Review Article

Chambered warm moist air eyelid warming devices – a review

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ABSTRACT.

Background.
Eyelid warming is an important treatment for meibomian gland dysfunction (MGD). Specialized chambered devices, using warm moist air have been developed.
Purpose.
To critically evaluate the literature on the safety and efficacy of chambered warm moist air devices in MGD treatment and pinpoint areas of future research.
Methods.
PubMed and Embase were searched on 06 June 2021. The search term was '(warm OR heat OR steam OR goggle OR spectacle OR moist air) AND (meibomian OR MGD OR blepharitis OR eyelid OR dry eye OR DED)'. All relevant articles with available English full text were included.
Results.
Eighteen articles assessing the application of chambered warm moist air eyelid warming devices were identified. In single-application studies, steam-based eyelid warming increased the eyelid temperature and improved symptoms, lipid layer thickness, and tear film breakup time (TBUT). In treatment studies, the steam-based devices improved TBUT and

symptom scores. However, in the only randomized controlled trial (RCT) comparing chambered steam-based heat to hot towel treatment, there was no difference between groups for the primary outcome measure; the proportion of subjects noting symptom improvement after 4 weeks.

Conclusion.

Currently available chambered warm moist air eyelid warming devices are safe and effective at raising eyelid temperature to therapeutic levels and improving signs and symptoms of dry eye. However, it is not clear if they provide a greater benefit than other eyelid warming therapies. Further well-conducted RCTs comparing moist and dry heat devices should be conducted on patients across the range of DED severities and subtype spectrum.

Key words: Blephasteam – dry eye disease – eyelid warming devices – meibomian gland dysfunction – warm moist air

Introduction

The tear film is a complex and dynamic protective layer covering the cornea and conjunctiva. The tear film is made up of water, proteins, mucins, vitamins, and fatty acids that all have different roles in maintaining a healthy ocular surface (Willcox et al. 2017). The tear film presents a physical and immunological barrier to the external environment and protects the ocular surface against dehydration and irritation (Akpek & Gottsch 2003; Barabino et al. 2012). Maintaining tear film homeostasis is essential for good visual quality and ocular surface health. Dry eye disease (DED) represents a loss of tear film homeostasis, resulting in symptoms such as dryness, grittiness, and foreign body sensation, as well as damage and inflammation of the ocular surface (Craig et al. 2017). Dry eye disease (DED) causes a substantial reduction in quality of life (Schiffman et al. 2003; Miljanovic et al. 2007; Uchino & Schaumberg 2013), affecting social life (Uchino & Schaumberg 2013), work productivity (Uchino &

Schaumberg 2013; Uchino et al. 2014; McDonald et al. 2016), sleep quality (Magno et al. 2021), and health care costs (Yu et al. 2011; McDonald et al. 2016). Dry eye disease (DED) is a highly prevalent condition, affecting a large proportion of the world's population (Stapleton et al. 2017). The prevalence of DED varies depending on the criteria used and the population studied, but estimates range from 5 to 50% across the globe (Stapleton et al. 2017). Due to its high prevalence, DED was in 2014 estimated to have yearly direct and indirect costs of 55.8 billion USD in the US alone (Yu et al. 2011).

Clinically, it is often valuable to divide DED into two major etiological categories: aqueous-deficient dry eye (ADDE), which is characterized by diminished aqueous tear production from the lacrimal gland and evaporative dry eye (EDE), categorized by increased evaporation from the ocular surface (Bron et al. 2017). Evaporative dry eye (EDE) is considered the most frequent cause of DED, although patients often present with elements of both types (Craig et al. 2017).

Meibomian gland dysfunction (MGD) is likely the primary driver behind EDE in most cases (Stapleton et al. 2017). Despite primarily being associated with EDE, MGD is also prevalent in patients with Sjögren's syndrome, an important cause of ADDE (Sullivan et al. 2018). Meibomian gland dysfunction (MGD) is characterized by reduced meibum quality and quantity and disruption of the meibum's ability to reduce ocular evaporation and stabilize the tear film (Arita, Morishige, et al. 2017; Bron et al. 2017). The tear film's three primary components are (1) the mucins, produced by the conjunctival goblet cells and other secretory cells (Hodges & Dartt 2013), (2) the aqueous tear fluid produced by the lacrimal gland and conjunctiva, and (3) the lipid layer consisting mainly of meibum from the meibomian glands (Cwiklik 2016) (Fig. 1). The meibomian glands, located in the tarsal plates of the eyelids, produce meibum in the secretory acini and guide the meibum through central ducts onto the ocular surface along the eyelid margin (Knop et al. 2011). Meibum secretion is
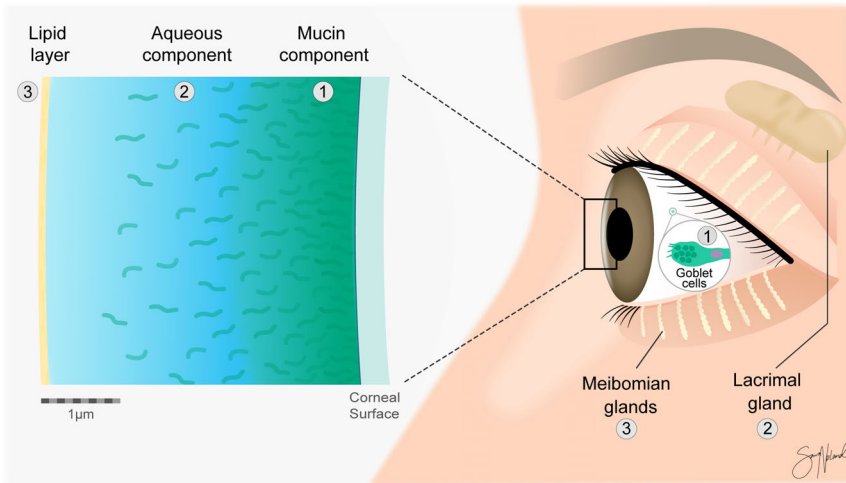
Fig. 1. A cross-section of the pre-corneal tear film. The three main components of the tear film are marked. (1) The mucin produced by the conjunctival goblet cells increases water retention and tear film viscosity. (2) The aqueous component of the mucoaqueous layer is produced by the lacrimal gland and conjunctiva and makes up a majority of tear film volume. (3) The outer lipid layer mainly consists of lipids produced by the meibomian glands and reduces surface tension and ocular evaporation. Copyright, Sara Tellefsen Nøland.

regulated by blinking and the co-ordinated contraction/relaxation of the obicularus oculi muscle and Riolan's muscle that surrounds the orifice of each meibomian duct.

