

Efficacy of topical medroxyprogesterone acetate 1 % and topical doxycycline reduce MMP-9 and TGF- β 1 expression as corneal ulceration due to alkali burn: literature review



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ABSTRACT

Corneal alkali burn is a typical ophthalmology emergency which requires immediate management and treatment. Alongside conventional treatment, medroxyprogesterone and doxycycline are considered potent add-on treatments. This literature review was conducted to determine their impact towards corneal wound healing after an alkali burn. It was proven from studies extracted from literature searching among various databases that medroxyprogesterone and doxycycline proven to reduce the inflammatory condition of corneal wounds after alkali trauma. In addition, they are subjected to reduce matrix metalloproteinase (MMP-9) and transforming growth factor (TGF- β 1), which are abundant and over-expressed in a corneal wound and could cause excessive inflammation and neovascularization of cornea, which results in hazy and disintegrated corneal tissue after recovery. Therefore, the usage of topical medroxyprogesterone acetate 1% and doxycycline is proven beneficial for patients with corneal wounds after being exposed to alkali burns.

Keywords: alkali, burn, cornea, doxycycline, medroxyprogesterone.

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INTRODUCTION

Ocular chemical injury is an ophthalmology emergency which requires immediate medical treatment. Among them, alkali injury is more common and more dangerous. Alkali injury involves pH change, leading to ulceration and proteolysis, which could destroy collagen. Because of its lipophilic traits, it could penetrate the eye better than acid and cause damage. Damaged tissue will provoke more inflammatory chemokines and cytokines, which could induce cataracts and extensive damage towards the ciliary body and trabecular meshworks.¹ Ocular alkali burn should be immediately irrigated until physiological pH is restored. Management is followed by the administration of conventional medical treatments such as antibiotics, cycloplegic agents, artificial tears, and steroid drops.²

In addition to conventional medical treatment, there are several options

for corneal alkali burn medical treatment. Topical doxycycline and medroxyprogesterone acetate 1 % should be considered as alternatives. Doxycycline is an antibiotic. However, besides its antimicrobial, doxycycline is an anti-inflammatory agent that could reduce inflammation by suppressing matrix metalloproteinases (MMP). Doxycycline reduces the expression of epithelial gelatinase and neutrophil collagenase. In addition, doxycycline suppresses the degradation of alpha-1 antitrypsin and improves the scavenging of reactive oxygen species (ROS). The processes could improve corneal healing after an alkali burn.³ Medroxyprogesterone, on the other hand, could serve as a catalyst for corneal healing after an alkali burn. Even though medroxyprogesterone is an anti-inflammatory agent with a lower potential than corticosteroids, medroxyprogesterone also has the minimum effect on corneal tissue repair, especially on the corneal stroma. In addition, medroxyprogesterone

is accounted to suppress the transforming growth factor (TGF- β), which could make the cornea hazy if overexpressed during the healing phase.⁴

We conducted this literature review to determine the effects of topical doxycycline and/or medroxyprogesterone towards wound healing in corneal alkali burns. We determine the population of people with corneal alkali burn, the intervention of topical doxycycline and/or medroxyprogesterone acetate 1 %, control of none (single-armed) or any (double-armed), and outcome of wound healing and/or clinical results. Searching was conducted on various databases. Knowledge acquired in this review is expected to help clinicians obtain knowledge in this field and thus could be applied for better patient outcomes.

OVERVIEW OF OCULAR ALKALI BURN

Chemical injury towards the cornea

and conjunctiva is an ocular emergency which causes corrosion towards corneal tissue. It is found among 11.5% to 22.1% of all ocular traumas. Almost two-thirds of corneal chemical injuries are acquired among young men. In addition, children aged 1–2 years old are considered the population at risk. Most of them are caused by industrial accidents, whereas few of them have resulted from home accidents or assaults. Among all injuries, alkali contributed more than acid injury. Alkali accounted for 60% of corneal chemical injuries caused by various substances such as ammonia, potassium hydroxide, lye, magnesium hydroxide, and lime. All these substances can be found in multiple daily products such as cleaning agents, fertilizers, refrigerants, caustic potash, drain cleaners, airbags, firework sparklers, flares, plaster, mortar, cement, and whitewash.⁵

