Blepharitis is an inflammatory disorder of eyelids affecting all the age and ethnic groups probably because of poor hygienic condition. To find the prevalence of blepharitis, a lot of surveys have been conducted among school going children in India (Table 1) 1, 2-7. Blepharitis is common among different ocular morbidity and prevailing unhygienic conditions. Apart from poor hygienic conditions microbial infection, clogged meibomian gland, dandruff, eyelash mite and allergy are some of the major causes of this disease 8. Blepharitis mainly starts with poor hygiene, allergy or meibomian gland dysfunctioning followed by blockage of meibomian gland and decreased production of meibom 8-10. Different causes of blepharitis have been summarized as schematic representation in the figure 1.

Classification and diagnosis

Based upon anatomic location, blepharitis classified as anterior, posterior and mixed type blepharitis. In anterior blepharitis, Inflammation occurs on the base of eyelashes and follicles and it is characterized by redness in lid margin, superficial discomfort, eyelid ulceration, crusting around lashes, blurred vision, light sensitivity, stickiness of eyelidsin morningete 1, 8. In posterior blepharitis meibomian gland dysfunctioning happens and it is characterized by decreased meibom secretions...
with foamy tears, chalazia, eyelid scarring, corneal scarring, corneal neovascularization, corneal ulceration, marginal infiltration and pannus. Red swollen eyelids, burning sensations, ocular irritation, loss of eyelashes and misdirected eyelashes are common symptoms of Blepharitis. 

Techniques used to diagnose blepharitis are slit lamp examination and tear film stability test by using manual keratometry, placidokeratometry precorneal tear film interferometry. Confocal microscopy is the modern technique to diagnose presence of inflammatory cells. 

**Treatment and management**

Blepharitis is a common recalcitrant condition; complete recovery from this condition is not possible. The synthetic methods for treatment are not adequate. Topical antibiotics and warm compress is as a first line therapy. Among different antibiotics, macrolides are preferred in the treatment of blepharitis, because along with antibacterial effect it reduces inflammation as well. Long term therapy creates resistance. 

Topical steroids are using in chronic conditions of blepharitis to reduce inflammation, but it can use for less duration due to its complications like increased intraocular pressure. Oral antibiotics are preferred in chronic conditions. Calcineurin inhibitors are immunomodulatory agents given as topical, which also reduces the inflammation. 

They creates side effects like mild and transient ocular irritation and burning sensation. Omega 3 fatty acids are the supportive therapy in blepharitis to improve functioning of meibomian glands. Eyelid cleansing, warm compress and eyelid scrub are preferred to reduce some complications by removing the meibom clogging and removes microbes. 

Calcineurin inhibitors are immunomodulatory agents given as topical, which also reduces the inflammation. They creates side effects like mild and transient ocular irritation and burning sensation. 

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A detailed account on HCTs with synthetic drugs has been presented in the Table 2.

In past few decades some review articles published on treatment and management of blepharitis. 

![Diagram of Causes of Blepharitis]

**Table 1. Blepharitis survey reports of different places in India**

<table>
<thead>
<tr>
<th>Area of survey</th>
<th>No of subjects included in survey &amp; their age range</th>
<th>Percentage of population affected</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern India</td>
<td>633 (6-17yrs)</td>
<td>5.05%</td>
<td>[2]</td>
</tr>
<tr>
<td>Assam</td>
<td>208 (6-15 yrs)</td>
<td>2.38%</td>
<td>[3]</td>
</tr>
<tr>
<td>Thiruvananthapuram, Kerala</td>
<td>3130 (9-15 yrs)</td>
<td>0.3%</td>
<td>[4]</td>
</tr>
<tr>
<td>Ernakulam, Kerala</td>
<td>1100 (8-12 yrs)</td>
<td>3.81%</td>
<td>[5]</td>
</tr>
<tr>
<td>Kolar, South India</td>
<td>2680 (6-16 yrs)</td>
<td>3.64%</td>
<td>[6]</td>
</tr>
<tr>
<td>Uttar Pradesh</td>
<td>110 (3-12 yrs)</td>
<td>15.45%</td>
<td>[7]</td>
</tr>
</tbody>
</table>
blepharitis. Christopher (2016) and Katherine et al. (2015) discussed about synthetic drugs used for blepharitis, but didn’t include any treatment using natural products 1-8. Stephen et al. (2014) discussed about human clinical trials (HCTs) conducted with synthetic formulations for treatment of blepharitis, they also didn’t include any HCTs for drugs from natural origin10. In this review we have summarized the HCTs with synthetic drugs in conventional dosage forms, synthetic drugs in novel drug delivery systems and formulations from natural origin for the management of blepharitis (Table 3).