The fluidity of the meibum is essential for efficient draining of the glandular structures and delivery to the ocular surface. Whereas meibum from healthy donors has a phase-transition temperature of around 28°C, meibum from patients with MGD was found to require 32°C to achieve the same fluidity (Borchman et al. 2011). This difference in transition temperature equates to substantially different consistencies of the meibum at physiological temperatures,

where the eyelids often maintain a temperature around 33°C (Butovich et al. 2008). The difference in meibum properties is also seen at higher temperatures. Meibum from subjects with MGD showed similar viscosity at 38.5°C as meibum from healthy donors heated to 36.0°C (Borchman 2019). Eyelid warming treatments are, therefore, a key approach for MGD treatment (Asbell et al. 2011; Jones et al. 2017). By raising the temperature of the eyelids, the viscosity is reduced, and secretion of meibum from the glandular structure becomes easier (Fig. 2). The treatment generally consists of delivering localized heat to the eyelids and
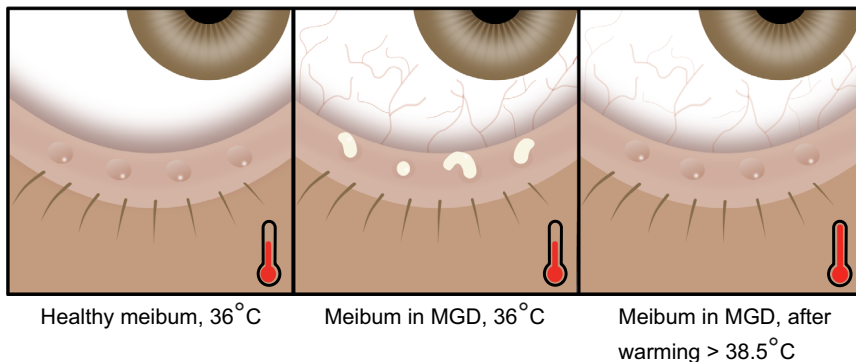
warming and softening the meibum before applying pressure to express the softened meibum.

The least expensive and most accessible eyelid warming strategy consists of applying warm, wet towels over the closed eyelids for 5–10 min, reheating the towel every two minutes to maintain heat (Geerling et al. 2011). When heated to between 40 and 47°C and reheated at least every two minutes, hot towels maintain sustained therapeutic temperatures during the entire treatment period and effectively increase eyelid temperatures (Olson et al. 2003; Blackie et al. 2008, 2013; Murakami et al. 2015). However, if not reheated, hot towels quickly lose heat and drop below adequate levels of heat for eyelid warming (Lacroix et al. 2015; Bitton et al. 2016). Thus, patient education and compliance with treatment are essential for a successful outcome. As a response to this, commercially available options, including eyelid warming masks (Lacroix et al. 2015), warm moist air at-home eyelid warming devices (Doan et al. 2014), and in-office treatment devices (Lane et al. 2012), have been developed.

Access to effective at-home treatments will likely remain key in treating MGD. Thus, ensuring the efficacy, safety, and ease of use of at-home eyelid warming treatments remain essential. This review aimed to critically evaluate the current literature on chambered moist air eyelid warming systems and help clinicians and patients make informed decisions regarding this treatment of MGD.

Methods

PubMed and EMBASE, via Ovid, were searched on 06 June 2021, using the search term '(warm OR heat OR steam OR goggle OR spectacle OR moist air) AND (meibomian OR MGD OR blepharitis OR eyelid OR dry eye OR DED)'. First, all articles were screened for broad relevance to the topic, based on title and abstract. Second review articles, case reports, and articles without English full text were excluded. Third, duplicates in the two searches were removed. Finally, the full text of the resulting articles of interest was then checked against the inclusion criteria. The inclusion criteria were studies evaluating the efficacy and safety of chambered warm moist air

Fig. 2. An idealized representation of the effect of successful eyelid warming. The increased meibum viscosity at lower temperatures seen in patients with meibomian gland dysfunction (MGD) can be mitigated through elevated eyelid temperatures. The left panel illustrates normal meibum, and the middle panel shows the thickened meibum in a patient with MGD, at 36°C. The right panel shows the reduced meibum viscosity observed after successful eyelid warming in the patient with MGD. Copyright, Sara Tellefsen Nøland.

eyelid warming systems for treating MGD or DED. Cool-air moisture devices (Ogawa et al. 2018) and non-chambered heating masks (Arita, Morishige, et al. 2017; Tichenor et al. 2019; Jeon & Park 2021) were not included.

Results

Overview of included studies

The search term '(warm OR heat OR steam OR goggle OR spectacle OR moist air) AND (meibomian OR MGD OR blepharitis OR eyelid OR dry eye OR DED)' yielded 1005 results in PubMed, stretching from March 1964 to May 2021. Based on the title and abstract, 31 articles of interest were further screened in full text. Using EMBASE, 805 entries were returned, with results ranging from 1974 to May 2021. Based on the titles and abstracts, 24 articles of interest were flagged for further assessment. Of these, two did not have English full text and the 22 remaining were all also retrieved in the search using PubMed. After assessing full texts, 18 articles were deemed relevant and included in the review. A depiction of the process can be seen in Fig. 3. The included articles were published between June 2005 and December 2020, describing studies conducted across several different countries such as the United Kingdom (Mitra et al. 2005; Spiteri et al. 2007; Purslow 2013;

Bilkhu et al. 2021), Germany (Pult et al. 2012; Kremers et al. 2020), the United States (Murakami et al. 2015), China (Ren et al. 2018), New Zealand (Turnbull et al. 2018; Wang et al. 2020), Japan (Matsumoto et al. 2006), Singapore (Lam et al. 2014; Sim et al. 2014; Yeo et al. 2016), France (Doan et al. 2014), Italy (Villani et al. 2015), and Europe (Benitez Del Castillo et al. 2014)). In total, eight articles described the results of five prospective trials (Matsumoto et al. 2006; Benitez Del Castillo et al. 2014; Doan et al. 2014; Lam et al. 2014; Sim et al. 2014; Villani et al. 2015; Yeo et al. 2016; Ambaw et al. 2020), while 10 articles described only single application of the device used (Mitra et al. 2005; Spiteri et al. 2007; Pult et al. 2012; Purslow 2013; Murakami et al. 2015; Ren et al. 2018; Turnbull et al. 2018; Kremers et al. 2020; Wang et al. 2020; Bilkhu et al. 2021). One study described both the effects of single application and prolonged use of warm moist air treatment (Matsumoto et al. 2006). Only one RCT assessing treatment response was found, an assessor-masked RCT from the Singapore National Eye Centre with the ClinicalTrials.gov registration number NCT 01448369, first described by Sim et al. (2014). Table 1 presents an overview of the studies assessing the effects of a single application of a chambered warm moist air eyelid warming device while Table 2 highlight

the results of the treatment studies with prolonged follow-up. Studies are arranged by publication year, from oldest to newest in both tables.

