# Toxic Keratopathy As A Result of Abuse With Topical Anestetics And Its Treatment With Amniotic Membrane Transplantation And Collagen Cross-Linnking - Clinical Cases

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***Abstract - Toxic keratopathy (TK) is characterized by damage and dysfunction of the cornea due to its exposure to drugs that cause anatomical disruption and disturbance of metabolic processes. The most common reported cause is chronic and uncontrolled abuse of topical anesthetics. The combined surgical treatment approach (transplantation of amniotic membrane and collagen cross-linking) has a positive effect on the processes of restoration of the damaged ocular surface.***

***Purpose: The aim of this study was to evaluate the response of subjective symptoms and objective signs of treatment with AMT and collagen cross-linking in patients with toxic keratopathy in abuse of topical anesthetic.***

***Materials and Methods: This retrospective study for the period 2012-2016 included 7 eyes of 4 patients - men of working age 27-41, treated in the Specialized Eye Hospital in the city of Varna diagnosed with toxic keratopathy associated with the abuse of topical anesthetic. In each patient the following were carried out: best corrected visual acuity (BCVA), biomicroscopy, staining with fluoresce in, evaluation of subjective symptoms (pain, tearing, photophobia in grades 0-mild to 4-severe) and objective signs (size and depth of corneal ulcer, corneal edema), photo documentation, in vivo confocal microscopy(IVCM) and anterior segment optical coherence tomography (AS-OCT).***

***Results: The combined surgical approach of transplantation of amniotic membrane (AMT) and CXL proves to be an effective method of suppression and eradication of pathological vicious circles leading to corneal blindness and disorganization of the architectonics of the anterior ocular surface. The results of the monitoring show that there is a statistically significant (P <0.001) difference in the assessment of pain, photophobia and watery tearing preoperative, a week after treatment and at the end of the study period. The analysis carried out in the preoperative and postoperative period showed a significant difference in visual acuity. The other objective signs - size and depth of corneal defect, also showed a statistically significant difference in response (p <0.001).***

***Conclusion: The success of treatment of toxic keratopathy is in early diagnosis, to prevent misuse of a topical anesthetic and reduce contact time. Combined surgery is a method of choice in these difficult treated cases.***

***Keywords - Toxic keratopathy, transplantation of amniotic membrane, collagen cross-linking.***

## INTRODUCTION

Toxic keratopathy (TK) is characterized by an injury or dysfunction of the cornea due to its exposure to drugs with a negative effect on its anatomy and metabolism. A large number of chemicals, systemic drugs and preservatives in eye drops, especially benzalkonium chloride (BAC), can cause TK. The most common reported cause is chronic and uncontrolled abuse of topical anesthetics. Their prolonged impact on the cornea suppresses reepitelizationand causes total cell apoptosis in the corneal stroma, followed by scarring and thinning. The large spectrum of clinical effects includes: punctate keratopathy, persistent epithelial defects, annular stromal infiltration, corneal edema, Descemet membrane folds, loss of endothelial cells, neurotrophic ulcers, keratomalacia, secondary infectious keratitis, corneal scarring, and perforations (8). Symptoms of TK are generally nonspecific - from mild to severe pain, photophobia, epiphora, hyperemia, chemosis. The effects of the topical anesthetic may be direct or indirect (5), but the exact mechanism of the toxicityis not yet fully clear. Up to now there are three theories described. According to supporters of the first theory, the toxic effect of topical anesthetic is direct. It leads to impaired migration and adhesion of corneal epithelial cells and thus to delayed wound healing (7). Instilling even a single dose of the anesthetic causes a violation of intercellular connections and a significant reduction in the number of microvilli and microplicaeof corneal and conjunctival epithelium. These effects are reversible at concentrations of less than 0.01 mmol / l (6). In addition to affecting the epithelium, local anesthetics exert a direct toxic effect on other corneal layers as well. Through their direct cytotoxic effects they distort the metabolism and the glycolysis of keratocytes and endothelial cells (10), thus reducing their viability (9). Topical anesthetics impair Na + / K + pump in endothelial cells. As a result, increasing of the osmotic pressure and

