Long-term Management of Severe Ocular Surface Injury due to Methamphetamine Production Accidents

Running title: Management of Ocular Surface Injuries in Methamphetamine Production Accidents

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Abstract

Purpose: To report the clinical features and management of patients with ocular surface damage during methamphetamine production accidents.

Methods: This is a retrospective, non-comparative interventional case series of 5 patients with methamphetamine production related ocular injuries referred to Cincinnati Eye Institute between 1999 and 2014.

Results: Four out of five cases were white young men with severe bilateral ocular injury and extremely poor vision. All eyes except one (9 out of 10) were diagnosed with total or near total ocular surface failure. Limbal stem cell transplantation was performed in 8 out of 10 eyes. Keratolimbal allograft was followed by penetrating keratoplasty in 7/10 eyes. Ocular surface stability was achieved in 7 out of 10 eyes after keratolimabl allograft. Post-operative visual acuity was better than 20/200 in 4 out of 10 of eyes. Keratolimbal graft rejection occurred in 3 out of 10; the rate of rejection of penetrating keratoplasty was also three out of ten.

Conclusion: Methamphetamine related accidents can lead to severe bilateral ocular injuries. Although stem cell transplantation procedure's success is guarded in most of these patients due to severe conjunctival inflammation and accompanying ocular comorbidities, as well as personality issues, compliant patients can achieve good visual function with ocular surface transplantation and subsequent keratoplasty.

Key words: methamphetamine, ocular surface, keratolimbal allograft, chemical injury

Introduction

Amphetamine type stimulants are the second most widely used class of illicit drugs worldwide [1]. Particularly, methamphetamine production and use has had a tremendous surge in the last two decades all across the globe.

This is because the drug can be easily made in small clandestine laboratories, with fairly low-cost over-the-counter ingredients such as pseudoephedrine. However, methamphetamine production involves other dangerous ingredients such as anhydrous ammonia (in fertilizer), lye (sodium hydroxide), swimming pool cleaner (hydrochloric acid), red phosphorous (matches), ethyl ether (engine starter fluid), Drano and lighter fluid (butane) [2].

Each year the number of methamphetamine lab incidents grows according to the Drug Enforcement Administration [3]. In a study performed in Iowa, almost 10 percent of patients admitted in a burn unit in a period of 16 months suffered from facial and ocular injuries related to methamphetamine production accidents [4]. These accidents typically occur from an explosion caused by the mixing of flammable liquid ingredients, caustic agent spills or propane gas container explosions. Recently, the so-called “shake-and-bake” has emerged as a rough new method where the raw materials are mixed in 2-liter soda bottles. Hence the chances of accidents are tremendously higher and this could be translated into a substantial increase in the number of methamphetamine related burn injuries.

In the largest retrospective analysis of methamphetamine-associated burns, the face was the most frequently injured area with 70% involvement. Ocular surface burns were diagnosed in nearly 20% of cases in that study [5].

To our knowledge there is only one short report specifically focusing on ocular injuries due to methamphetamine related burns in the literature [4]. Lee et al. [6] also mention three cases of ocular injury due to anhydrous ammonia injuries associated with methamphetamine production in a letter.

We sought to review a series of cases with ocular injury due to methamphetamine manufacturing accidents, which were referred to the Cincinnati Eye Institute for treatment of ocular injuries. The focus of the current study is to report the long-term management and outcomes of these patients.

Patients and Methods

This is a retrospective chart review study of five patients with methamphetamine production related ocular injuries between January 1999 and May 2014. After obtaining approval of the ethics committee, the charts of the patients fitting the inclusion criteria were reviewed. The inclusion criteria comprised all methamphetamine production related ocular injuries that were referred to the Cincinnati Eye Institute's cornea clinic for evaluation and management, with a minimum of one-year follow up.

The assessed parameters included demographics, the causative chemical agent according to patients' statement, presenting features prior to management, indications for ocular surface procedure, preoperative Snellen best spectacle–corrected visual acuity (BSCVA),

intra- and postoperative complications and the course of the disease including post operative BSCVA and ocular surface stability up to the last follow up. The ocular surface stability was determined based on the presence or absence of late fluorescein staining (conjunctival epithelium on the cornea). The ocular surface condition was classified as stable, partially failed, or totally failed. A stable ocular surface had an intact corneal epithelium devoid of conjunctivalization or inflammation. A partially failed ocular surface was defined as an eye with areas of abnormal conjunctival epithelium on the cornea as well as regions of normal looking cornea. Total ocular surface failure or visually significant failure was defined as total compromise of the ocular surface with complete corneal conjunctivalization and/or inflammation substantially impacting the patient's vision.