Chambered warm moist air eyelid warming devices

The defining feature of a chambered warm moist air eyelid warming device is the use of steam as an indirect carrier of moist heat within an enclosed chamber surrounding the eyelids and ocular surface. This allows the heating elements to not be in direct contact with the skin but use the warm water vapour to distribute heat evenly to all areas of the ocular surface. In the included studies, two different designs for achieving this effect were used. One article described an actively heated, single-chambered device (Matsumoto et al. 2006), while the remainder utilized different goggle designs with either active heating or latent heat profiles (Mitra et al. 2005; Spiteri et al. 2007; Pult et al. 2012; Purslow 2013; Benitez Del Castillo et al. 2014; Doan et al. 2014; Lam et al. 2014; Sim et al. 2014; Murakami et al. 2015; Villani et al. 2015; Yeo et al. 2016; Ren et al. 2018; Turnbull et al. 2018; Kremers et al. 2020; Wang et al. 2020; Bilkhu et al. 2021).

Blephasteam (Théa Pharmaceuticals, Newcastle-under-Lyme, UK) was the only named, commercially available device described in the included articles (Pult et al. 2012; Purslow 2013; Benitez Del Castillo et al. 2014; Doan et al. 2014; Lam et al. 2014; Sim et al. 2014; Murakami et al. 2015; Villani et al. 2015; Yeo et al. 2016; Turnbull et al. 2018; Kremers et al. 2020; Bilkhu et al. 2021), with the remaining studies using unnamed prototypes or research versions of devices (Mitra et al. 2005; Matsumoto et al. 2006; Spiteri et al. 2007; Ren et al. 2018; Wang et al. 2020). Blephasteam is a latent heat device that uses preheated thermal elements to warm moistened ring inserts so that the inside of the goggles reaches 100% humidity and the desired temperature of around 42°C. The goggles must be plugged into a power outlet for 15 minutes before application to allow the thermal elements to reach 50°C (Doan et al. 2014). The goggles are then worn for 10 min, allowing the warm water vapour to provide even heat on the eyelids,

Initial search term:

"(warm OR heat OR steam OR goggles OR "spectacle" OR "moist air")
AND (meibomian OR MGD OR blepharitis OR eyelid OR "dry eye" OR DED)"

PubMed:

Embase via Ovid:

| 1,005 results | 805 results |

Exclusion based on titles and abstracts:

| 31 articles | 24 articles |

Exclusion based on article type and language:

| 27 articles | 22 articles |

Exclusion of duplicates:

| 27 articles |

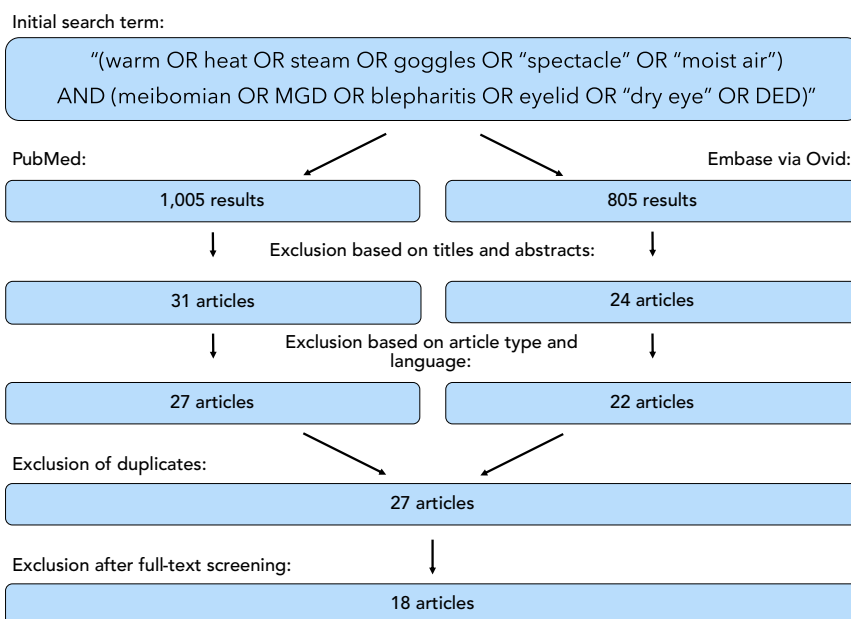Exclusion after full-text screening:

| 18 articles |

Fig. 3. Flow chart of the literature search conducted.

Table 1. Studies assessing short-term effects of single application of device.