corneal swelling occur (10). A patient with TK resulting from misuse of Alcainewas examined by in vivo confocal microscopy, and ednothelial cellular polymorphism was observed (11). The laser microscopy revealed a decreased number of endothelial cells and compensatory expansion of the survivors (12). Local anesthetics inhibit the conducting of nerve impulses in the cornea and lead to the loss of its sensitivity. Thus they cause reduced tear secretion, decreased frequency of blinking and impaired stability of the tear film (11). This in turn leads to greater exposure of the cornea to external factors and a higher risk of reduced resistance of epithelial cells to toxins and microbial agents. Excessive and prolonged use of anesthetics can damage corneal nerves and cause the formation of neurotrophic ulcers. In turn, persistent epithelial defects facilitate bacterial colonization and the development of secondary bacterial keratitis (13). According to the second theory, the mechanism of action of topical anesthetics is a formation of antigens from the disrupted cells and the subsequent formation of antigen-antibody complexes. It is supposed that they are responsible for the formation of annular stromal infiltrates (14). Supporters of third theory abide bythe thesis that preservatives, such as benzalkonium chloride, in local anesthetics can cause toxic keratopathy and worsen the patient's condition (5).

The pathogenetic vicious circle of toxic effects leads to a cascade of reactions that are difficult to be affected by medicated therapy. Transplantation of amniotic membrane (AMT)proved to be a method of choice in the treatment of refractory ocular surface processes. It has been used successfully to treat patients with persistent corneal epithelial defects, chronic ulcers and burning of the anterior surface (15), (16). In the presence of an intact limbus, amniotic membrane(AM) increases epithelial migration to the basal membrane, enhances the adhesion of the basal epithelium, stimulates cell differentiation and inhibits apoptosis. AM is composed of avascular stroma and hypocellularity, a basement membrane and a monolayer of epithelial cells. It is also characterized by specific immunological inertness, and an anti-inflammatory, antibacterial and scarring reduction effect, due to the stimulation of the proliferation of stem cells and epithelial cells of the ocular surface. It has been proved that AM expresses an epidermal, hepatocyte, and keratinocyte growth factor. Protease inhibitors in AM inhibit the effect of proteinases secreted from keratinocytes, polymorphonuclear leukocytes and damaged epithelial cells, leading to a damage of the corneal stroma (17). Furthermore, AM acts as a biological contact lens – it reduces pain and protects the regenerating epithelium from the frictional force caused by the movement of nictitating eyelids. As a mechanical barrier, AM protects the cornea from the harmful effects of inflammatory cells and proteins in tears (18). A second method of choice is cross-linking, which was originally introduced as a method to stop the progression of keratoconus, and in recent years expanded its therapeutic limits and entered as adjunctive therapy in difficult to treat infectious keratitis caused by bacteria, fungi or parasites.

## MATERIALS AND METHODS

In this retrospective study (2012-2016) were included 7 eyes of 4 patients - men of working age 27-41. All of them were treated in Specialized Eye Hospital - Varna, Bulgaria and were diagnosed with toxic keratopathy associated with the abuse of topical anesthetic. For each patient, the following were carried out: BCVA, biomicroscopy, staining with fluorescein, evaluation of subjective symptoms (pain, tearing, photophobia in grades 0-mild to 4-severe) and objective signs (size of ulcerative defect, corneal edema), photo documentation, IVCM and AS-OCT. The patients were followed for one to 3 months. The corneal defect was grouped by size (grade 1 to 4 mm, grade 2 from 4 mm to 7 mm, and grade 3-over 7 mm), depth (grade 1> 20% grade 2 20-50%, grade 3> 50 % of the corneal thickness) and the position (central or peripheral portion).

### *Amniotic membrane*

Since 2015 cryopreserved human AM has been used from the tissue bank Bioregeneration Sofia and since 2016-cryopreserved AM (AloAM) has been used from the Center for translational medicine and cellular therapy in the Medical University-Varna in compliance with the validated methodology. AM is an allograft product received as a donation by healthy Bulgarian donors in planned caesarean section, in compliance with all regulations concerning donation.