**DISCUSSION**

In synthetic therapy eye drops of antibiotics alone or in combination with steroids are given for the management of blepharitis. Azithromycin, erythromycin, norfloxacin, tobramycin, moxifloxacin, doxycycline and minocycline are the most commonly used antibiotics. These are recommended for the short term applications because of development of antibiotic resistance, steroid induced intra ocular pressure raise and other complications as listed in the Table 2. Novel drug delivery systems and formulations with natural origin are reported to be more effective and safe with minimum side effects 31, 32.

Azithromycin, a broad spectrum antibiotic is prescribed in the form of eye drops. In a study reported by Jodi Luchs (2010) azithromycin combined with durasite drug delivery vehicle in Azasite® and this combination contains polycarbophil known to improve the bio adhesiveness of formulation followed by drug penetration to cornea, conjunctiva and eyelids and further improves effectiveness in the treatment of blepharitis 13, 33, 34. Low dose Povidone iodine is very safe and effective antiseptic in ocular tissues. It interacts with cells via poisoning electron transport system, inhibits cellular respiration and

<table>
<thead>
<tr>
<th>Drug Class, Dosage form &amp; ophthalmic application</th>
<th>Dosage</th>
<th>Duration of Treatment</th>
<th>Side effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin 1% &amp; 1.5% (Antibiotic solution)</td>
<td>1 drop, Twice daily/ 1 drop, Once daily</td>
<td>2 days/ 12 days</td>
<td>Eye irritation, blurred vision, dry eyes, stuffy nose.</td>
<td>[10]</td>
</tr>
<tr>
<td>Erythromycin (Antibiotic ointment)</td>
<td>1 drop, Twice daily</td>
<td>2-8 weeks</td>
<td>Stinging, burning, temporary blurred vision, redness.</td>
<td>[9]</td>
</tr>
<tr>
<td>Norfloxacin 0.3% (Antibiotic solution)</td>
<td>2 drops, every 2 hours/ 2 drops, 4 times daily</td>
<td>1 day/ 6 days</td>
<td>Eyelid itching, swelling or crust, tearing, bad taste in mouth, light sensitivity.</td>
<td>[22]</td>
</tr>
<tr>
<td>Tobramycin 0.3% &amp; Dexamethasone 0.1% (Antibiotic &amp; Steroids suspension)</td>
<td>1 drop, every 12 hours</td>
<td>12 weeks</td>
<td>Redness, discomfort, light sensitivity, blurred vision.</td>
<td>[10]</td>
</tr>
<tr>
<td>Tobramycin 0.3% &amp; Loteprednol 0.5% (Antibiotic &amp; Steroids suspension)</td>
<td>1 drop, 4 times, daily</td>
<td>14 days</td>
<td>Increased IOP, lacrimation disorders, photophobia, corneal deposits.</td>
<td>[10]</td>
</tr>
<tr>
<td>Moxifloxacin 0.5% &amp; Dexamethasone 0.1% (Antibiotic &amp; Steroids suspension)</td>
<td>1 drop, 4 times, daily</td>
<td>7 days</td>
<td>Watery eyes, pain, redness, itchiness.</td>
<td>[10]</td>
</tr>
<tr>
<td>Doxycycline 100mg (AntibioticCapsules/Tablet)</td>
<td>Twice daily</td>
<td>8 weeks</td>
<td>Loss of appetite, nausea, vomiting, diarrhoea, sensitivity to sun, adult teeth discolouration, headache.</td>
<td>[23, 24]</td>
</tr>
<tr>
<td>Doxycycline 300mg (AntibioticCapsules/Tablet)</td>
<td>Once daily</td>
<td>3 weeks</td>
<td>Loss of appetite, vomiting, diarrhoea, sensitivity to sun, hives, adult teeth discolouration, headache.</td>
<td>[25]</td>
</tr>
<tr>
<td>Minocycline 50mg (Antibiotic Capsules)</td>
<td>Twice daily</td>
<td>2 months</td>
<td>Stomach upset, dizziness, unsteadiness, drowsiness, swollen tongue, mouth sores.</td>
<td>[26]</td>
</tr>
<tr>
<td>Itraconazole 200mg (Antifungal agent Capsules)</td>
<td>Once daily</td>
<td>7 days</td>
<td>Stomach upset, headache, unpleasant taste, skin rashes, joint/ muscle pain.</td>
<td>[27]</td>
</tr>
<tr>
<td>Cyclosporine 0.05% (Calcineurin inhibitors emulsion)</td>
<td>1 drop, every 12 hour</td>
<td>12 weeks</td>
<td>Discharge, tearing, visual blurring, redness.</td>
<td>[28]</td>
</tr>
<tr>
<td>Tacrolimus 0.03% (Calcineurin inhibitors Ophthalnic ointment)</td>
<td>Twice daily, applying in eyelid margin</td>
<td>28 days</td>
<td>Soreness, eye discomfort, eyelid itching.</td>
<td>[29, 30]</td>
</tr>
</tbody>
</table>
Table 3. Human clinical trials with novel drug delivery systems and formulations of natural origin in treatment of blepharitis