First author/ year/country	Masking	Device (other study arms)	Sample study arm (controls)	Outcome
Mitra M 2005 GB (Mitra et al. 2005)	Assessor-masked	Warm moist air device (inactivated device, untreated controls)	Healthy subjects; $n = 8$, per group	6/8 using activated and 1/8 using inactivated device had improved symptom scores, while none of the untreated controls improved. Those using the activated device had improved LLT compared to both other groups.
Matsumoto Y 2006 JP (Matsumoto et al. 2006)*	No	Warm moist air device	MGD; $n = 15$ Healthy subjects; $n = 20$	Eyelid and cornea temperature increased with 1–2°C to around 36°C. VAS, TBUT, and LLT improved after treatment in subjects with MGD. Schirmer test and OSS did not change.
Spiteri A 2007 GB (Spiteri et al. 2007)	Assessor-masked	Blephasteam prototype (untreated controls)	Dry eye without SS; $n = 12$ ($n = 12$) Dry eye with SS; $n = 17$ ($n = 14$)	Symptom score and LLT improved in those with the device. Controls showed no change over time.
Pult H 2012 DE (Pult et al. 2012)	Assessor-masked	Blephasteam (hot towel)	Healthy subjects; $n = 20$ (crossover)	The temperature stayed above 38°C longer than non-reheated towels. VA, hyperemia, and OSS improved with Blephasteam.
Purslow C, 2013 GB (Purslow 2013)	No	Blephasteam	Healthy subjects; $n = 25$	The ocular surface temperature increased from around 35°C to around 38°C. Hyperemia improved. VAS, VA, OSS, TBUT, and IOP were unchanged.
Murakami DK 2015 US (Murakami et al. 2015)	No	Blephasteam (Bundle method, rice bag, MediBeads, Eye-ssential, MGDRx EyeBag, Tranquileyes XR)	Healthy subjects; $n = 5$ (crossover)	The internal lower lids were heated to 38°C, on par with other commercial options, but less than the Bundle method of hot towel application (40°C).
Ren Y 2018 CN (Ren et al. 2018)	No	Warming moist chamber goggles (sodium hyaluronate eyedrops)	VDT-associated dry eye, $n = 22$ (crossover)	VAS, TMH, TBUT, and LLT improved from baseline with Blephasteam. No change in IOP, BRI, or VA. Blephasteam yielded better VAS and TBUT scores at 60 min post-treatment than the eyedrops.
Turnbull PRK 2018 NZ (Turnbull et al. 2018)	Assessor-masked	Blephasteam (TearsAgain, MGDRx Eyebag)	No MG dropout, $n = 6$ ($n = 8$, $n = 7$) Mild MG dropout, $n = 11$ ($n = 8$, $n = 8$) Severe MG dropout, $n = 8$ ($n = 12$, $n = 13$)	TBUT, LLG improved with treatment, no difference between treatments. Greater severity of MG dropout was tied to increased improvement. No change in TMH, corneal temperature variation, or evaporation rates.
Kremers I 2020 DE (Kremers et al. 2020)	No	Blephasteam (hot towel, sauna)	Healthy subjects, $n = 49$ ($n = 41$, $n = 9$) MGD, $n = 44$ ($n = 31$, $n = 5$)	The eyelids were heated to 38°C with Blephasteam, which was higher than towels heated to 40°C and reheated every 2 min, and equivalent to 10 min in an 85°C sauna.
Wang MTM 2020 NZ (Wang et al. 2020)	Double-masked	Research latent heat device at 55°C (45°C, 50°C)	Healthy subjects, $n = 15$ (crossover)	None of the settings heated the eyelid beyond 38°C. LLG and TBUT improved in all groups. TBUT improved more in the 55°C group. VA was unchanged in all groups; no adverse events were reported.
Bilkhu P 2020 GB (Bilkhu et al. 2021)	No	Blephasteam + liposomal spray (no treatment)	Healthy subjects, $n = 40$ (crossover)	SANDE, DLP, LLT, and TMH significantly improved with treatment. No significant change in TBUT, evaporation rates, or blink rate with treatment.

BRI = bulbar redness index, DLP = dynamic tear film lipid layer pattern, IOP = intraocular pressure, LLG = lipid layer grade, LLT = lipid layer thickness, MG = meibomian gland, MGD = Meibomian gland dysfunction, OSS = ocular surface staining, SS = Sjögren's syndrome, TBUT = tear film breakup time, TMH = tear meniscus height, VA = visual acuity, VAS = visual analogue scale, VDT = video display terminal.
* Results of two-week treatment arm of study presented in Table 2.

softening the meibum (Purslow 2013). An illustration of the Blephasteam system is shown in Fig. 4.

Eyelid temperature after application of the device

Four studies evaluated eyelid temperature during or after applying latent heat goggles (Pult et al. 2012; Murakami et al. 2015; Kremers et al. 2020; Wang et al. 2020). A 10-minute application of the standard Blephasteam device, which is preset to warm to 50°C, warmed the outer eyelids to a temperature between 38.1°C and 40.6°C (Pult et al. 2012; Murakami et al. 2015; Kremers et al. 2020) and the internal eyelid surface to 38°C (Murakami et al. 2015). Using a research prototype of Blephasteam with three preset temperature settings, Wang et al. found that warming the latent heat device to 45°C, 50°C, and 55°C increased the outer eyelid temperature to 36.0°C, 36.3°C, and 37.3°C, respectively (Wang et al. 2020).

Changes in objective and subjective measurements

Figure 5 presents an overview of the changes in symptom scores and the

Table 2. Studies including treatment over time.

First author/ year/country	Device (other study arms)	Design	Sample	Protocol	Outcome	Adverse events
Matsumoto Y 2006 JP (Matsumoto et al. 2006)*	Warm moist air device (hot towels)	Prospective, open-label, controlled	MGD; $n = 10$, per group	10 min, twice daily, 2 w	VAS and LLT improved in both groups, TBUT increased in the warm moist air device group only. No change in OSS in either group.	ND
Benitez del Castillo JM 2014 BE, DE, NL, PL, ES, CH, GB (Benitez Del Castillo et al. 2014)	Blephasteam	Single-group prospective	MGD; $n = 73$	10 min, twice daily, 3 w	VAS and hyperemia improved. Sch. I, TBUT, and tear film osmolarity unchanged.	VA and IOP were unchanged. No adverse events were reported.
Sim HS 2014 SG (Sim et al. 2014)	Blephasteam (hot towels, EyeGiene)	Assessor-masked RCT	MGD; $n = 24$ ($n = 24$, $n = 17$)	10 min, twice daily, 3 mo	No difference between groups after 1 month. A greater proportion had symptom improvement after 3 mo of Blephasteam treatment than after hot towels. No difference between the groups for the number of clogged MGs, TBUT, meibum viscosity, or Sch. I at any timepoint.	VA unchanged after 3 mo.
Lam SM 2014 SG (Lam et al. 2014)	Blephasteam (hot towels, EyeGiene)	A subsample of Sim 2014	MGD; $n = 10$ ($n = 10$, $n = 12$)	10 min, twice daily, 3 mo	No difference between Blephasteam, hot towel, and EyeGiene treatment in any clinical parameter. Eyelid warming reduced lysophospholipid and changed PUFA-containing phospholipid expression when groups were pooled.	ND
Doan S 2014 FR (Doan et al. 2014)	Blephasteam	Single-group prospective	MGD; $n = 96$	10 min, twice daily, 3 w	VAS, hyperemia, and meibum quality improved. TBUT, osmolarity, and Sch. I did not change.	No change in VA or IOP. No adverse events were observed.
Villani E 2015 IT (Villani et al. 2015)	Blephasteam	Single-group prospective	MGD, not responding to WC; $n = 18$	10 min, twice daily, 3 w	OSDI and TBUT improved. OSS and meibum quality did not change.	No adverse events were observed.
Yeo S 2016 SG (Yeo et al. 2016)	Blephasteam (hot towels, Lipiflow, EyeGiene)	A supplemental study to Sim 2014	MGD; $n = 22$ ($n = 22$, $n = 24$, $n = 22$)	10 min, twice daily, 3 mo	Tear film evaporation rates did not change with Blephasteam treatment. No difference between groups.	ND

IOP = intraocular pressure; LLT = lipid layer thickness; MG = meibomian glands; MGD = meibomian gland dysfunction; mo = months; ND = not described; OSDI = ocular surface disease index; PUFA = polyunsaturated fatty acids; RCT = randomized controlled trial; SANDE = symptom assessment in dry eye; Sch. I = Schirmer test; TBUT = tear film breakup time; VA = visual acuity; VAS = visual analogue scale; w = weeks; WC = warm compresses.
* Results of short-term efficacy and safety of single-application of device is presented in Table 1.

most commonly measured objective parameter, tear film breakup time (TBUT), at baseline and follow-up, for those receiving chambered warm moist air eyelid warming devices in the studies presenting these values.

