

## Blepharitis: A Review on Human Clinical Trials with Synthetic and Natural Remedies

Vyshma Kizhupully Viswambaran, Anavadhya K. A.,  
Gopika Chandrababu, Amritha Babu, Gayatri Rajeev and Swati Gupta\*

Amrita School of Pharmacy, Amrita Institute of Medical Sciences,  
Amrita Vishwa Vidyapeetham, AIMS-Ponekkara PO, Kochi, Kerala -682041, India.

\*Corresponding Author E-mail: [swatigupta@aims.amrita.edu](mailto:swatigupta@aims.amrita.edu)

<https://dx.doi.org/10.13005/bpj/2072>

(Received: 10 September 2020; accepted: 07 December 2020)

**Blepharitis is an eyelid disorder characterized by inflammation and pain. It affects all the ages and ethnic groups. Primary cause of blepharitis is poor hygienic condition. Topical antibiotics are the preferred first line therapeutic agents along with eyelid cleansing and warm compresses are recommended. Topical steroids, oral antibiotics and calcineurin inhibitors are also recommended in severe conditions. However, recurrence of disease, dose related side effects and safety regimen are still uncertain with these agents. Blepharitis needs a long term treatment, thus novel formulations and products with natural components may be considered more reliable to overcome such issues. In this review article we have discussed human clinical trials (HCTs) conducted with conventional synthetic drugs, novel drug delivery systems developed with synthetic drugs and drugs of natural origin and other supportive measures. As compared to synthetic drugs, formulations with natural origin were found to be safe with minimum side effects.**

**Keywords:** Blepharitis; Synthetic drugs; Novel drug delivery systems; Natural drugs; Clinical trials.

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) <sup>1, 2-7</sup>. 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 <sup>8</sup>. Blepharitis mainly starts with poor hygiene, allergy or meibomian gland dysfunctioning followed by blockage of meibomian gland and decreased

production of meibom <sup>8-10</sup>. 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 eyelids in morning etc <sup>1,8</sup>. 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 <sup>1, 8</sup>.

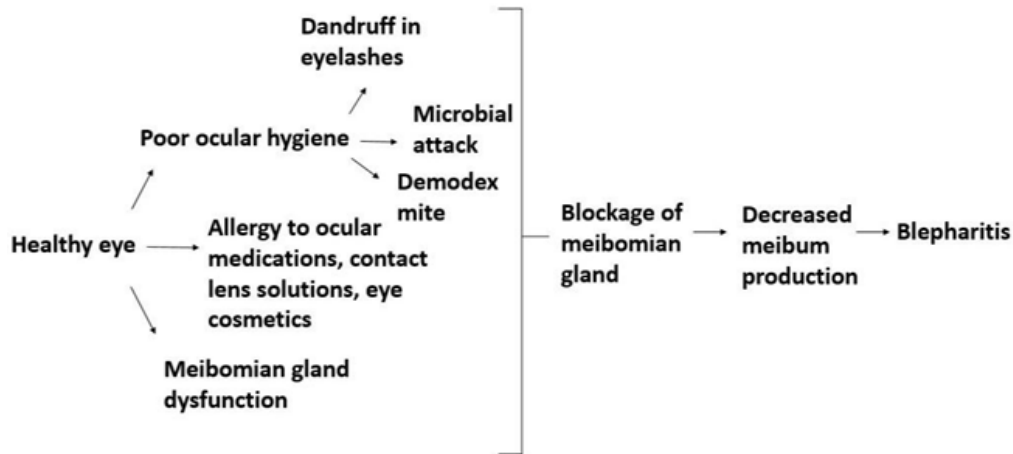
Techniques used to diagnose blepharitis are slit lamp examination and tear film stability test by using manual keratometry, placidokeratometry precorneal tear film interferometry <sup>1</sup>. Confocal microscopy is the modern technique to diagnose presence of inflammatory cells <sup>10, 11</sup>.

**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 <sup>12</sup>. 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 <sup>13</sup> Long term therapy creates resistance <sup>14</sup> 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 <sup>15</sup> Oral antibiotics are preferred in chronic conditions <sup>16</sup> Calcineurin inhibitors are immunomodulatory agents given as topical, which also reduces the inflammation <sup>1, 8, 9</sup> They creates side effects like mild and transient ocular irritation and burning sensation <sup>17, 18</sup> Omega 3 fatty acids are the supportive therapy in blepharitis to improve functioning of meibomian glands <sup>19, 20</sup> Eyelid cleansing, warm compress and eyelid scrub are preferred to reduce some complications by removing the meibom clogging and removes microbes <sup>12, 21</sup>. A detailed account on HCTs with synthetic drugs has been presented in the Table 2 <sup>22-30</sup>.

