the follow-up examination, the progression of corneal thinning had stopped, an

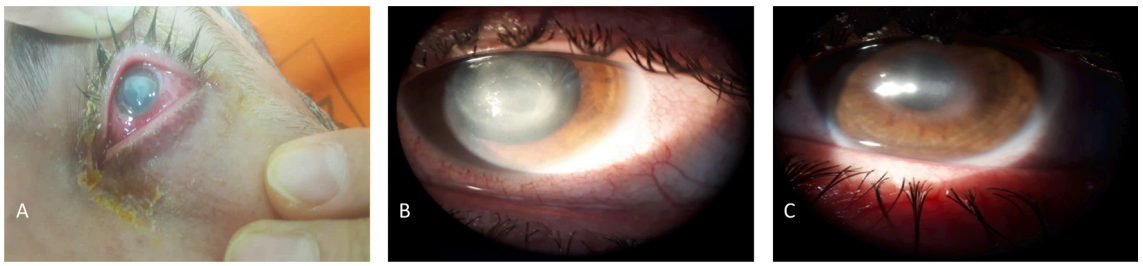

Fig. 1. The photograph of the patient is shown on the day of visit (A), day 12 after receiving three courses of the orthokine (B), and in the last follow-up visit 4 weeks later (C). In A periorbital edema, abundant purulent discharge, and severe redness of the left eye were evident. Due to blepharospasm, the eyelids were opened by hand for imaging. In C the corneal edema and infiltration had completely disappeared and only traces of corneal opacity were visible at the ulcer site.

improvement in the corneal melting was clinically evident, and the patient's vision had increased. At the patient's last visit, corneal edema and infiltration had completely disappeared and the only traces of corneal opacity were visible at the ulcer site.

Orthokine therapy is a new method of treating inflammatory disease and the results have been confirmed by clinical researches. In this method, anti-inflammatory substances are extracted from the blood of the patient and are administered to the desired area of treatment. In other words, this technique uses the natural and biological ability of the body to regenerate itself [7–8] and primarily affects IL-1 [7,12].

Signaling proteins such as IL-1 are secreted by the body's cells during infection or tissue damage. The body responds to these conditions by inflammation. If the inflammation does not disappear within a few days, chronic inflammation will develop. The antagonist to the biological inflammatory factor IL-1 is ideal for natural and non-invasive treatment [11]. This natural protein, IRAP, prevents the aggressive reaction of IL-1 and, by reducing inflammation and swelling in the damaged tissue, it also reduces pain [10,14–15].

Several recent studies have supported the use of orthokine therapy [16–18]. This method is particularly very suitable for use in osteoarthritis, cartilage damage and for tendon, ligament, muscle and back pain. The study findings indicate that the use of autologous conditioned serum (ACS) in the treatment of osteoarthritis is effective and safe and can increase tissue regeneration and reduce degenerative mechanisms [19–20]. This method can be used to treat inflammatory conditions as well as those caused by traumatic injury [21].

There are many anti-inflammatory cytokines in orthokine and it has been shown to increase fibroblast growth, hepatocyte growth and transforming growth factors [20,22], Extensive phase III clinical trials have confirmed the safety and efficacy of recombinant IRAP in humans [20]. The advantage of orthokine treatment compared to other treatments is that it is biological and uses only the body's own proteins and repair factors. This is accomplished by obtaining blood from the patient and processing as required. The serum is then administered to the patient [23–24].

The results of our study showed that the treatment of a infectious refractory corneal ulcer by administration of localized drops of orthokine led to the reduction of purulent secretions, suppression of pain, improvement in the progression of corneal melting and, ultimately, an improvement in vision. Orthokine therapy is a new treatment that is recognized as safe and inhibits and strengthens the body's natural defense mechanisms against inflammation to reduce pain and improve performance. At the same time, it may release growth factors into the area that minimize local tissue destruction and may actually promote healing and repair of these tissues. For a stronger generalization of the results, clinical studies with a larger sample sizes and a longer follow-up period must be conducted to evaluate the effectiveness of orthokine on inflammatory diseases of the eye such as infectious corneal ulcers.

CRediT authorship contribution statement

Kamran Mansouri: Visualization, Investigation, Supervision. **Gelavizh Rostaminasab:** Conceptualization, Software. **Touraj Ahmadi Jouybari:** Conceptualization. **Masood Bagheri:** Conceptualization, Methodology, Data curation, Writing – original draft, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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