INTRODUCTION

Alkali ocular injury is defined as trauma toward eye integrity caused by alkali burn. Alkali injury is a serious condition that requires immediate treatment. It could cause permanent damages such as corneal scarring and blindness even though it is immediately treated. Various efforts were made to restore corneal clarity, such as corneal transplantation. However, the long-term result has not been satisfying up to date. Alkali corneal injury was more prevalent than acid ocular injury. A study in The United States from 2010 to 2013 showed that there was 144,149 chemical ocular injury throughout the period with median age of 32 years old and 56.6% male. The study found that alkali injuries were more prevalent than acid injuries (53.6% vs 46.4%).

Alkali ocular injury causes disintegration of the cornea by changes in pH level, proteolysis, ulceration, and impairment of collagen synthesis. Doxycycline was found to alter the remodeling of human conjunctival and skin fibroblasts. Doxycycline also reduced collagenolytic degradation of the cornea due to chemical injury by inhibiting matrix metalloprotease (MMP) activity, including in other non-infectious corneal ulcers. This study aimed to determine the efficacy and safety of topical doxycycline to manage corneal alkali burns. A systematic review was conducted in adherence to the PRISMA statement.

Method: Searching was conducted in five databases and inclusion and exclusion criteria were applied afterwards. Three studies were found, considered good, and eligible for inclusion after appraisal using SYRCLE critical appraisal tools for animal studies. All studies used mice models.

Result: We found a significant reduction of IL-1β, IL-6, MMP-8, MMP-9, α-SMA, and NF-κB by doxycycline usage starting from two days of usage. In addition, mRNA angiogenic factors and corneal neovascularization decreased after doxycycline usage. This contributes to better corneal repair after trauma, reflected by better corneal healing and opacity scores after doxycycline usage compared to other groups.

Conclusion: Doxycycline management improved outcomes for patients with corneal alkali burn by decreasing inflammatory cytokine and promoting tissue repair.

Keywords: alkali, burn, chemical, cornea, doxycycline.
Table 1. Keywords being used for literature searching

<table>
<thead>
<tr>
<th>Database</th>
<th>Keywords</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td>(“Doxycycline”[Mesh]) AND (“Corneal Injuries”[Mesh])</td>
</tr>
<tr>
<td>Wiley Online</td>
<td>“doxycycline” AND (“alkali” OR “base”) AND (“cornea” OR “ocular” OR “eye”)</td>
</tr>
<tr>
<td>ProQuest</td>
<td>“doxycycline” AND (“alkali” OR “base”) AND (“cornea” OR “ocular” OR “eye”)</td>
</tr>
<tr>
<td>Cochrane Library</td>
<td>“doxycycline” AND (“alkali” OR “base”) AND (“cornea” OR “ocular” OR “eye”)</td>
</tr>
<tr>
<td>Science Direct</td>
<td>“doxycycline” AND (“alkali” OR “base”) AND (“cornea” OR “ocular” OR “eye”)</td>
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</table>

Doxycycline is a semisynthetic tetracycline antibiotic that serves as a broad-spectrum antibiotic. It was found in the early 1960s and has been used in various cases, such as pulmonary fibrosis, chronic periodontitis, and nasal polyps.\(^\text{12-15}\) Doxycycline was also found to alter the remodeling of human conjunctival and skin fibroblasts.\(^\text{16,17}\) In addition to the cornea, doxycycline negatively affected corneal scar production by inhibiting neovascularization and inflammatory cell infiltration.\(^\text{18,19}\) Doxycycline was also found to reduce collagenolytic degradation of the cornea due to chemical injury by inhibiting matrix metalloprotease (MMP) activity, including in other noninfectious corneal ulcers.\(^\text{20}\) However, there was still not enough evidence of the effect of doxycycline on corneal injury caused by alkali burns. In addition, even though more practical and have fewer side effects, topical doxycycline research is still new compared to systemic doxycycline for alkali corneal burn. Therefore, we conducted this study to find the relationship between topical doxycycline administration and corneal healing after corneal alkali injury. The findings of this study were expected to help clinicians and researchers provide care to patients and conduct further research on this field of study.