Results

The mean age of patients was 29.6 ± 4 years at the time of injury. Four of five cases were white young men, who suffered from severe bilateral ocular injuries and were referred to us with extremely poor vision. There was only one female patient among our cases; she was Caucasian as well. The injuries were unanimously bilateral however with asymmetrical severity of involvement. All but one patient could identify the particular chemical substance by which the injury occurred. All of the identified chemicals were alkaline in nature, the most common being anhydrous amonia (40%). All of the patients gave a false history on initial admission. Plumbing was the most common falsely reported activity during which the accident happened. However, every patient eventually gave the history of methamphetamine production accident. The patients were referred to us for

treatment between 3 months to 3 years after the causative accident. The injuries were extremely damaging to the ocular surface. Nine out of 10 eyes were diagnosed with total ocular surface failure, manifested as total conjunctivalization/ neovascularization of cornea with late fluorescein surface staining, inflammation and scarring of the ocular surface, as well as symblepharon, ankyloblepharon and foreshortening of fornices. In addition to ocular surface abnormalities, 5/10 had cataracts and 3/10 had high intraocular pressure at initial assessment visits. Pre-op visual acuity was very poor in most eyes with 9/10 of eyes having BSCVA of counting finger at three feet or less.

The mean follow up time was 30.6 ± 24 months (range 12-59 months). Indications for surgical intervention included ocular surface failure and corneal opacity in all eyes. All of the patients had total ocular surface failure with 100% surface late staining complete scarring and conjunctivilization. Previous treatments such as amniotic membrane or buccal mucosal grafts were ineffective in those cases that underwent those procedures. Keratolimbal allograft (KLAL) was performed in 8/10 of eyes. Penetrating keratoplasty (PK) followed KLAL in 7/10 eyes. Ocular surface stability was achieved in 7/10 of eyes after keratolimbal allograft. Post-operative visual acuity was better than 20/200 in 4/10 of eyes. Keratolimbal graft rejection occurred in 3/10; the rate of rejection of penetrating keratoplasty was also 3/10.

There was no intra-operative complication in any of eyes undergoing KLAL or PK. The major post-operative complication was KLAL or PK rejection. There were two KLAL and one PK rejection episodes. In one case KLAL rejection was initially resolved with medical treatment, but eventually the graft progressively failed. The other two cases of

rejection (one KLAL and one PK) were not responsive to medical treatment and failed rapidly.

Table 1, summarizes the key parameters of interest in five patients.

Three of our cases (6 eyes) had poor compliance. Two of them had poor follow up as well. The two patients who were more compliant (4 eyes) achieved much better visual outcomes between 20/40 to 20/300. The poor visual outcome in two of our patients is most likely due to lack of follow up.

Discussion

Previous studies in the past decade estimated that between 2 to 4 percent of burn unit admissions in hospitals located in endemic regions of the U.S. were methamphetamine related and the numbers are estimated to rise [7, 8].

Since the upsurge of methamphetamine related accidents in the last two decades, investigators have noticed significant differences in the forms and severities of injuries caused by this type of accident. It was observed that methamphetamine burn patients have significantly more fluid loss than the same percentage of body surface involvement in a non-methamphetamine related burn patients. Also, despite the younger age, the mortality with comparably sized burns was significantly higher [7].

Ocular injuries are commonly reported in methamphetamine manufacturing accidents [5]. In predominantly farming regions of the U.S. where the problem is endemic as high as 60% of burns involve ocular injury [9].

Similar to previous reports on severity of injuries in this group of patients [9], ocular injuries are routinely very severe. In our cases the injuries were invariably bilateral and had severely compromised the vision. One reason could be the nature of the hazard; these accidents cause chemical injury, but also damage the tissues by thermal burn and traumatic force of the explosion. Moreover, the primary causative agent was frequently reported to be an alkali. One of the key ingredients for so called “dry cooking of meth” is anhydrous ammonia. This alkaline substance is primarily used in farming to develop fertilizers. Most of our patients reported working with anhydrous ammonia when the accident occurred, similar to previous reports [6, 9].

Boolm et al. reported anhydrous ammonia as the most common cause of chemical injury with 40% of cases of all chemical injuries in a tertiary hospital in southern Illinois; interestingly 75% of which were injured during manufacturing of methamphetamine. The authors also found that anhydrous ammonia exerts a combined thermal-chemical effect on tissues resulting in considerably greater damage to the tissue compared to non-methamphetamine related chemical injuries. This might explain the disproportionate severity of injuries seen in multiple studies in victims of methamphetamine production accidents [9].