Alkali agents are more dangerous compared to acid agents as they are lipophilic and thus have better penetration towards corneal tissue. Alkali agents which penetrate corneal tissue will cause saponification of fatty acids in cell membranes. This is followed by corneal stroma penetration and destruction of collagen bundles and proteoglycan ground substances. Wounded tissues will secrete proteolytic enzymes, which could cause more destruction of tissues and cells, leading to more damage.⁶ Alkali chemical injuries cause several symptoms, such as severe pain, epiphora, reduced visual acuity, and blepharospasm. Alkali chemical injuries are classified into four grades according to severity. Classification by Roper Hall group corneal burns into four stages based on prognosis, cornea wound, and extension of damage towards conjunctiva/limbus (Table 1).^{2,7} In addition, the most recent classification was made by Dua *et al.*, which added clinical findings and an analogue scale as a percentage into the classification. This classification has been more popular to be used lately (Table 2).⁸

The initial treatment of this trauma is to administer irrigation to restore corneal pH to physiological pH. Following steps are done according to the grading of corneal burn. Grade I and II corneal ulcers could be treated by medical treatment alone as they

Table 1. Roper Hall classification of ocular surface burns.^{2,8}

Grade	Prognosis	Cornea	Conjunctiva/limbus
I	Good	Corneal epithelial damage	No limbal ischemia
II	Good	Corneal haze, iris details visible	<1/3 limbal ischemia
III	Guarded	Total epithelial loss, stromal haze, iris details obscured	1/3–1/2 limbal ischemia
IV	Poor	Cornea opaque, iris, and pupil obscured	>1/2 limbal ischemia

Table 2. Dua classification of ocular surface burns.

Grade	Prognosis	Clinical findings	Conjunctiva involvement (%)	Analogue scale (%)
I	Very good	0 clock hours of limbal involvement	0	0/0
II	Good	<3 clock hours of limbal involvement	<30	0.1–3/1–29.9
III	Good	3–6 clock hours of limbal involvement	30–50	3.1–6/ 31–50
IV	Good to guarded	6–9 clock hours of limbal involvement	50–75	6.1–9/51–75
V	Guarded to poor	9–12 clock hours of limbal involvement	75–100	9.1–11.9/75.1–99.9
VI	Very poor	Total limbus involvement (12 clock hours)	100	12/100

have good prognosis. Medical treatment is aimed at improving corneal epithelium healing and improving collagen synthesis. In addition, medical treatment is also aimed at minimizing collagen breakdown and controlling inflammation.⁸ Medical treatment includes antibiotics, cycloplegic agents, artificial tears, and steroid drops.^{2,5,9} In addition, other treatments such as ascorbic acid, doxycycline, citrate drops, medroxyprogesterone, and platelet-rich plasma eye drops could be considered.^{4,9} Surgical procedures should be conducted in severe degree burns to remove necrotic tissues, which could reduce re-epithelization as a result of excessive inflammation. Surgical procedures which could be conducted such as debridement of necrotic epithelium, amniotic membrane transplantation, limbal stem cell transplant, cultivated oral mucosal epithelial transplantation, and Boston keratoprosthesis.^{10,11}

CORNEAL WOUND HEALING ON ALKALI BURN

Corneal wound healing is a complex process involving cascades of events to repair corneal cells. It consists of various phases, from re-epithelization, keratinocyte proliferation, migration, and differentiation, to remodelling of the extracellular matrix.¹² According to the kinetics, corneal wound healing is separated into the initial latent phase and closure phase. The initial phase involves the rearrangement of cellular and subcellular, thus inducing epithelial cells migration from the wound edge.^{12,13} Closure phase involves cascades of events which start with cell migration and proceed by proliferation, differentiation, and restoration of the initial epithelial layer.

