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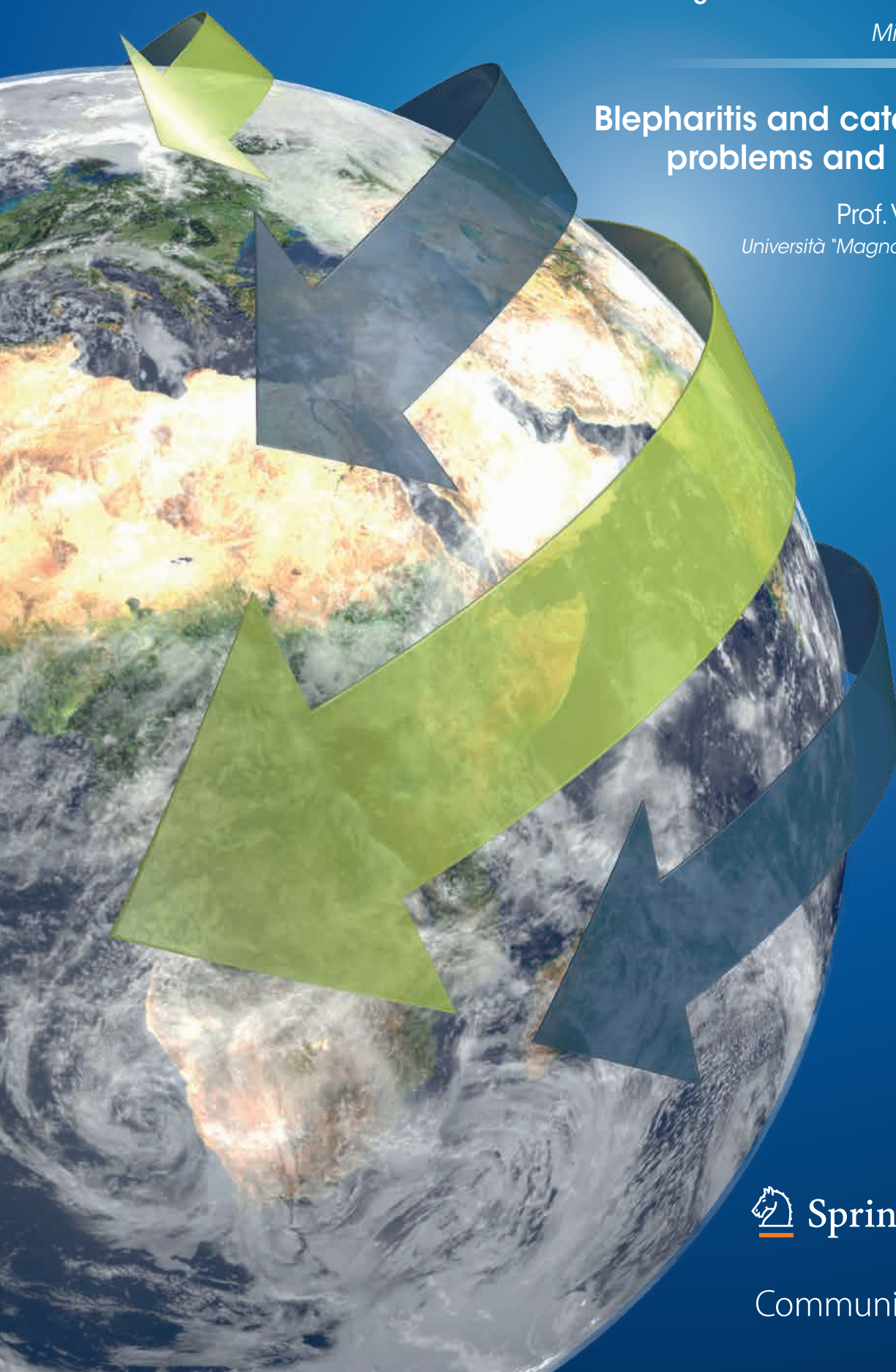
CONFERENCE INSIGHT