### *CXL*

The CXL procedure was performed under sterile conditions in the operating room. A conventional protocol CXL for keratoconuswas used to prepare a CXL. After a topical anesthesia with 5% Alcaine, the superficial corneal epithelium was removed. There was an instillation of riboflavin every 3 minutes on the corneal surface, within 30 minutes, followed by corneal irradiation for 3 minutes using a UVX lamp with a 365nm wavelength, 3 MW / cm2 radiation, and a distance of 5 cm.

### *Surgical technique*

The operations on all patients were performed by a single surgeon. The main steps were observed of the algorithm for AMT. AM was preheated at room temperature - for 10 minutes before surgery. Preoperative topical anesthesia with Alcaine 5% was administered. Some of the patients were under subconjunctival anesthesia due to severe subjective symptoms. On the first stage, after pre-epithelial

abrasion and polishing of Bowman membrane, classical cover technique was performed on all patients on the entire cornea and limbus, and the amniotic membrane was suture with continuous, conjunctivo-episcleral 8-0 Vycril sutures.

The second stage was carried out by a combined procedure: cross- linking + AMT coverage type. The third stage was to stabilize the situation by supporting transplants of coverage type. Despite the treatment one patient was diagnosed with descemetocele and was operated on by a filler type amniotic transplant procedure. The corneal surface needed to be stabilized before performing a keratoplasty. A "sandwich" technique was used by placing pre-measured and precutted several pieces of AM in the area of the defect. The last piece was orientated so that the epithelium was in contact with the corneal surface. The pieces were fixed to the edge of the defect with single interrupted sutures 10-0 Nylon. On the top, coverage type AM was transplanted.

All the patients were fitted with soft silicone hydrogel contact lens after the operation.

***Postoperative***

All the patients were prescribed medical therapy that included a combination of a systemic antibiotic and two local antibiotics (quinolone + aminoglycoside), NSAIDs (systemic and local), artificial tears, epitheliotonic gels. The therapy was titrated depending on the extent and rate of recovery. The patients were observed every day during the hospitalization period. The observation was carried out weekly during the first month after hospital discharge and once to twice a month, depending on their condition, after this period.

## RESULTS

All the patients were men of average age 34 (27 - 41). They all reported that they had used Alcaine (0.5% proparacainehydrochloride solution/drops) (Alcon Laboratories) in different intervals - from once every 30 minutes to once every hour to reduce the pain. All four patient were with different initial diagnosis. Two of them were diagnosed with trauma-one of them has perforated injury and another one with chemical burn. The third one had initial diagnose keratitis electrica and the last one was with keratoconjunctivitis.

As for the way the patients had received anesthetic, all of them reported that they had purchased it of their own will (without a prescription) from a pharmacy, and one of them was even recommended an anesthetic by two independent pharmacies for reducing the complaints. All the patients were hospitalized with complaints such as: pain, blurred vision, photophobia and tearing. The average score of their pain on entry was 3.5 (range 0 to 4), and BCVA ranged from PPLC to 0.04. The clinical findings at the time of the hospital admission were: mixed hyperaemia, epithelial defects (grade 3), corneal edema, ring stromal infiltrates with / without the presence of hypopyon. In four of them, swabs were taken for microbiological testing, and in only one patient Streptococcusalfa-haemolyticus was isolated. In the rest, the cultures remained sterile.

There was a prescription of medical treatment with systemic antibiotics, antibiotic drops - fluoroquinolones and aminoglycosides, topical and systemic NSAIDs, preservative free artificial tears and epitheliotonic gels. In all patients, AMT was performed repeatedly for pain relief and support of reepithelization. In two of them, a combined procedure of collagen cross-linking and AMT was carried out as a second stage of treatment. In the course of the treatment for one of the patients it was necessary to perform penetrating keratoplasty in one eye.