Results of single-application studies
In the single-application studies, ocular comfort or symptoms were measured in six studies (Mitra et al. 2005; Matsumoto et al. 2006; Spiteri et al. 2007; Purslow 2013; Ren et al. 2018; Bilkhu et al. 2021). Symptoms, as measured by the symptom assessment in dry eye (SANDE) questionnaire (Bilkhu et al. 2021), visual analogue scale (VAS) (Matsumoto et al. 2006; Ren et al. 2018), or not specified symptom scores (Mitra et al. 2005; Spiteri et al. 2007), improved in five of these studies (Mitra et al. 2005; Matsumoto et al. 2006; Spiteri et al. 2007; Ren et al. 2018; Bilkhu et al. 2021). One study found no change in VAS score in 25 healthy subjects (Purslow 2013). The symptom scores at baseline and follow-up are presented in Fig. 5A, for the studies including these values (Matsumoto et al. 2006; Purslow 2013; Ren et al. 2018; Bilkhu et al. 2021).

Several different objective measures were reported in the single-application studies. Tear film breakup time (TBUT) was found to improve in four (Matsumoto et al. 2006; Ren et al. 2018; Turnbull et al. 2018; Wang et al. 2020) of the six studies assessing it (Matsumoto et al. 2006; Purslow 2013; Ren et al. 2018; Turnbull et al. 2018; Wang et al. 2020; Bilkhu et al. 2021). The five studies presenting pre- and post-treatment TBUT values are presented in Fig. 5C (Matsumoto et al. 2006; Purslow 2013; Ren et al. 2018; Wang et al. 2020; Bilkhu et al. 2021). The results did not appear to be affected by whether TBUT was measured non-invasively (Purslow 2013; Ren et al. 2018; Wang et al. 2020; Bilkhu et al. 2021) or by fluorescein-based TBUT assessment (Matsumoto et al.
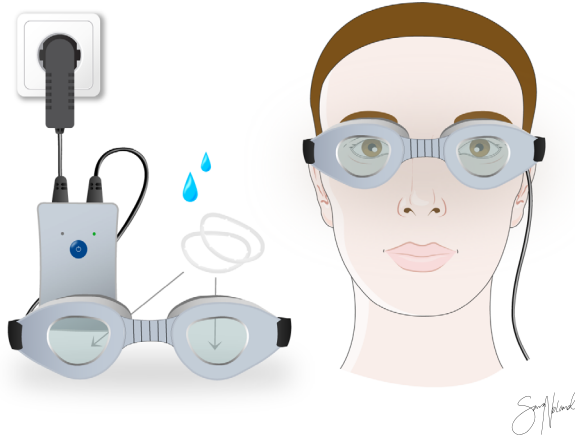
Fig. 4. The Blephasteam system is preheated for 15 min before inserting the moist rings, and the device is worn. Standard use is a twice daily 10-min application of the device. Copyright, Sara Tellefsen Nøland.

2006). Lipid layer thickness (Mitra et al. 2005; Matsumoto et al. 2006; Spiteri et al. 2007; Ren et al. 2018; Bilkhu et al. 2021), lipid layer grade (Turnbull et al. 2018; Wang et al. 2020), and lipid layer patterns (Bilkhu et al. 2021) improved in all single-application studies that included these measurements. Three studies assessed ocular surface staining (OSS), and all three found improvement with treatment (Matsumoto et al. 2006; Pult et al. 2012; Purslow 2013). Visual acuity was evaluated in four studies (Pult et al. 2012; Purslow 2013; Ren et al. 2018; Wang et al. 2020), three of which found no change with treatment (Purslow 2013; Ren et al. 2018; Wang et al. 2020), and one study found an improvement from baseline (Pult et al. 2012). Two studies found tear meniscus height to improve (Ren et al. 2018; Bilkhu et al. 2021), while another found no change (Turnbull et al. 2018) with treatment. Intraocular pressure (Purslow 2013; Ren et al. 2018) and tear evaporation rates (Turnbull et al. 2018; Bilkhu et al. 2021) were not affected by treatment.

Results of treatment studies
Symptoms were assessed in all five populations enrolled in studies with follow-ups (Matsumoto et al. 2006; Benitez Del Castillo et al. 2014; Doan et al. 2014; Sim et al. 2014; Villani et al. 2015). One study found improvement in the ocular surface disease index (OSDI) in subjects not responding to the initial warm compress treatment after three weeks of subsequent Blephasteam treatment (Villani et al. 2015). All three studies using VAS noted improvement in symptoms after

treatment (Matsumoto et al. 2006; Benitez Del Castillo et al. 2014; Doan et al. 2014). One study using SANDE, which includes a VAS score for both symptom frequency and severity, found that around 80% of participants had improved both frequency and severity of dry eye symptoms after Blephasteam treatment (Sim et al. 2014). Mean symptom scores at baseline and follow-up are presented in Fig. 5B for the studies including these values (Matsumoto et al. 2006; Benitez Del Castillo et al. 2014; Doan et al. 2014; Villani et al. 2015).

In studies with follow-up, TBUT was most frequently reported among the clinical parameters (Matsumoto et al. 2006; Benitez Del Castillo et al. 2014; Doan et al. 2014; Sim et al. 2014; Villani et al. 2015). Two studies found improvement in TBUT with treatment (Matsumoto et al. 2006; Villani et al. 2015), while the remaining three did not note change from baseline (Benitez Del Castillo et al. 2014; Doan et al. 2014; Sim et al. 2014). Fig. 5D shows the mean TBUT values at baseline and follow-up from the articles that included these values (Matsumoto et al. 2006; Benitez Del Castillo et al. 2014; Doan et al. 2014; Villani et al. 2015). Ocular hyperemia improved in both studies in which it was assessed (Benitez Del Castillo et al. 2014; Doan et al. 2014). Lipid layer thickness improved in the one study measuring this (Matsumoto et al. 2006). The meibum's lipid composition changed with treatment, with a decrease in lysophospholipids and an increase in polyunsaturated fatty acid (PUFA)-containing phospholipids (Lam et al.