16th International Congress of the Società Oftalmologica Italiana (SOI)
23rd Annual Meeting on Cataract and Refractive Surgery

Milan, 16-19 May 2018

Blepharitis and cataract surgery: problems and new solutions

Prof. Vincenzo Scorcìa
Università "Magna Graecia" di Catanzaro



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Blepharitis and cataract surgery: problems and new solutions

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Introduction

Blepharitis is a much more prevalent ophthalmological condition than usually appreciated. In fact, blepharitis is the most common condition diagnosed in patients seeking medical eye examination because of eye discomfort or irritation. Blepharitis is typically characterized by inflammation and thickening of the eyelid margins, presence of eyelid crusts and a foamy tear film, the latter due to fatty acid saponification. Meibomian blepharitis also causes or greatly exacerbates most cases of dry eye and the two conditions are often comorbid. The concurrent presence of blepharitis along with dry eye aggravates significantly the patient's discomfort.

Acknowledging and diagnosing blepharitis is also critical in the context of cataract surgery. A prospective multicenter observational study on 100 patients (mean age 72.4) showed that blepharitis was present in up to 60% of patients undergoing phacoemulsification for cataract treatment^[1]. Nevertheless, blepharitis in cataract patients is still frequently overlooked. Assessing the presence and severity of blepharitis in the pre-operative phase, possibly by means of severity scores associated with both symptoms and clinical signs of meibomian gland dysfunction, has several important implications for both pre-operative measurements and post-operative outcomes of cataract surgery. It is necessary, first and foremost, to guarantee an accurate pre-operative keratometry or topography analysis. The presence of a dry-eye condition, without a stable tear film, can in fact lead to inaccurate keratometry, possibly causing errors in the IOL that propagate as post-operative refractive errors. It is thus paramount to assess precisely the stability of the tear film. The degree of ocular surface fluorescein staining and tear break-up time should also be used to gauge the stability of the tear film on the eye surface and, consequently, the degree of function of the meibomian glands.

Moreover, taking blepharitis into account may help to minimize the risk of post-operative intraocular infection. It is well established that most intraocular infections are actually caused by the patient's own ocular flora^[2].

The species involved include saprophytic bacteria often involved in blepharitis and living on the eye surface, such as *Staphylococcus epidermidis*, *Pseudomonas* sp., *Staphylococcus aureus* or *Propionibacterium* sp. During the surgical procedure these bacteria can be brought within the eye. Eliminating these bacteria is therefore necessary to reduce the risk of endophthalmitis.

Finally, the treatment of blepharitis is required to alleviate post-operative discomfort. Some post-operative discomfort is unavoidably experienced by patients, even following a flawless ocular surgical procedure. This is due to eye surface alterations caused by the epithelial erosion resulting from operative eye exposure, light toxicity, eye drops and neurotrophic alterations of the surgical corneal cut. If, in addition, any previous alteration due to meibomian gland dysfunction is left untreated, major discomfort is almost certain. The involvement and increase of inflammatory factors due to blepharitis can further compromise visual acuity.

Currently, the standard therapy for blepharitis^[3] involves a combination of:

- warm compresses and eyelid hygiene
- antibiotics, both oral tetracycline class antibiotics and topical antibiotics
- topical corticosteroids.

The strength of evidence supporting these interventions, however, is rather modest (rating IIIA).

Moreover, posterior blepharitis is often difficult to manage. Since the treatment of blepharitis is recommended even in mild cases, as chronic inflammation may cause permanent damage to the meibomian glands, improving and extending the therapeutic options for blepharitis is a topic of great medical interest.