Pain is one of the subjective sypmtom which determines the quality of treatment. The results of the monitoring show that there is statistically significant ($p<0.001$) difference in the assessment of pain, photophobia and epiphora on hospital admission and about a week after the treatment with AM and at the end of the study period.

The first objective sign is visual acuity. The results of the analysis in the preoperative and postoperative period showed a significant difference in visual acuity. After the treatment (between 1-3 months) BCVA ranged from 0.07 to 0.6. The other objective signs, such as size and depth of the ulcer defect, also showed a statistically significant difference in the response in the first week and about one month later ($p <0.001$). The observation of the patients showed that the average time to complete epithelialization after AMT is 30-45 days.

Observing of the microstructural changes in the AM, transplanted on the ocular surface, as well as observing changes in the cornea was performed.

## CLINICAL CASES

***Case 1***

A man aged 36 years was admitted to hospital with complaints of pain, loss of vision, photophobia and tearing for 20 days. The complaints started after "lightingwith electrocautery". To reduce pain, throughout the period he instillated a topical anesthetic - Alcaine 5%, which is sold freely in several pharmacies. The patient first sought medical assistance on the tenth day after the "illumination", complaining ofblurred vision, irritation and abundant secretion. The medical documentation at that moment showed the following: BCVA on right eye = 0.5-0.6, BCVA(with pin hole) on left eye = 0.2?; TOD = 17.0mmHg, TOS = 12.9mmHg (pneumatic tonometer). Biomicroscopy: OD-cornea: epithelial erosion; OS - cornea epithelial erosion, edema, Descemet membrane folds. Referred for urgent hospital admission and surgical treatment.

Ten days later (when he was admitted in our hospital):BCVA on right eye = 0.04;BCVA on left eye = counting fingers in front of the eye, TOD = N, TOS = (+) manual. On the biomicroscopy:

OD: eyelid swelling; conjunctiva- pronounced mixed hyperaemia; pronounced chemosis, profuse whitish discharge; cornea - nonhomogeneous edema, deepitelization , annular infiltrate in middle 1/3 (epithelial defect size grade 3, depth grade 2); anterior chamber - moderately deep, clear contents; iris - normal structure and topography, pupil - round, centrally located in miosis, posterior eye segment- cannot be examined(Figure 1a).

OS: eyelid swelling, floppy eyelid syndrome; conjunctiva - pronounced mixed hyperaemia, chemosis, profuse whitish discharge; cornea - extensive erosion (epithelial defect size grade 3, depth grade2), reduced homogeneous transparency, edema and Descemet membrane folds; the remaining eye structures cannot be examined (Figure 2a).

Discharge was taken for microbiology and antibiogram. Streptococcusalfa-haemolyticus was isolated. There was a prescription of treatment with systemic antibiotics, antibiotic drops - fluoroquinolones and aminoglycosides (in compliance with the antibiogram), topical and systemic NSAIDs, preservative free artificial tears and epitheliotonic gels. Several repeated AMT were performed to reduce the pain and support re-epithelization. On the second stage of the treatment, a combined procedure was performed: collagen cross-linking and AMT.

A month after treatment we observed reduced infiltration of both eyes, improvement of subjective symptoms and the transparency of the cornea, and increaseof visual acuity (Figure 1b,c,d,e), (Figure 2b,c,d,e).

***Case 2***

A man aged 27 years was admitted to the hospital with active bacterial keratitis and long history of conjunctivitis of both eyes (3 months), followed by keratitis unresponsive to ongoing medical treatment. To reduce the pain he instillatedAlcaine 5% without being prescribed by a doctor. He was referred for treatment in the Specialized Eye Hospital - Varna. At the time of hospital admission: BCVA of both eyes PPLC. Biomicroscopy showed pronounced objective signs in both eyes - bilateral corneal infiltrates with circular central thinning and hypopyon about 2-3mm (epithelial defect size and depth grade 3; Figure 2a, c, d). Three weeks after treatment, including repeated AMT, we observed reduced infiltration of both eyes, improvement in the transparency of the cornea, absorption of the hypopyon, improvement of visual acuity and subjective symptoms (Figure 2d, e). Despite the fact that the treatment showed a trend for improvement, on the 45day the left eye was with descemetocele and perforation. The corneal surface needed to be stabilized before performing a penetrating keratoplasty, and AMT filler type and coverage type were made. The result after AMT was restoring of the anterior chamber (Figure 2g). Three days later a penetrating keratoplasty was performed (Figure 3h).