Another possible reason that could explain the extent of the damage is the delay in reporting the incident and especially seeking primary medical care. The patients tended to give false histories and were generally less compliant with medications and follow-ups. Oral immunosuppressive medications are the mainstay of management of stem cell transplantation after the procedure. Our patients received our systemic immunosuppressive protocol. This regimen consists of tacrolimus, mycophenolate

mofetil, and a short course of oral prednisone (3 months or less) [10, 11]. Dose adjustment is required for tacrolimus based on blood levels taken each month; tacrolimus is usually tapered off at 12 to 18 months. Mycophenolate mofetil was continued for our patients for the minimum of 24 to 36 months considering the remaining inflammation and tolerance to the medication.

Topical prednisolone was continued at 4 times daily for the first 3 months and tapered by 1 drop per month until a proper maintenance dose was achieved. Topical cyclosporine was continued twice daily during the follow-up period, and the topical fluoroquinolone was stopped after the epithelium was healed. We start postoperative topical management of the penetrating keratoplasty as early as 4 hours after the surgery with cyclosporine 0.05% 2 times daily, prednisolone acetate 1% 4 times daily, and a fourth-generation fluoroquinolone 4 times per day.

This study has its limitations. It is very likely that our patients have been the most severely affected cases of methamphetamine related accidents; on the other hand, some other unidentified cases may be missed because they have refused to give the correct history. However, most of previous studies reported a poor follow-up and thus their data is collected from much shorter follow-ups and neither have reported the outcome of treatment.

It has been shown that the average methamphetamine patient's hospital stay costs is 60 percent more than other non-methamphetamine related burn patients [12]. Likewise , the costs of ophthalmic care could be comparatively higher in such patients.

The victims of such injuries are typically young individuals who have nearly lost sight in both eyes. The severity of the damage is extreme and often multiple ocular procedures

and regular long-term follow-ups with several ophthalmic subspecialties are required to increase the chance of a better visual outcome; The costs of healthcare becomes even more challenging since most of these patients are uninsured.

While appropriate emergent care, is key to the management of all chemical/thermal injuries, it is important to address future care by timely referral of the patients for tailored long-term management.

In summary, methamphetamine related accidents typically lead to severe bilateral ocular injuries and often blindness. Although, stem cell transplantation's success is limited in most of these patients due to severe conjunctival inflammation and accompanying ocular comorbidities, this procedure is of great value in the long-term management, particularly in compliant patients. In one of our patients the preoperative VA of counting fingers at two feet reached the functional vision of 20/40 five years after transplantation. The two of our cases (4 eyes), who had good compliance did very well in long-term follow-up compared to the rest of the cases with very poor compliance and/or follow-up.

While it is difficult to draw a solid conclusion with few numbers of cases, we observed that the outcomes of the management in our cases were highly related to the degree of compliance.

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Table and Figure legends

Eye No.	*Pre-op VA*	*Previous Surgical Treatments*	*Surgical Management*	*KLAL Failure /Rejection Cause Features Outcome*	*PK Rejection/Failure Cause Features Outcome*	*Additional Procedures*	*VA in Last f/u*	*Ocular Surface Condition in Last f/u*	*Total f/u (mo)*	*Compliance*

Table 1. Key features of management and follow up of five cases of ocular injury due to methamphetamine explosion.

Figure 1. Pre and post op slit lamp images of a 28 year old white female who was referred four months after a methamphetamine production accident to both eyes. The left eye was affected more with severe scarring and symblepharon in both fornices. In the last follow up 34 months after ocular surface transplantation, the right eye was completely quiet with intact epithelium. The left eye had peripheral corneal neovascularization, intact epithelium but with a dense deposit due to non healing corneal epithelial defect.