Rationale

Here we report the design and outcome of BLEPHA 01-2017 (NCT03301844), a recent clinical trial assessing the efficacy, safety, compliance and patient satisfaction of a novel eyelid cleansing treatment in patients affected by bilateral posterior blepharitis. The trial was completed in our center in early 2018. The BLEPHA 01-2017 study compared the standard wet warm gauze treatment with Blephapad Combo (*Figure 1*). Blephapad Combo is a combination product integrating hygienic wet wipes containing Hy-Ter[®] solution (sodium hyaluronate and terpinen-4-ol) with a heatable pad capable of releasing heat in a controlled manner. The Blephapad Combo heatable tablet has the unique feature of changing color when its temperature exceeds 43°C. This visual mark allows patients to gauge, in a simple and straightforward manner, the right temperature for treatment. In contrast, when the practitioner generally prescribes a “warm compress”, the patient is often left to guess what the optimal temperature would be.

The Hy-Ter wipes included in Blephapad Combo are enriched with the active ingredient terpinen-4-ol. Terpinen-4-ol is a monocyclic terpene alcohol with several properties of ophthalmologic interest: it is a powerful antibacterial and acaricidal and also displays anti-inflammatory activity, suppressing the production of several inflammatory mediator molecules such as TNF- α , IL-1 β , IL-8, IL-10 and PGE-2^[4,5].

Study design

BLEPHA 01-2017 was an open label, randomized, controlled study with a closed sequential design.

The main objective of BLEPHA 01-2017 was to compare the efficacy of two treatments in improving meibomian gland dysfunction. During the study, each patient applied Blephapad Combo to one eye and the standard treatment to the other eye, in accordance with the randomization procedure, twice daily for four weeks.

With the aim of assessing the pathology as objectively as possible, a score composed of six grading scales was used. Each individual scale takes into account a different measure of meibomian gland functionality:

- 1) Lid margin findings of vascularity (score 0-3): score depending on the presence and severity of hyperemia and telangiectasia.
- 2) Plugging of gland orifices (score 0-3): score depending on the amount of plugged meibomian gland openings.
- 3) Lid margin irregularity (score 0-2): Eyelid margin irregularity and notching are typical findings in eyelid inflammation. Score depending on the amount of notching.
- 4) Lid margin thickening (score 0-2): As above, margin thickening is a typical eyelid tissue response to inflammatory stimuli. Score depending on the amount of thickening.
- 5) Partial glands (score 0-3): The presence of partial glands is a sign of meibomian gland stenosis. In this study, the glands