METHODS

We conducted a systematic review based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.\(^\text{21}\) We determined the population of corneal alkali burns injury, the intervention of topical doxycycline, control of other medication (double-armed) or none (single-armed), and outcome of efficacy and safety. Searching was conducted on PubMed, Wiley Online, ProQuest, Cochrane Library, and Science Direct using keywords described in Table 1.

Studies found will be assessed for eligibility for inclusion using criteria. Authors set inclusion criteria as follows: (1) clinical trial on human/animal model;
(2) studying population of corneal trauma; (3) studying topical doxycycline as intervention; (4) studying efficacy and/or safety as an outcome. In addition, the authors decided to exclude studies that met these criteria: (1) involving a population with co-occurrence of other trauma (e.g., acid trauma, physical trauma); (2) inaccessible studies; (3) studies written not in English.

Selected studies will be included and appraised using Newcastle-Ottawa Scale for critical appraisal of the human model and the SYRCLE risk of bias tool for animal model. Studies will be grouped into good, fair, or poor quality studies. Included studies will be extracted for study characteristics, including authors, year, location, study design, aim, sample size, sample characteristics, and study outcomes. In addition, studies will be qualitatively analyzed for study outcomes to synthesize information about the objective of this study. To control bias, all of these processes (searching, selection, inclusion, appraisal, extraction, analysis) were conducted by XX independent reviewers (AA, BB, CC), with all discrepancies met throughout the processes discussed to achieve final decisions.

**RESULTS**

We found three studies after thorough searching and inclusion (Figure 1). All studies involved animal models, which were done in mice models.

All studies were appraised using SYRCLE critical appraisal tools and considered eligible after thorough appraisal and evaluation (Table 2). There was one study whose full paper could not be retrieved (Khoshdel et al.). However, information acquired from the abstract was sufficient to be extracted in this study. All studies were conducted in Asia with various comparators but involving doxycycline. It was noted that there were various changes in cytokines in all studies. Studies by Bian et al. and Yi et al. found that there was a decrease in MMP-9 after the use of doxycycline for two and three days, respectively. In addition, the study by Bian et al. noted a decrease in IL-1β, IL-6, and MMP-9 after two days of administration. Khoshdel et al. showed decreased TNF-α and Rel- α activity after 7 and 28 days on both NAC and NAC + doxycycline groups. In addition, the same study found less expression of angiogenic factors and corneal neovascularization levels in the doxycycline combination arm. All thorough results and study characteristics can be seen in Table 3.

**DISCUSSIONS**

Fully integrated corneal keratocytes are transparent due to their stationary status. However, corneal injury disrupts the integrity of the cornea and transforms keratocytes into myofibroblasts. Corneal myofibroblast mainly consists of overexpressed α-SMA. Various cytokines and growth factors play roles in corneal healing after alkali trauma. Among them, TGF-β1 plays the most important role as it alters tissue regeneration. TGF-β1 is severely upregulated after injury to induce the transformation of keratocytes into myofibroblasts, impacting corneal recovery. TGF-β1 is accounted as a potent chemotactic factor for various cells such as monocytes, neutrophils, and macrophages. TGF-β1 also stimulates MMP-9 expression in corneal tissue. NF-κB contributed to compete with TGF-β1 to take control of MMPs expression. MMP-9 contributed to the degradation of the cornea’s basement membrane, which could promote pathologic ulcer and perforation of the corneal stroma. While NF-κB is accounted for angiogenesis mediator, contributing to the cornea's transparency
Table 3. Study characteristics and results