2014). However, meibomian gland function scores showed inconclusive results. Meibum quality score improved in one study (Doan et al. 2014), but not in the other study that assessed this (Villani et al. 2015). Meibomian gland score did not change in the only article that included this measure (Sim et al. 2014). Ocular surface staining (OSS) (Matsumoto et al. 2006; Villani et al. 2015), Schirmer test values (Benitez Del Castillo et al. 2014; Doan et al. 2014; Sim et al. 2014), visual acuity (Benitez Del Castillo et al. 2014; Doan et al. 2014; Sim et al. 2014), intraocular pressure (Benitez Del Castillo et al. 2014; Doan et al. 2014), tear film osmolarity (Benitez Del Castillo et al. 2014; Doan et al. 2014), and tear film evaporation rates (Yeo et al. 2016) were unchanged from baseline with treatment in all studies assessing these parameters.

Results compared to other treatments in treatment trials
Two of the populations followed over time were compared to control groups receiving other treatments (Matsumoto et al. 2006; Sim et al. 2014). One was a two-week open-label study comparing an unnamed warm moist air device against hot towel treatment (Matsumoto et al. 2006). The other was a three-month assessor-masked randomized controlled trial (RCT) comparing Blephasteam to hot towels and Eye-Giene (Eyedetec Medical Inc., Danville, CA, USA) treatment (Sim et al. 2014).

Although no direct statistical comparison between the two groups in the first study was conducted, the warm moist air device showed a numerically greater improvement in VAS score than hot towels (Matsumoto et al. 2006). The VAS scale for ocular tiredness changed from 34 to 82, for dryness from 32 to 80, and for discomfort from 23 to 82, in those receiving warm moist air treatment, where increasing score indicated improvement. Similar numbers for hot towel treatment were from 46 to 60, from 36 to 61, and from 44 to 66. Only those receiving treatment with the warm moist air device had a significantly improved TBUT after two weeks. Tear film breakup time (TBUT) changed from 4.7 to 8.6 in the treatment group and from 4.0 to 4.7 in those receiving hot towels (Matsumoto et al. 2006).

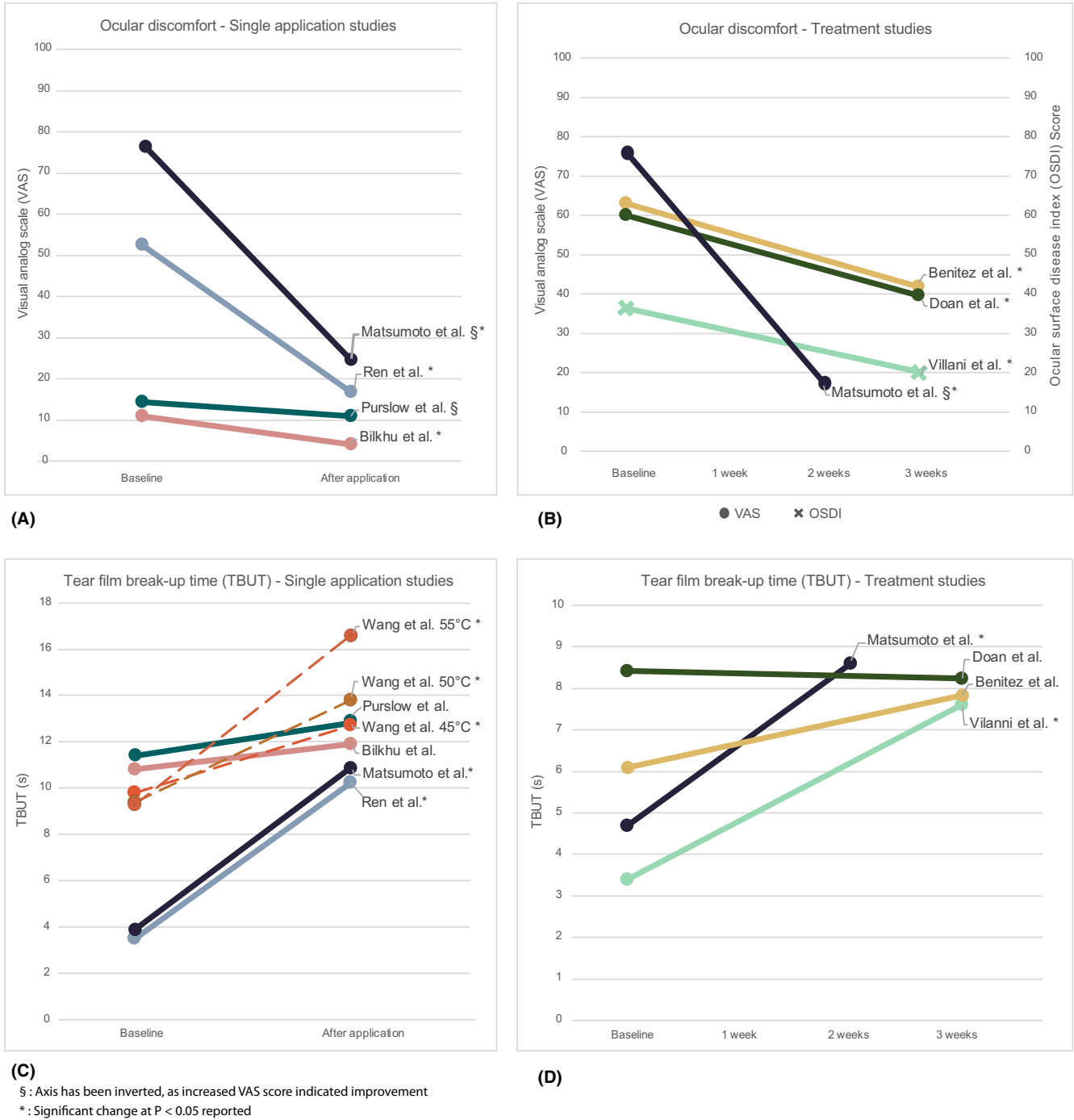The only RCT assessing Blephasteam treatment (NCT 01448369),

(A)

(B)

● VAS ✖ OSDI

(C)

(D)

§ : Axis has been inverted, as increased VAS score indicated improvement
* : Significant change at P < 0.05 reported