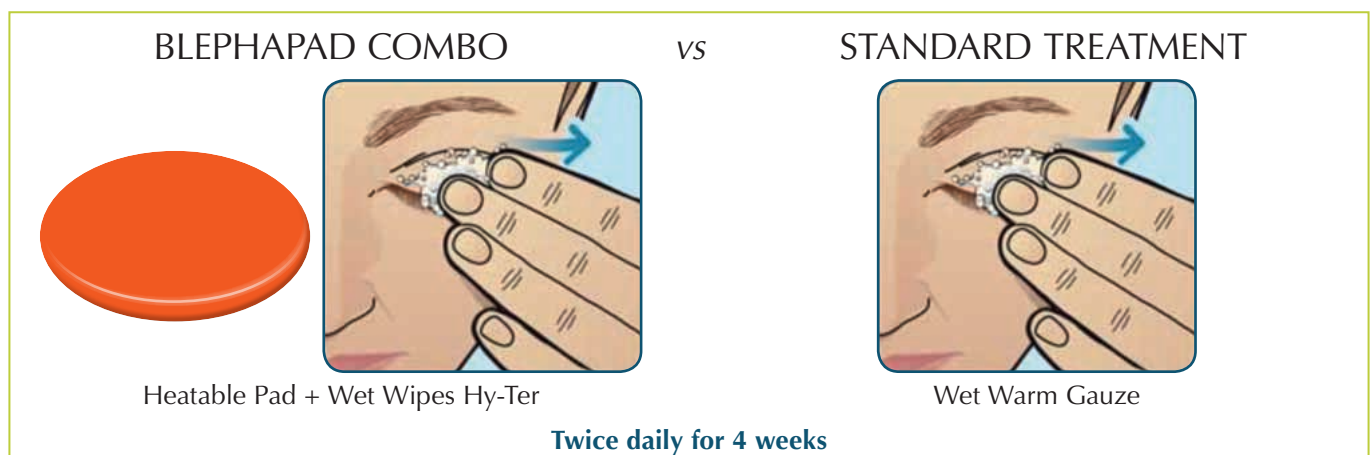


Figure 1. Characteristics of Blephapad Combo vs standard treatment

were assessed by means of infrared examination of the middle two-thirds of eyelid, a section including normally from 16 to 24 glands. Score depending on the number of partial glands (Figure 2).

6) Gland dropout (score 0-2): As above, but score depending on the count of complete gland dropout.

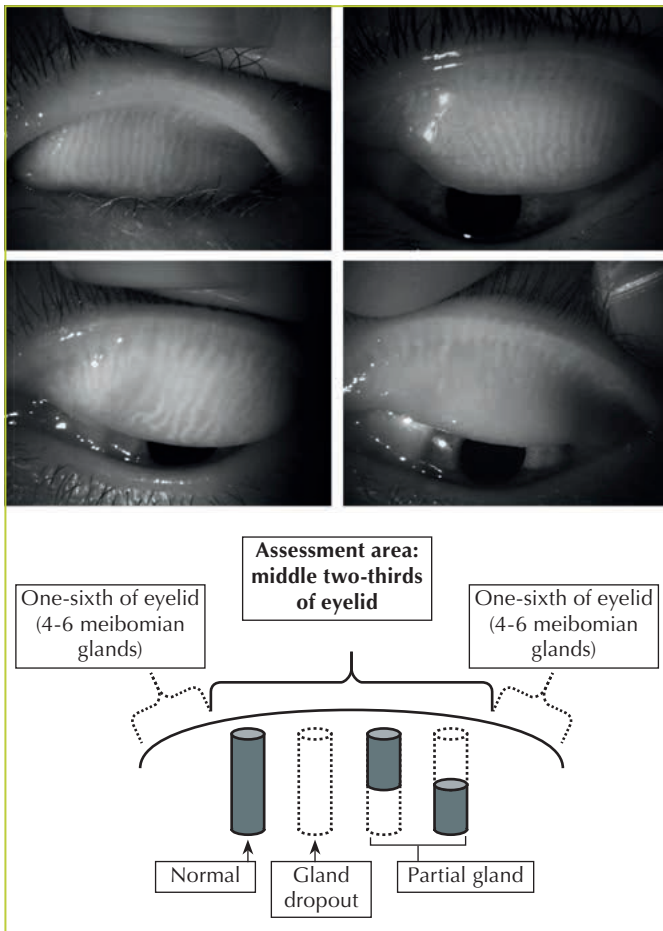


Figure 2. Presence of partial glands (score 0-3), a sign of meibomian gland stenosis

The main outcome of the study was the percentage change of the total score of the grading scales for meibomian gland dysfunction, from baseline to week 4. Four possible outcomes were taken into account for the change in meibomian gland dysfunction: improved in the study treatment arm, improved in the standard treatment arm, improved in both or improved in neither.

The secondary outcomes were:

- patient preference (for the study treatment, for standard treatment or no difference)
- compliance with the study treatment (assessed by counting applications and through a patient diary)
- ocular and systemic safety.

In the BLEPHA 01-2017 closed sequential design strategy, enrollment and data analysis were taking place during the study. This choice allows reduction of the amount of data necessary to obtain statistically significant conclusions. In particular, the greater the difference in efficacy between treatments, the lower the number of patients that need to be enrolled to obtain statistical significance. The difference between the standard treatment and Blephapad Combo was plotted sequentially as each patient was evaluated, and significance established using the plot in Figure 3. In this method, patients responding to the standard treatment are counted on the X axis and patients responding to the study treatment are counted on the Y axis. When the plot exits the shaded area and reaches the upper (study treatment better), lower (standard treatment better) or middle (no difference) region, significance is reached, and the study can be stopped.