<table>
<thead>
<tr>
<th>Formulation/Method</th>
<th>Type of trial, Preferred dosage and duration of therapy</th>
<th>Major findings</th>
<th>Side effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azasite® (Azithromycin 1% ophthalmic solution in durasite)</td>
<td>Randomised, prospective placebo controlled study in 10 patients. 1-2 drops Once daily for One month</td>
<td>Effective for anterior and posterior blepharitis. Improves drug bioavailability, tissue penetration, sustained delivery</td>
<td>Foreign body sensation, stinging, sticky eye sensation</td>
<td>[13]</td>
</tr>
<tr>
<td>0.25% Povidone iodine and DMSO gel</td>
<td>Retrospective chart review, 17 patients. Twice daily applying in eyelid margin, One week</td>
<td>Effective in treatment of blepharo conjunctivitis and demodex blepharitis</td>
<td>No reported adverse effects</td>
<td>[35-37]</td>
</tr>
<tr>
<td>Tea tree face wash (Terpineol containing face wash)</td>
<td>Retrospective study, 135 patients with demodetic blepharitis. Scrubbing on eyelids and eyelashes, 4 weeks</td>
<td>Essential oil of tea tree oil, 4 Terpineol kills demodex folliculorum. Safe and effective in ocular tissues. Blephapad combo more effective than standard treatment. Useful in patients with blepharitis and meibomian gland dysfunction.</td>
<td>Skin dryness, burning and redness in people with acne. Soreness, itching, redness</td>
<td>[39, 41, 42]</td>
</tr>
<tr>
<td>Blephapad combo. (Wet wipes containing 4 Terpineol, hyaluronic acid and aloe)</td>
<td>Open study without comparator, 18 patients. Place wet wipes, 3-5 mints with slight pressure. Twice daily, 4 weeks</td>
<td>Essential oil of tea tree oil, 4 Terpineol kills demodex folliculorum. Safe and effective in ocular tissues. Blephapad combo more effective than standard treatment. Useful in patients with blepharitis and meibomian gland dysfunction.</td>
<td>Skin dryness, burning and redness in people with acne. Soreness, itching, redness</td>
<td>[39, 41, 42]</td>
</tr>
<tr>
<td>Blephagel® Poloxamer gel based cosmetic cleanser</td>
<td>Open study without comparator, 35 female subject. Eyelid cleansing and massaging twice daily, 21 days</td>
<td>Essential oil of tea tree oil, 4 Terpineol kills demodex folliculorum. Safe and effective in ocular tissues. Blephapad combo more effective than standard treatment. Useful in patients with blepharitis and meibomian gland dysfunction.</td>
<td>Skin dryness, burning and redness in people with acne. Soreness, itching, redness</td>
<td>[39, 41, 42]</td>
</tr>
<tr>
<td>MGO Manuka honey eye cream. (Treated eyes and control eyes were compared in baseline)</td>
<td>Randomised, paired eye investigator-masked trial, 25 healthy human subjects. Applied at night on eyelids, 14 days</td>
<td>Essential oil of tea tree oil, 4 Terpineol kills demodex folliculorum. Safe and effective in ocular tissues. Blephapad combo more effective than standard treatment. Useful in patients with blepharitis and meibomian gland dysfunction.</td>
<td>Skin dryness, burning and redness in people with acne. Soreness, itching, redness</td>
<td>[39, 41, 42]</td>
</tr>
<tr>
<td>Posiformin 2% bibrocathol ointment. (2% bibrocathol Treatment group compared with placebo group)</td>
<td>Multi-center, randomized, double-masked, placebo-controlled parallel-group comparison study, 197 patients. Apply 3 times on eyelids, daily, 2 weeks</td>
<td>Compared to placebo, patients received bibrocathol shows high improvement.</td>
<td>Ocular discomfort</td>
<td>[47]</td>
</tr>
<tr>
<td>Indraductal meibomian gland probing. (Pre-treatment compared with post treatment after 6 months)</td>
<td>Longitudinal study, 16 blepharitis patients. Occluded gland probed with 2 mm maskin cannula.</td>
<td>Targets mainly severe posterior blepharitis patients. Safe and long effective procedure</td>
<td>No worsen symptoms and adverse effects.</td>
<td>[48]</td>
</tr>
</tbody>
</table>
destabilize cell membrane. In two different studies, Povidone iodine has been reported in the form of gel formulation for topical application in the eyelashes and eyelids for demodex blepharitis and blepharo-conjuctivitis without any reported side effects 35-38.