1	HM	Amniotic membrane grafts (twice) and Lensectomy	1. KLAL 2. PK (3 mo after KLAL)	Acute KLAL rejection initially resolved by medical therapy later recurred as progressive graft failure secondary to glaucoma manifested by corneal edema	None	Secondary IOL, Tube shunt	$20/60^{-2}$	Stable	56	Compliant
2	LP	Amniotic mem grafts (twice), Tube shunts and Lensectomy	1. KLAL 2. PK (6 mo after KLAL)	Progressive KLAL failure Secondary to glaucoma manifested by epithelial irregularity	PK failure secondary to hypotony manifested by corneal edema	Secondary IOL, Tube shunt, Pars plana Vitrectomy/ Retinal detachment repair, Repeat PK (twice)	20/300	Stable		
3	CF at 3 ft	None	1. KLAL 2. PK (3 mo after KLAL)	None	None	Phaco	20/125	Stable	14.3	Poor follow up and Non Complaint
4	HM	None	KLAL	KLAL rejection due to stopping steroid drops by the patient manifested by neovascularization	PK failure due to stopping steroid drops by the patient manifested by corneal edema	Phaco, Repeat PK	HM	Total surface failure		
5	LP	Amniotic membrane graft	KLAL	None	None	Symblepharon lysis, Buccal membrane graft	HM	Stable	12	Non Compliant
6	LP	Amniotic membrane graft	None	None	None	-	LP	Total surface failure		
7	20/300	None	1. KLAL 2. PK	None	None	Tube shunt, Phaco	20/40	Stable	59	Compliant
8	CF 2 ft	None	1. KLAL 2. PK	None	None	Tube shunt, Phaco	20/50	Stable		
9	HM	Tarsorrhaphy	1. KLAL 2. PK + sectoral KLAL	Sectoral KLAL failure manifested by limbal injection and neovascularization because of non compliance	PK rejection manifested by endothelial rejection line because of non compliance	Inferior sectoral KLAL	20/200	Partial surface failure	12	Non Compliant
10	HM	Tarsorrhaphy	None	None	None	None	HM	Total surface failure		

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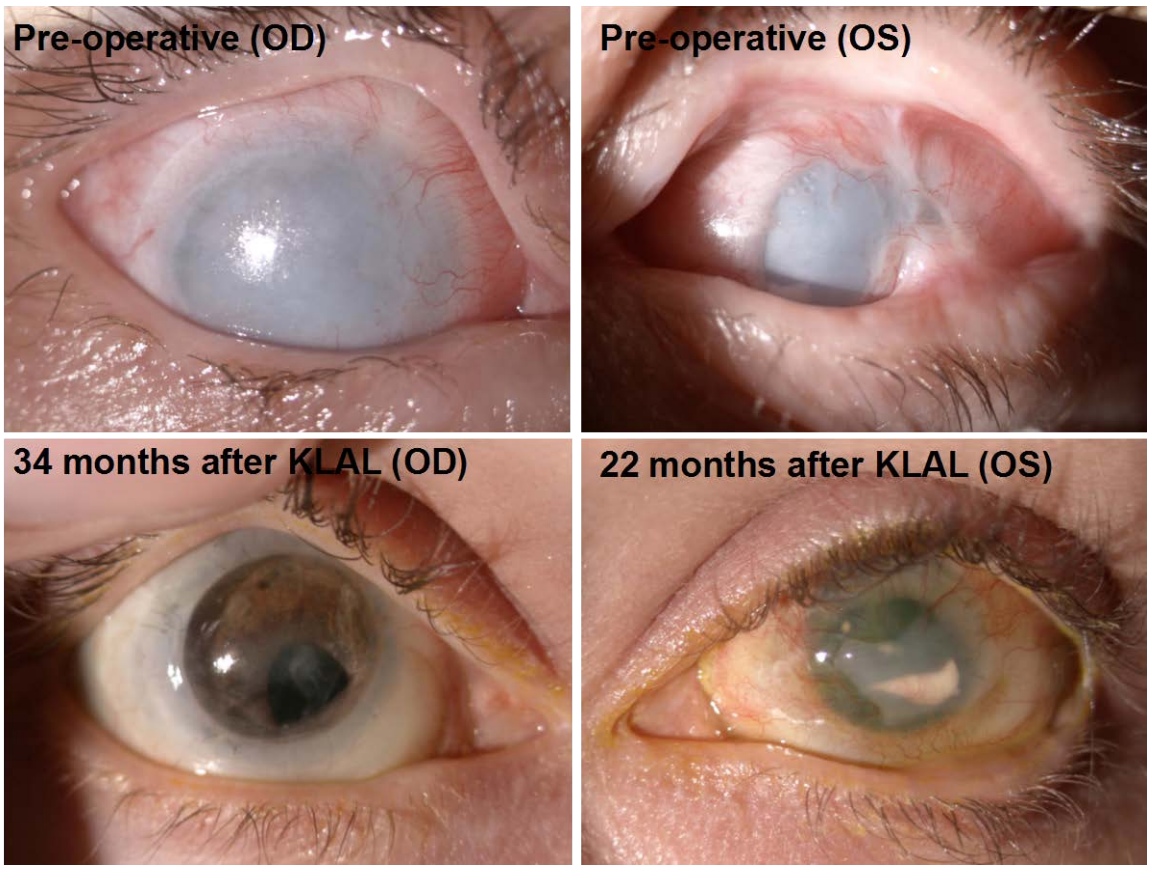
Pre-operative (OD)
Pre-operative (OS)
34 months after KLAL (OD)
22 months after KLAL (OS)

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