## DISCUSSION

Topical anesthetics are one of the most widely used drug groups in ophthalmic practice, ranging from outpatient study and getting to big surgery. In the references, there are good descriptions of their toxic effects on the anterior surface of the eye, especially on the cornea as a result of their chronic and uncontrolled abuse (19).

The results of this study demonstrate the important role of AM for the improvement of subjectivesypmtoms and objective sign in patients with toxic keratopathy caused by Alcaine abuse. Pain is the factor that drives patients to apply topical anesthetic, which is a leading cause of toxic keratopathy. Treatment with AM significantly reduces the degree of this important objective symptom. By adhesion of the membrane to the injured surface and the coating of nerves, it is an essential biological dressing for protecting the cornea from the harmful effects of inflammatory cells and proteins in tears. It also acts as a biological contact lens that protects the regenerating epithelium from the friction forces generated by the movements of the nictitating eyelids. It retains the moisture of the ocular surface and protects it from drying out, by retaining tears. Thus, on the one hand, it creates conditions for re-epithelialization, and on the other, it reduces the pain syndrome. (26) Burcu et al. 2013 demonstrated similar results in a study of eight eyes of seven patients with toxic keratopathy after application of a topical anesthetic. They proved that AMT facilitates early relief of pain and eliminates the need for application of a local anesthetic. In addition to the positive effect on pain, we demonstrate that AM has a positive effect on other important subjective factors - tearing and photophobia. There was an improvement in visual acuity in all our 4 patients.

CXL opens up new possibilities for the treatment of corneal diseases. There are increasingly more reports of the effectiveness of the method in the treatment of infectious keratitis. Several studies have revealed that CXL can be successfully used for treatment of non-infectious keratitis (21,23,24,25). In two of our patients, cross-linking was conducted.Our pooled results showed faster recovery and higher visual acuity in patients with the procedure carried out, compared to the group of patients without cross-linking carried out. (22) Gao et al. explored the effects of CXL to stop the melting of the cornea in rabbit eyes after alkali burns. They proved that the method can prevent and slow down keratomalacia too. They proved that CXL reduces the destruction of corneal collagen fibers and the infiltration of inflammatory cells in the cornea. (21). In a study of eight patients with corneal ulcers,

irresponsible to conservative antibiotic treatment, MitraZamanietet al.reported that in 75% of cases after CXL corneal melting stopped. These findings are consistent with similar studies revealing the positive effects of CXL for the treatment of corneal diseases occurring with stromal melting (23,24,25).

## CONCLUSION

The treatment of toxic keratopathy is based on early diagnosis, on the prevention of the misuse of a topical anesthetic and on reducing contact time. The combined surgical approach in that case, transplantation of amniotic membrane and CXL, proves to be an effective method of suppression and eradication of pathological vicious circles leading to corneal blindness, and disorganization of the anterior surface architectonic.