Fig. 5. Change in symptom scores and tear film breakup time (TBUT) reported in the studies providing numerical values at baseline and follow-up. (A) Change in symptoms after a single application of device (Matsumoto et al. 2006; Purslow 2013; Ren et al. 2018; Bilkhu et al. 2021). (B) Change in symptoms after sustained use of the device (Matsumoto et al. 2006; Benitez Del Castillo et al. 2014; Doan et al. 2014; Villani et al. 2015). (C) Change in TBUT after a single application of device (Matsumoto et al. 2006; Purslow 2013; Ren et al. 2018; Wang et al. 2020; Bilkhu et al. 2021). All three temperatures used in Wang et al. are presented (dashed lines) (Wang et al. 2020). (D) Change in TBUT after sustained use of the device (Matsumoto et al. 2006; Benitez Del Castillo et al. 2014; Doan et al. 2014; Villani et al. 2015).

first described by Sim et al. (Sim et al. 2014), found no significant difference between groups in the predefined efficacy outcome, which was the proportion of subjects noting improvement in frequency and severity of VAS eye discomfort at the four-week follow-up. However, at the additional three-month follow-up, a significantly higher proportion of those receiving Blephasteam treatment ($\approx 80\%$) had improved scores than those receiving hot towel treatment ($\approx 50\%$) (Sim et al. 2014). In the EyeGiene group, $\approx 40\%$ of participants noted improved scores, however, this group was significantly different from the hot towel group at baseline, possibly due to high level of dropout. Eight of the 25 subjects enrolled dropped out partially due to the inability to activate the warming units, reducing the effective sample size below the calculated minimun sample size of 22 per group. No statistical

comparison was made between Eye-Giene and Blephasteam. Of note, there were significant differences between the three groups at baseline (p = 0.0008), relative change in symptoms scores were not presented in the study, and what constituted a clinically relevant improvement in symptom score was not described (Sim et al. 2014).

In a 32 participant subsample from the same RCT (NCT 01448369), Lam et al. noted no appreciable difference between the three groups in VAS symptom score, the number of blocked meibomian glands, Schirmer score, TBUT, or OSS score after three months of treatment (Lam et al. 2014). They, therefore, deemed the treatments equivalent and subsequently pooled the groups for tear fluid lipidome analysis before and after routine eyelid warming treatments. Interestingly, in the subsample, the group receiving Blephasteam treatment showed the lowest mean improvement in symptom score from baseline to 12 weeks. Blephasteam treatment yielded a mean VAS score improvement of 0.40 for ocular discomfort, compared to 3.85 in those receiving hot towel treatment and 9.70 for the EyeGiene group (Lam et al. 2014). The difference between those receiving Blephasteam and EyeGiene was not significant (p = 0.06). When the three groups were pooled, the authors noted a reduction in lysophospholipids and numerous PUFA-containing diacylglyceride species and increased expression of PUFA-containing phospholipids (Lam et al. 2014).

Using the same inclusion criteria as in the initial study (NCT 01448369), the researchers later assessed LipiFlow (Johnson & Johnson Vision, Jacksonville, FL, USA) treatment in 25 participants in the same clinic (NCT 01683318), first described in Zhao et al. (Zhao et al. 2016). Tear evaporation rates were then assessed in the groups receiving Blephasteam, LipiFlow, hot towel, or EyeGiene treatment from either trial in a 2016 article (Yeo et al. 2016). The authors found no difference in ocular evaporation rates after Blephasteam treatment, or between any of the four groups after four or twelve weeks of treatment (Yeo et al. 2016). Only those receiving LipiFlow, and the pooled population of all four groups noted a significant improvement in evaporation rates (Yeo et al. 2016). When adjusting for baseline differences,

there was no difference between the four groups in the likelihood that the treatment would decrease the evaporation rate from above to below the mean of the total population at baseline (66 W/min) in a logistic regression model (Yeo et al. 2016).

Lastly, 37 participants from both the initial RCT (NCT 01448369) and the later trial assessing LipiFlow alone (NCT 01683318) were assessed for changes in lipid mediators after treatment (Ambaw et al. 2020). The authors noted no appreciable differences between the pooled group of the three eyelid warming modalities and those receiving LipiFlow (Ambaw et al. 2020). The authors further pooled the results for all four groups. They concluded that heat-based MGD therapy decreased expression of pro-inflammatory mediators produced by lipoxygenase and oxidative stress (Ambaw et al. 2020).

Discussion

Chambered warm moist air heat devices have been shown safe and effective in both short- and long-term studies (Tables 1 and 2). Steam-based latent heat devices increased eyelid temperatures and improved tear film parameters without adverse effects in the single-application studies (Table 1). In the treatment studies, symptoms consistently improved with 2-weeks to 3-months of treatment, while improvement in clinical signs varied between studies (Table 2). The only RCT with follow-up conducted found that treatment with a chambered steam-based device (Blephasteam) was more likely to provide relief of symptoms than hot towels after three months of treatment (Sim et al. 2014). However, no difference between groups was noted at the four-week follow-up (the main outcome variable) and the magnitude of this improvement was not shown.

The ability of an eyelid heating device to provide sustained heat to the eyelids without adverse effects, such as thermal burns, is essential. Based on the results in the single-application studies, Blephasteam appeared to effectively heat the eyelids to therapeutic levels (38–40°C) (Pult et al. 2012; Murakami et al. 2015; Kremers et al. 2020) while remaining comfortable to use (Spiteri et al. 2007; Ren et al. 2018; Bilkhu et al. 2021). In a recent study of

the ex-vivo thermochemical properties of meibum, 41.5°C was found to likely be the optimal temperature for softening the meibum from patients with MGD (Borchman 2019). However, already at 38.5°C, the fluidity of the meibum was shown to be similar to that of healthy donors at baseline (36°C) (Borchman 2019). This is supported by the findings in the single-application studies that noted improvement in lipid layer thickness (Mitra et al. 2005; Matsumoto et al. 2006; Ren et al. 2018; Bilkhu et al. 2021), indicating an increased expression of meibum after application.

The benefits of applying wet or dry heat have been debated, with studies reaching differing conclusions (Arita et al. 2015; Murakami et al. 2015). The evaporation of remaining moisture after wet heat treatment could accelerate cooling after cessation of application (Arita et al. 2015). Kremers et al. found external eyelid temperatures to fall rapidly after Blephasteam treatment, from around 38°C immediately after application to roughly baseline temperature (≈35°C) only two minutes later (Kremers et al. 2020). The fall in temperature after applying hot towels replaced at least every two minutes or after having a sauna was more gradual. Based on these findings, it is plausible that the eyelids could lose heat more rapidly after warm moist air eyelid warming treatments than after application dry heat, affecting ensuring eyelid hygiene routines if these are to be performed. However, more research is needed to explore differences between modalities and possible clinical implications.