The corneal epithelium has many stem cells distributed along the corneoscleral junction and limbus, enabling life-long

proliferation and regeneration in case of trauma or wound. Various substances, like growth factors and cytokines, support this process. There are multiple growth factors and cytokines involved in corneal wound healing, such as epidermal growth factor (EGF), transforming growth factors (TGF) α and β , insulin-like growth factors (IGF), platelet-derived growth factors (PDGF), fibroblast growth factors (FGF), keratinocyte growth factors (KGF), thymosin- β 4 (T β 4), hepatocyte growth factors (HGF), tumour necrosis factor (TNF), and interleukins (IL).^{13,14}

Injury to corneal epithelium induces cytokine release, essential in epithelial-stromal interaction. IL-1 α is released from wounded epithelium to corneal stroma, provoking underlying stromal keratocytes into apoptosis.¹⁴ IL-1 α influences other stromal keratocytes to secrete matrix metalloproteinase (MMP). MMP has an essential role in cell migration by degrading extracellular matrix and modifying cellular adhesive properties. In addition, MMP also impacts the extracellular matrix microenvironment, thus promoting cell proliferation.^{15,16} Corneal epithelial also produced TGF- β 2 due to the absence of a basement membrane. TGF- β 2 encourages the transformation of keratocytes into myfibroblasts which could secrete extracellular matrix. Other cytokines and growth factors also promote corneal wound healing. Restoration of the basement membrane further disables secretion of TGF- β 2 to the corneal stroma, which reduces myfibroblast regeneration. However, activated keratocytes continue to secrete IL-1 α for extracellular matrix remodelling.¹⁶

There were various cases of TGF- β 1 overexpression in corneal ulceration which could worsen the progression of wound healing.^{17,18} TGF- β 1 is severely overexpressed in corneal injury, which induces myfibroblast proliferation in corneal tissue. In addition, TGF- β 1 accounts for the excessive infiltration of monocytes, neutrophils, and macrophages as their chemotactic factor.¹⁹ This phenomenon will induce more corneal epithelium inflammation, slowing healing. TGF- β 1 also accounted for improving the expression of MMPs, especially MMP-9. MMP-9, unlike any other MMPs, has different traits which are more harmful

than beneficial to corneal tissue. MMP-9 induced basement membrane degradation, resulting in pathologic ulcer and corneal stroma perforation. In addition, prolonged basement membrane exposure could provoke more inflammation due to continuous expression of TGF- β as long as the basement membrane is exposed.^{19,20} TGF- β 1 also provokes over-expression of NF- κ B, which initially plays a role as a mediator of angiogenesis. Excessive NF- κ B expression contributes to pathologic neovascularization, which results in a hazy cornea. Therefore, corneal alkali burn, which becomes pathologic, could be explained by excessive proliferation of myfibroblast and neovascularization, thus resulting in more opaque corneal than physiologically healed corneal wounds.²¹

TOPICAL MEDROXYPROGESTERONE ACETATE 1 % & DOXYCYCLINE ROLE IN CORNEAL RECOVERY

Applying topical medroxyprogesterone acetate 1 % and doxycycline reduced inflammation of corneal alkali burn and enhanced corneal re-epithelization and recovery. One study showed that topical medroxyprogesterone acetate inhibited the expression of MMP. In addition, medroxyprogesterone acetate also inhibited phosphorylation of p38 MAPK, which IL-1 β induced.²² Therefore, significantly less collagen degradation by corneal fibroblasts was noted in the intervention group. Other studies observed that medroxyprogesterone acetate also reduced the expression of various MMP subtypes such as MMP-1, -2, -3, and -9 in multiple cells such as the human uterine stromal cells of the endometrium and many other types of cells. Reduced IL-1 β synthesis reduces collagen degradation by corneal fibroblast and reduces expression and activation of MMP, resulting in a balance of collagen content in the corneal stroma.²³ IL-1 β also proven to increase the synthesis of NF- κ B, which highly accounted for signalling corneal fibroblast formation and creating hazy cornea conditions after recovery.²⁴ Another study on rabbit cornea performed by Gross *et al.* showed that topical medroxyprogesterone administration inhibited vascularization, tumor growth,

and collagen lysis in the cornea, thus improving clinical outcome and wound healing cornea after the disintegration of corneal tissue.⁴ A study by Gong *et al.* on human endometrial adenocarcinoma cells showed that medroxyprogesterone administration reduces the expression of TGF- α and - β .²⁵ Study on a mouse with mammary adenocarcinomas showed that medroxyprogesterone administration lower TGF expression, especially TGF- β 1 which is responsible for excessive inflammation and neovascularization of corneal wound due to alkali burn.^{24,25}