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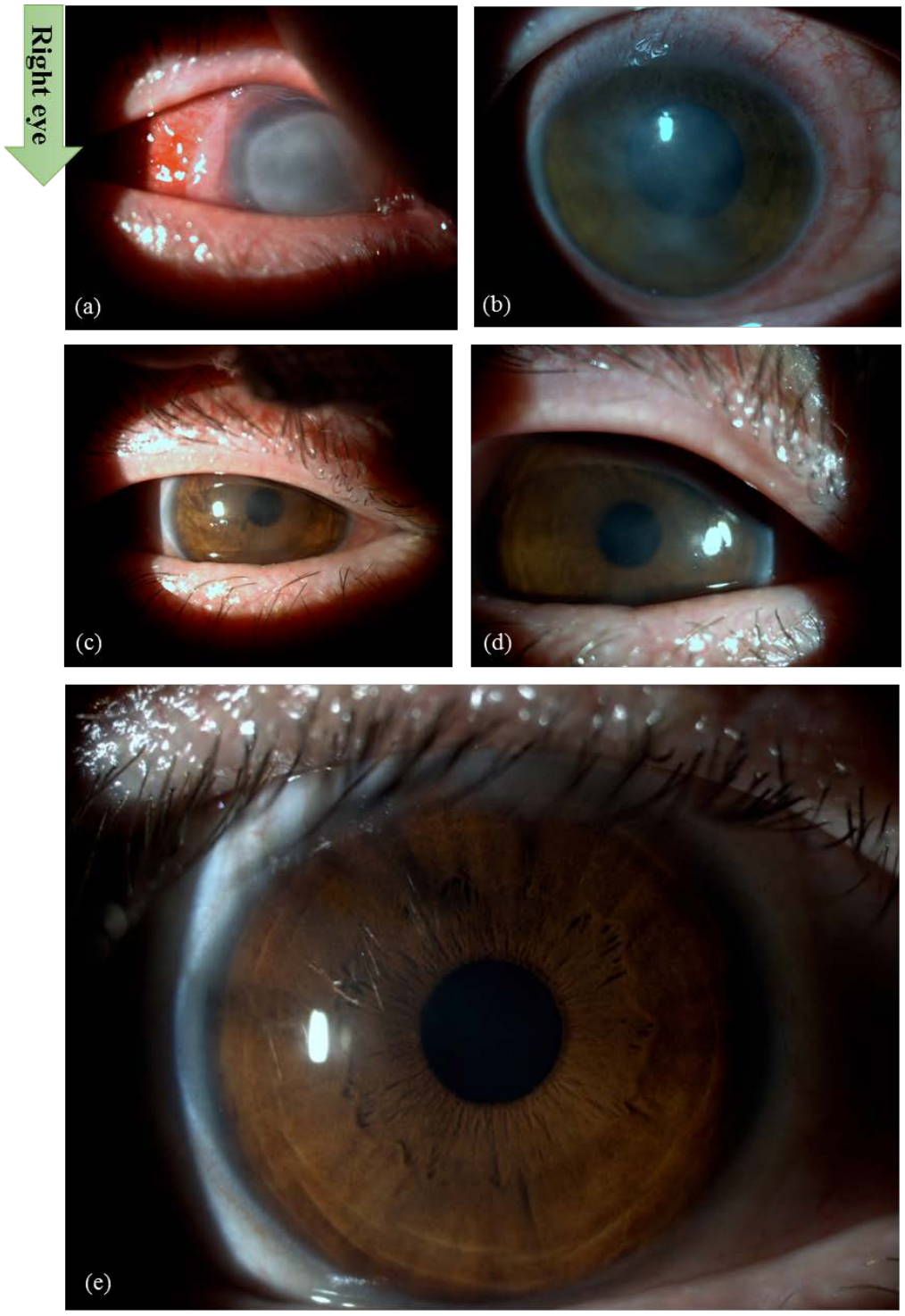


Fig. 1. Patient aged 36 years: (right eye) with toxic keratopathy caused by abuse of Alcaine 5%. (a) four days after hospital admission, (b) two weeks after initiation of treatment, (c) 30 days later (d) two months later, (e) three months later.