The direct effect of the initial temperature of latent heat devices has been assessed (Wang et al. 2020). A research prototype of Blephasteam improved TBUT in participants with minimal-to-mild dry eye symptoms significantly more when the device was preheated to 55°C than 50°C or 45°C, without observed adverse effects. The commercially available Blephasteam device currently only has a single heat-setting, which is 50°C (Wang et al. 2020). Increasing this to 55°C could thus potentially benefit patients using this device. However, further studies into the safety and efficacy of increased baseline temperature on patient with more severe MGD are needed to confirm the findings.

Several benefits of steam treatment were noted in both the single-application and treatment studies when assessing those receiving Blephasteam or other chambered steam-based eyelid warming devices. When assessing participants with MGD, symptom scores and TBUT improved in all single-application studies that assessed these measures (Matsumoto et al. 2006; Spiteri et al. 2007; Ren et al. 2018; Turnbull et al. 2018). Similarly, symptoms significantly improved with steam treatment in all prospective studies reporting this (Matsumoto et al. 2006; Benitez Del Castillo et al. 2014; Doan et al. 2014; Villani et al. 2015) (Fig. 5B). Additionally, when assessed alongside a control group receiving hot towel treatment, only Blephasteam was found to improve TBUT significantly (Matsumoto et al. 2006). However, only one RCT with follow-up has been conducted (Sim et al. 2014). Furthermore, a possible benefit with the Blephasteam device not found with other eyemasks is the ability to blink freely, promoting the natural excretion of meibum, and the option to read or watch videos during treatment (Doan et al. 2014).

The only prospective RCT conducted to date had several methodological shortcomings that weaken the conclusions drawn. There was a significant difference in symptom severity scores across the three groups at baseline (p = 0.0008), with lower VAS scores in the EyeGiene group (23.6) than the groups receiving hot towels (52.8) and Blephasteam (41.4) (Sim et al. 2014). The main outcome measure was the proportion of participants noting improvement in severity and frequency of symptom on a VAS scale in each group after four weeks, the predefined study duration (NCT 01448369). However, the authors did not define what qualified as a clinically relevant improvement or report the mean change in symptom score per group (Sim et al. 2014). This is important to note, as the researchers found no difference in mean change in symptom score between the groups in an article describing a subsample from the same study population (Lam et al. 2014). In fact, in the subsample of 32 participants, the group receiving Blephasteam seemed to have the lowest mean symptom improvement of the three groups, on the borderline of

being significantly different from the EyeGiene group (p = 0.06). The supplemental material further described that in the Blephasteam group, only 1/10 noted an improvement of more than five units on the VAS scale for ocular discomfort, and 2/10 on the summed global score. Similar numbers for the hot towel group were 3/10 and 3/10 and for the EyeGiene group 7/12 and 6/12 respectively (Lam et al. 2014).

To assess what constitutes a clinically relevant change, the 'minimal clinically important difference' is a valuable tool (Jaeschke et al. 1989). This measure describes the smallest change in a relevant score that would, barring adverse side-effects, warrant a change in a patient's clinical treatment. There is no consensus-based minimal clinically important difference for SANDE or other VAS scores for dry eye discomfort. For the OSDI score, which also stretches from 0 to 100, the minimal clinically relevant difference has been reported to range from 7.0 to 9.9 units across all OSDI categories (Miller et al. 2010). When assessing the initial repeatability and validity of the SANDE questionnaire, 50% of answers on the VAS scale varied more than 10 units when the same participant was reassessed by mail a few days after being assessed in the clinic (Schaumberg et al. 2007). Additionally, in general, pain management literature, the minimal clinically relevant difference in VAS pain scales from 0 to 100 ranged from 8 to 40 units for acute pain (Olsen et al. 2017) with a median of 23 units across 50 studies assessing chronic pain (Olsen et al. 2018). Based on this, changes smaller than 10 units on a VAS scale from 0 to 100 for ocular discomfort are unlikely to constitute clinically relevant improvement.

Overall, the results of both the single-application and treatment studies indicate that chambered warm moist air eyelid warming devices appear to be safe and effective at increasing eyelid temperature and improving dry eye signs and symptoms. However, due to shortcomings of the only prospective RCT conducted and the absence of statistical comparison between Blephasteam and EyeGiene (Sim et al. 2014), it is still unclear if chambered warm moist air eyelid warming devices provide additional benefits over other eyelid warming treatments.

A well-conducted RCT directly comparing chambered warm moist air eyelid warming to other at-home treatments, such as eye masks and hot towels, is needed to determine if steam-based heating provides any additional benefits. As dropout proved to be a challenge in the only RCT conducted, future studies should consider this by enrolling a larger initial sample size. Additionally, assessment of compliance with different treatments would provide useful information, as high preferential dropout rates could be indicative of generally low compliance in one or more groups. Furthermore, direct statistical comparison across all included treatment modalities should be conducted to avoid potential bias. Additionally, no study with a follow-up period longer than 12 weeks has been undertaken, thus, the long-term effects of prolonged habitual chambered warm moist air eyelid warming on the ocular environment are unknown. As MGD is a chronic condition and life-long treatment is often required, a study assessing benefits and adverse effects and compliance of prolonged steam-based treatment (at least 12–24 months) would provide useful information. Moreover, there is limited information about patient preferences for different eyelid warming modalities. Future comparative studies should assess patient preferences regarding effectiveness, costs, and ease of use of chambered warm moist air treatment and other modalities. Furthermore, the long-term effects of increasing the temperature of such devices by several degrees, both in terms of their safety and efficacy, should be explored in future studies.

A limitation of this review is the exclusion of any article without available English full text. However, this was a necessary step in ensuring a thorough assessment of all included studies, and critical evaluation of the findings. Additionally, due to the lack of prospective controlled trials, it was not possible to conduct a meta-analysis of the data, which could have provided useful insights.

Conclusion

Chambered warm moist air eyelid warming devices, such as Blephasteam, provide sustained heat and improve signs and symptoms of DED. The

approach appears to be a safe and an effective form of treatment for MGD. However, it is not clear if steam-based eyelid warming provides any benefits over other, more accessible treatments, and there is a need for larger, well-conducted RCTs directly comparing chambered warm moist air treatments to eyelid warming using hot towels and commercially available eyelid warming masks.

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