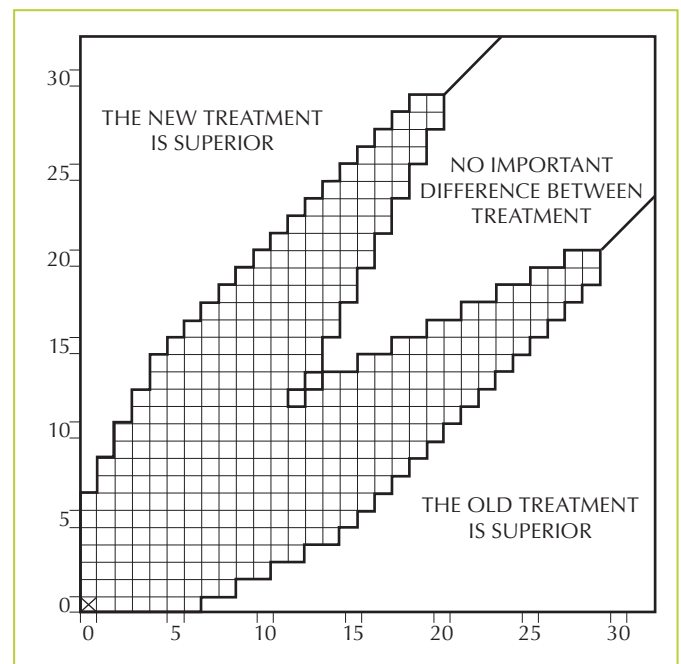


Figure 3. The plot used to establish significance in the BLEPHA 01-2017 study

Moreover, each eye was treated as a distinct experimental unit: for each patient, one eye was treated with the Blephapad Combo, while the other with the standard treatment. The assignment of the left or right eye to the study treatment was randomized according to a predefined randomization list. This strategy made it possible to further reduce the number of patients necessary to obtain a statistically significant result.

Thanks to the study design strategy, significance was reached after enrolling only 18 patients. Patient gender was equally rep-

resented (9 females and 9 males), while age distribution ranged between 43 and 82 years (mean age 66.9 years, standard deviation 9.03). Loss to follow-up was low: of 18 patients, only one missed the final follow-up visit, due to health problems unrelated to the treatment for blepharitis.

Results

We found that Blephapad Combo was superior to the standard treatment when measures of eyelid inflammation and meibomian gland dysfunction were compared at the end of the 4-week study period. At the final follow-up visit, the total score of the grading scales for meibomian gland dysfunction improved by 38.5% for the eyes treated with Blephapad, in contrast with 30% for the eyes treated with the standard treatment.

The secondary outcomes reinforce the superiority of Blephapad Combo with respect to the standard treatment. Out of the 18 patients enrolled, 17 expressed a preference for one treatment over the other. Of these, 12 patients (70.6%) preferred Blephapad