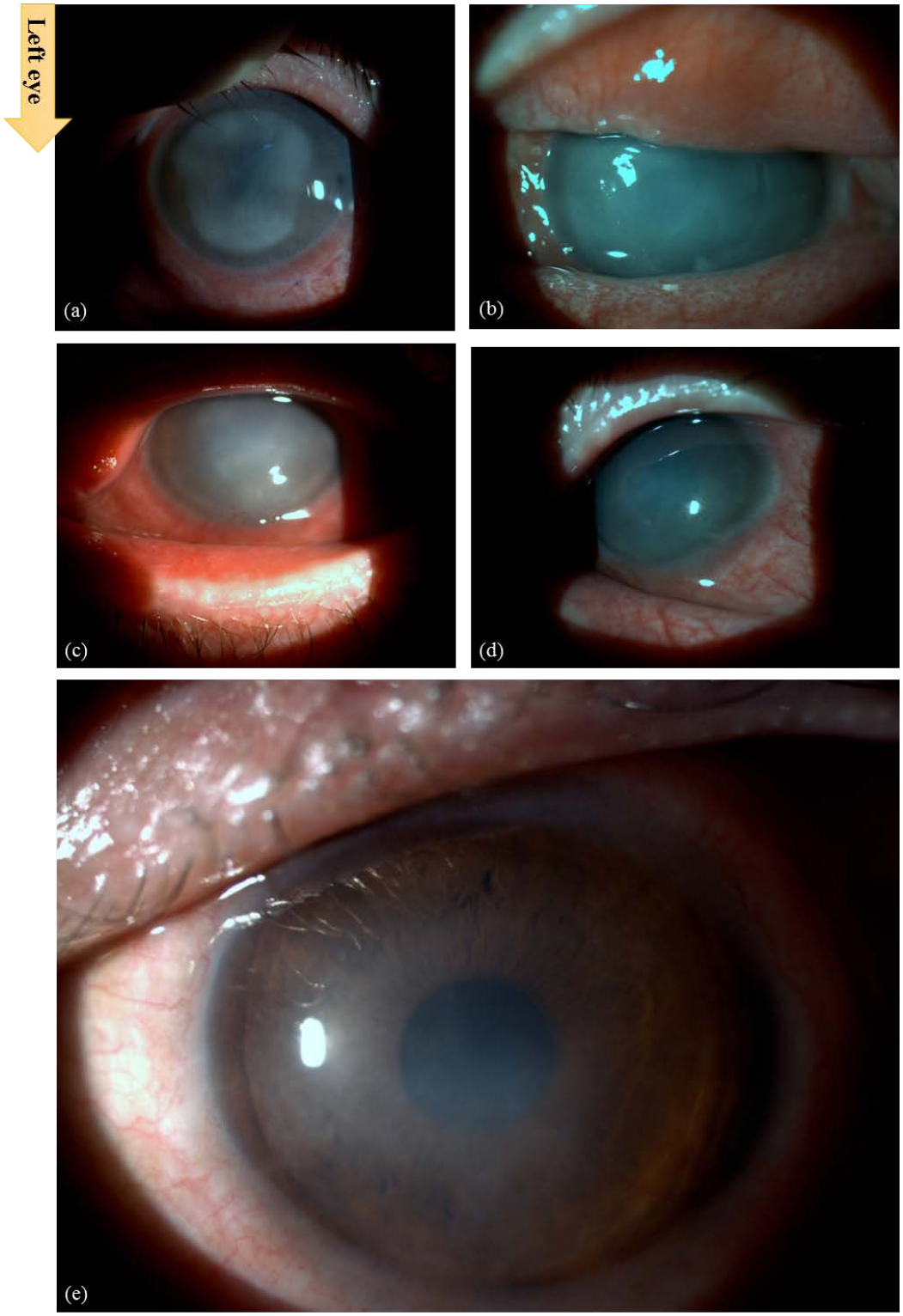


Fig.2. Patient aged 36 years: (left eye) with toxic keratopathy caused by abuse of Alcaine 5%. (a) four days after hospital admission, (b) two weeks after initiation of treatment, (c) 30 days later (d) two months later, (e) three months later.