Terpineol is the essential oil from tea tree oil which is very effective against microorganisms causing skin and ocular infection especially against demodex mite, within 4 weeks 39-41. The efficacy of terpineol has been studied in two different formulations of face wash and wet wipes 42. The wet wipes also had hyaluronic acid and aloe, which are very effective anti-inflammatory agent 43. Daily hygiene and use of tea tree face wash or wipes has been found to be very safe and effective in reducing the symptoms of all type of blepharitis44.

Blephagel® is a poloxamer based cosmetic gel for cleansing the eyelid in patients with sensitive skin or eyes or contact lens users. It removes mucus, debris, bacteria from eyelid and hydrates eyelid skin. Blephagel’s soothing effect help to use in periocular region routinely without any adverse effects 45.

Manuka honey has antibacterial and anti-inflammatory effect which helps to treat blepharitis symptoms. From study conducted in blepharitis patients with manuka honey loaded microemulsion eye cream found to be more safe and tolerable in periocular area without any adverse effects 46. Bibrocathol (4,5,6,7-Tetrabromo-1,3,2-benzodioxabismol-2-ol) is a topical antiseptic available as 2 or 5 % eye ointment with liquid paraffin, white soft paraffin, and lanolin. According to Pavel et al (2012), the ointment found to be safe and well tolerable in patients with blepharitis 47.

Fermon et al (2015) conducted HCT to treat meibomian gland dysfunctioning by intra-ductal meibomian gland probing using 2 mm cannula under biomicroscopy. Meibomian gland dysfunction is a major problem in severe posterior blepharitis. Long term relief is possible by single treatment itself 48.

CONCLUSION

Blepharitis is an inflammatory disorder of eyelids and manly observed in school going children with poor hygienic conditions. If remained unattended, this infection may lead to keratopathy, permanent eyelid morphology change, and corneal neovascularization. Topical antibiotics, steroids and calcineurin inhibitors are the recommended first line therapy but their safety and duration of treatment is largely unknown. When compared with synthetic agents, formulations developed with natural ingredients were found to be equally effective with minimum side effects for treatment of blepharitis.

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Conflicts of interest

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REFERENCES

8. Katherine D, Bennie HJ. Medical management of
30. Rahul B, Prachi K. Comparison of the safety and efficacy of topical Tacrolimus (0.03%) versus dexamethasone (0.05%) for subepithelial infiltrates after adenoviral conjunctivitis. Indian Journal of Ophthalmology; 67: 594-598 (2019).