Different to medroxyprogesterone, the application of topical doxycycline towards corneal alkali burn was studied more. There were several pieces of evidence of topical doxycycline benefits towards corneal healing in alkali burn-induced mice. A study by Bian *et al.* showed that doxycycline decreased IL-1 β , IL-6, MMP-8, and MMP-9 two days after administration.²⁶ This finding was supported further by Yi *et al.*, who, in a study, stated that there was a lower expression of MMP-9, α -SMA, and NF- κ B expression after three and seven days after topical doxycycline administration. The same study also mentioned an increase of TGF- β 1 after three, seven, and fourteen days after a trial in the control group.²⁷ Study by Khosdhel *et al.* showed a reduction of mRNA level of angiogenic factors in the doxycycline trial group. The same study also found reduced superoxide dismutase (SOD) activity, TNF- α , and Rel- α gene expression in the doxycycline trial group.²⁸

Doxycycline has several properties which mainly aim to improve corneal wound healing by reducing neovascularization and inflammatory process after disintegration towards the cornea, including corneal alkali burn. Doxycycline reduced IL-1 β expression, which explained the reduction of NF- κ B, which is highly involved in fibroblast formation and neovascularization which impact corneal wound healing.²⁴ In addition, doxycycline reduced the expression of TGF- β 1, which accounted for inflammatory reactions, excessive proliferation, and production of MMP-9, which could degrade the corneal basement membrane.^{29,30-33} These effects are observed in corneal alkali burns and

other occasions. Study by Mc Elvanney found that doxycycline administration was proven effective in stabilizing corneal rupture and reducing the possibility of perforation in pseudomonas keratitis infections.³⁴ Study by Wang *et al.* found that doxycycline and corticosteroids prevent the worsening of corneal erosion in patients, which was observed by 71% of asymptomatic patients after treatment.³⁰ Another study showed that doxycycline could improve the outcome of allograft survival after being conducted in mice with corneal alkali trauma.³⁵ Peng *et al.* showed that doxycycline prevented choroidal neovascularization in laser-injured mice. Another study also stated that doxycycline prevented neovascularization and inflammation of the corneal bed.^{35,36}

FURTHER PROSPECTS AND RECOMMENDATIONS

Topical medroxyprogesterone acetate 1 % and doxycycline have promising prospects in corneal alkali burn management. Those alternatives work in inhibiting expressions of TGF- β and MMP-9, which are most responsible for excessive inflammation, neovascularization, and fibrosis, which could worsen wound healing. In addition, those medications inhibit various cytokines and chemokines such as interleukin, NF- κ B, and many others. Therefore, these alternatives could be considered to be developed as a treatment for corneal alkali trauma.

However, evidence of medroxyprogesterone effectiveness has not been explicitly found in corneal alkali trauma. In addition, proof of doxycycline effectiveness has been explicitly found, but only in mice, and yet to be found in humans. Therefore, clinical evidence of clinical trials is still a long way to go. We recommend that clinical trials on doxycycline and/or medroxyprogesterone should be continued in other phases; thus, better and more substantial evidence could be collected in order to be applied in humans.

CONCLUSION

Topical Medroxyprogesterone acetate 1 % and doxycycline are potential treatments for corneal alkali burn, which intervene

with TGF- β and MMP-9 to reduce inflammation, neovascularization, and fibrosis to improve clinical outcomes. Further studies should be conducted involving human subjects to provide better and more substantial evidence on this field of study.

AUTHOR CONTRIBUTION

AJ responsible for the concept of the study, design of the study, literature search, statistical and data analysis, manuscript preparation, and manuscript review. LA responsible for the concept of the study, literature search, and manuscript review. RL responsible for the concept of the study and manuscript preparation. IZ responsible for design of the study and manuscript editing. R responsible for analysis of the data. CA responsible for the concept of the study.

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CONFLICT OF INTEREST

There is no conflict of interest for this manuscript.

ETHICAL CONSIDERATION

Not applicable.

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