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Location</th>
<th>Aim</th>
<th>Sample</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcome</th>
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| Bian et al.   | 2015 | China    | Investigate the efficacy of dexamethasone and doxycycline in controlling inflammation and MMP production in a combined model of alkali burn associated with dry eye | Female C57BL/6 mice aged 6-8 weeks                                      | 2 ul dexamethasone 0.1% | Naïve   | - Dexamethasone decreased IL-1β, IL-6, MMP-8, -9, -13, and TIMP-1 after 2 days (p<0.05)  
|               |      |          |                                                                      | 2 ul doxycycline 0.025%                                               |              |         | - Dexamethasone increased MMP-8 after 2 days (p<0.05)                   |
|               |      |          |                                                                      | Balanced salt solution                                                |              |         | - Neutrophil infiltration and myeloperoxidase activity were increased in the control group post injury |
| Yi et al.     | 2019 | China    | Evaluate the wound healing effect of doxycycline and its underlying mechanisms in a mice model of corneal alkali burn | Mice                                                                  | Ig/L doxycycline eye drops | Naïve   | - Better corneal healing and opacity scores in the doxycycline group compared to the control group (p<0.05)  
|               |      |          |                                                                      |                                                                        |              |         | - Increase of TGF-β1 at 3, 7, and 14 days after treatment in the control group (p<0.05)  
|               |      |          |                                                                      |                                                                        |              |         | - Lower MMP-9, alpha-SMA, and NF-κB expression at 3 and 7 days after treatment in the doxycycline group (p<0.05)  
| Khoshdel et al. | 2022 | Iran     | Analyze the single and combined effects of NAC and doxycycline on the inflammatory and angiogenic factors in mice model of the alkali-burned cornea | Mice                                                                  | 0.5% NAC + 12.5 ug/mL doxycycline eye drops | 0.5% NAC | - Increased SOD enzyme activity on day 28 in both groups (p<0.05)  
|               |      |          |                                                                      |                                                                        |              |         | - Decrease of TNF-α and Rel-α genes on days 7 and 28 in both groups (p<0.05)  
|               |      |          |                                                                      |                                                                        |              |         | - Decrease of miRNA level of angiogenic factors and corneal neovascularization level on intervention arm (p<0.05)  |

Abbreviations: NAC = n-acetyl cysteine, IL = interleukin, MMP = matrix metalloproteinase, TIMP = tissue inhibitor of metalloproteinase, TGF = transforming growth factor, SMA = smooth muscle actin, NF = nuclear factor, SOD = superoxide dismutase
MMP-9 could also alter the process of corneal wound healing. MMP-9 is accounted for angiogenesis and wound healing of various ocular trauma. MMP-9 is found in the injured cornea but not in the healthy cornea. MMP-9 was also identified in the population with alkali burns. According to a study, MMP-9 was proven to induce basal epithelial cell migration, thus intervening in subepithelial basement membrane region remodeling. Therefore, disruption towards MMP-9 and TGF-β1 expression by doxycycline in patients with corneal alkali burn and suppression of other immunomodulatory cytokines/chemokines could benefit wound healing and clinical outcomes. All three reports did not show any side effects of doxycycline, which also stated its safety to be used on all animal models.

This study was initiated to assess the effectiveness of doxycycline in the population with alkali corneal burns. The findings of this study could be used as a hallmark to advance studies involving human subjects. As the animal model limited this study, we recommend further studies to involve human populations with corneal alkali burn to make better and stronger findings, thus research in this field would be relevant.

CONCLUSION

Topical doxycycline was proven effective in the mice population's corneal wound healing after alkali burn by suppressing immunomodulatory cytokines and/or chemokines, especially TGF-β1 and MMP-9. These findings should be used as the foundation to advance the human population to provide better evidence and level of study.

CONFLICT OF INTEREST

There have been no competing interests regarding this manuscript.

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The authors declared that no financial support or funding was obtained for this study.

ETHICAL STATEMENT

This manuscript has followed the Committee on Publication Ethics (COPE) and International Committee of Medical Journal Editors (ICMJE) guidelines regarding publication ethics.

AUTHOR CONTRIBUTION

All authors contribute to the design, intelligent content description, literature quest, data collection, data processing, manuscript writing, manuscript editing, and manuscript review. The corresponding author is the guarantor and constructs the concept of the manuscript.

REFERENCES