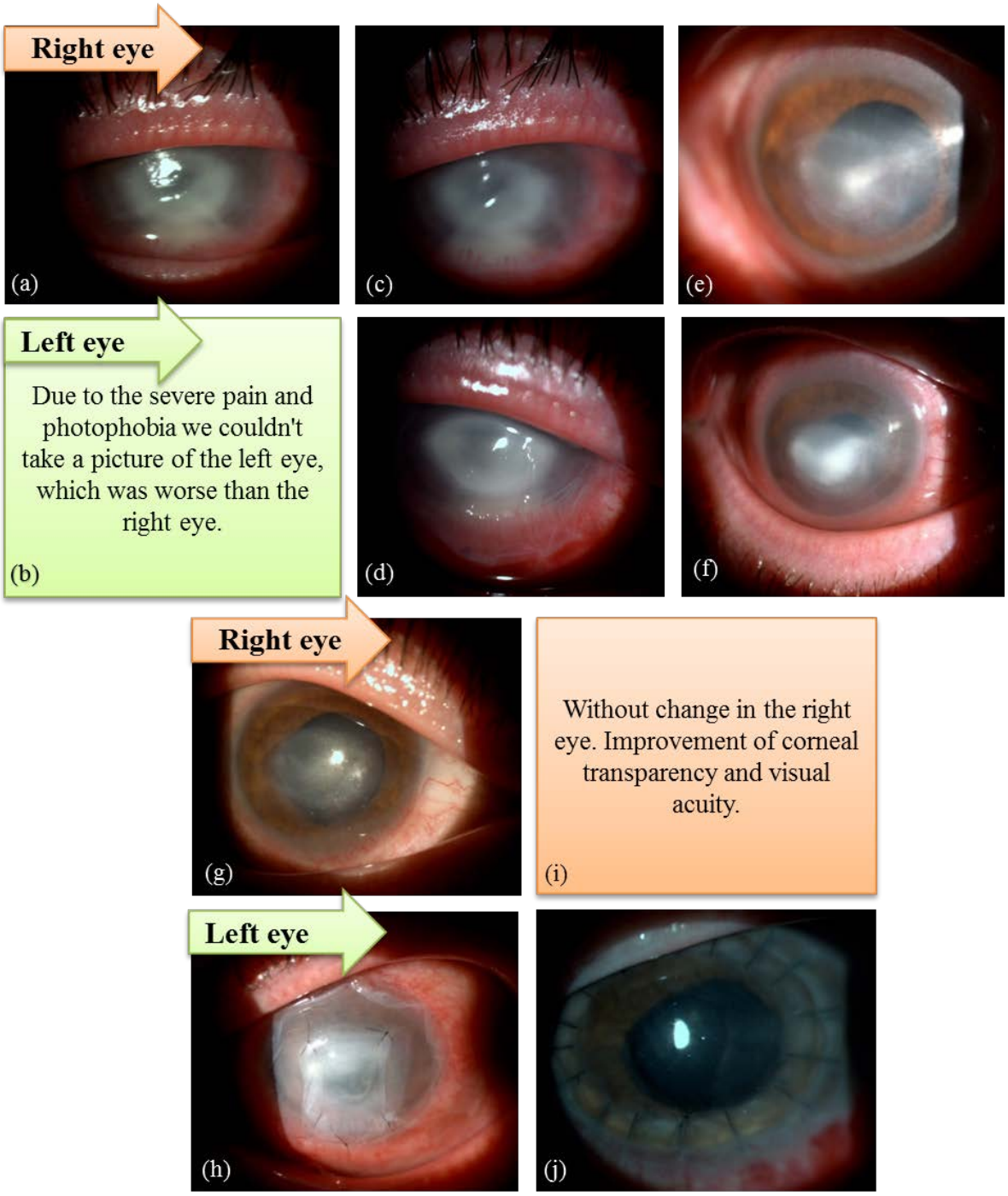


Fig. 3. Patient aged 27 years, with toxic keratopathy (a,c,e,g,i-right eye),(b,d,f,h,j-left eye). Photos (a,b) at adimission; (c,d) OD and OS after cover type AMT ; (e,f) three weeks after AMT – limiting of infiltration on both eyes, resorption of hypopyon; (g) OD 45 days: limiting of infiltrate; (h) OS45 days: despite the treatment - descemetocele with perforation. Filler type and cover AMT was performed ; (j) OS:three days after performing PRP.