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



**Fig. 1.** Causes of blepharitis

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

Area of survey	No of subjects included in survey & their age range	Percentage of population affected	Reference
Eastern India	633 (6-17yrs)	5.05%	[2]
Assam	208 (6-15 yrs)	2.38%	[3]
Thiruvananthapuram, Kerala	3130 (9-15 yrs)	0.3%	[4]
Ernakulam, Kerala	1100 (8-12 yrs)	3.81%	[5]
Kolar, South India	2680 (6-16 yrs)	3.64%	[6]
Uttar Pradesh	110 (3-12 yrs)	15.45%	[7]

blepharitis. Christopher (2016) and Katherine *et al.* (2015) discussed about synthetic drugs used for blepharitis, but didn't include any treatment using natural products<sup>1,8</sup>. 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 origin<sup>10</sup>. 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<sup>31,32</sup>.

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<sup>®</sup> 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<sup>13, 33, 34</sup>. 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 2.** Synthetic drugs used for the management of blepharitis

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

**Table 3.** Human clinical trials with novel drug delivery systems and formulations of natural origin in treatment of blepharitis

Formulation/Method	Type of trial, Preferred dosage and duration of therapy	Major findings	Side effects	Reference
Aziasite®(Azithromycin 1% ophthalmic solution in durasite) and DMSO gel	Randomised, prospective placebo controlled study in 10 patients. 1-2 drops Once daily for One month Retrospective chart review, 17 patients. Twice daily applying in eyelid margin, One week	Effective for anterior and posterior blepharitis. Improves drug bioavailability, tissue penetration, sustained delivery Effective in treatment of blepharo conjunctivitis and demodex blepharitis	Foreign body sensation, stinging, sticky eye sensation No reported adverse effects	[13] [35-37]
Tea tree face wash (Terpineol containing face wash) Blephapad combo. (Wet wipes containing 4 Terpineol, hyaluronic acid and aloe) Blephagel @Poloxamer gel based cosmetic cleanser. MGO Manuka honey eye cream. (Treated eyes and control eyes were compared in baseline)	Retrospective study, 135 patients with demodectic blepharitis. Scrubbing on eyelids and eyelashes, 4 weeks Open label, randomised controlled studies, 18 patients. Place wet wipes, 3-5 mints with slight pressure. Twice daily, 4 weeks Open study without comparator, 33 female subject Eyelid cleansing and massaging twice daily, 21 days Randomised, paired eye investigator-masked trial, 25 healthy human subjects. Applied at night on eyelids, 14 days	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. Effective and acceptable for routine use to patients with blepharitis and sensitive eyes. Manuka honey cream is a natural antibacterial and anti-inflammatory agent. Safe to use in blepharitis patients	Skin dryness, burning and redness in people with acne. Soreness, itching, redness Prickling, watering eyes	[39, 41, 42] [44] [45]
Posiformin 2% eye ointment. (2% bibrocathol Treatment group compared with placebo group) Intraductal meibomian gland probing (Pre-treatment compared with post treatment after 6 months)	Multi-center, randomized, double-masked, placebo-controlled parallel-group comparison study, 197 patients. Apply 3 times on eyelids, daily, 2 weeks Longitudinal study, 16 blepharitis patients. Occluded gland probed with 2 mm mask in cannula.	Compared to placebo, patients received bibrocathol shows high improvement. Targets mainly severe posterior blepharitis patients. Safe and long effective procedure	Ocular discomfort No worsen symptoms and adverse effects.	[46] [47] [48]

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-conjunctivitis without any reported side effects<sup>35-38</sup>.

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<sup>39-41</sup>. The efficacy of terpineol has been studied in two different formulations of face wash and wet wipes<sup>42</sup>. The wet wipes also had hyaluronic acid and aloe, which are very effective anti-inflammatory agent<sup>43</sup>. 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 blepharitis<sup>44</sup>. Blephagel® is a poloxamer based cosmetic gel for cleansing the eyelid in patients with sensitive skin or eyes or contact lens users. It removes mucous, debris, bacteria from eyelid and hydrates eyelid skin. Blephagel's soothing effect help to use in periorcular region routinely without any adverse effects<sup>45</sup>.

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 periorcular area without any adverse effects<sup>46</sup>. 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<sup>47</sup>.

Fermon *et al* (2015) conducted HCT to treat meibomian gland dysfunctioning by intraductal 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<sup>48</sup>.

## 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.

## ACKNOWLEDGEMENTS

I offer my deepest gratitude towards Amrita School of Pharmacy for their constant guidance and facilities.

### Conflicts of interest

The authors have no conflict of interest.

### Funding Source

Nil

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