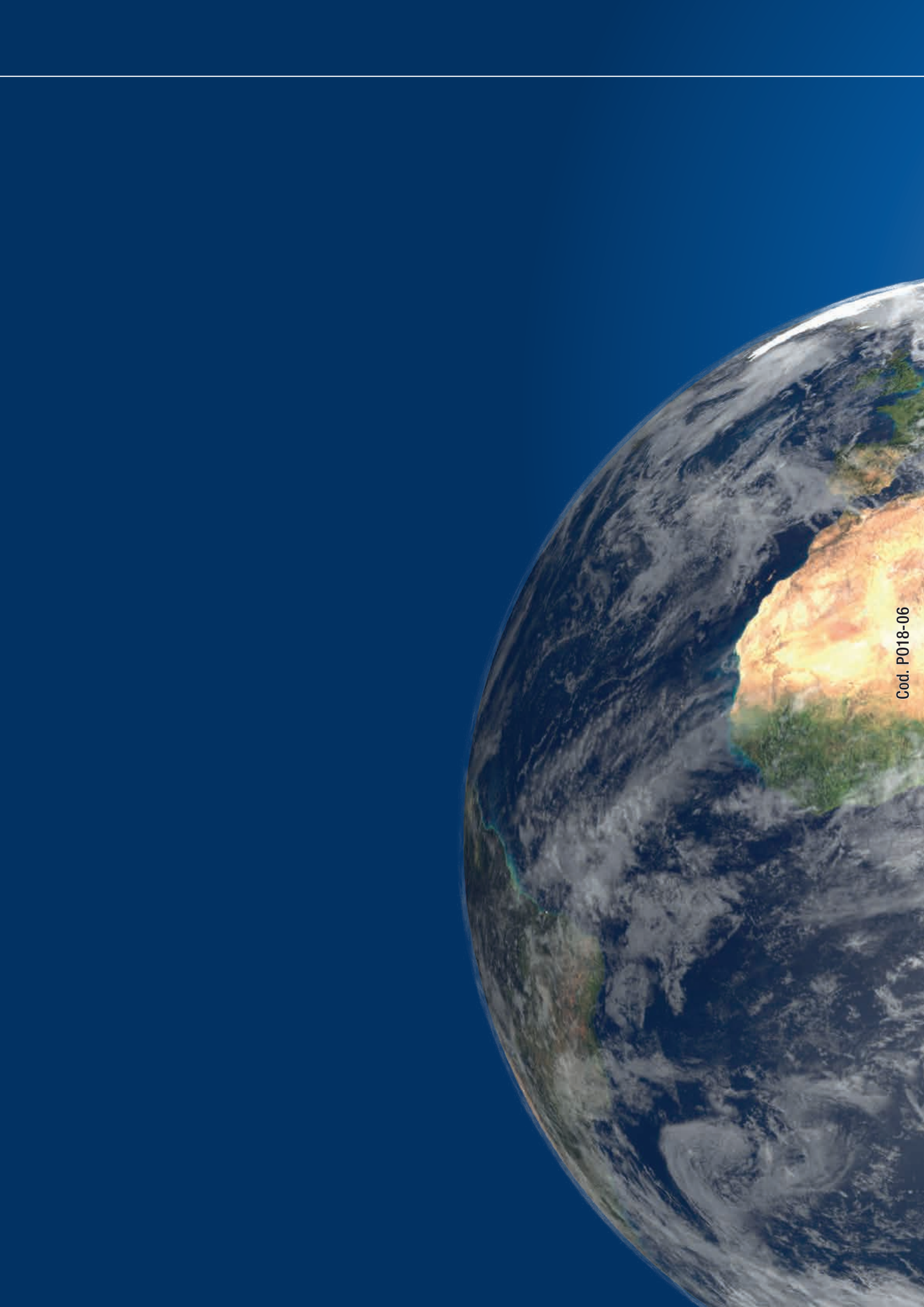
Combo, while only 5 (29.4%) were in favor of the standard treatment. According to the patients preferring Blephapad Combo, this treatment was simpler to understand and easier to execute. These patients also brought back less unused gauze, evidence of better treatment compliance. No adverse events related to the Blephapad Combo treatment, either local or systemic, were apparent after four weeks of usage, suggesting that Blephapad Combo is a safe treatment for blepharitis.

Conclusion

The BLEPHA 01-2017 study has shown that the treatment with Blephapad Combo is more effective than the standard (wet gauze) treatment in ameliorating meibomian gland dysfunction in patients with posterior blepharitis. Moreover, the ease of use of Blephapad Combo also resulted in markedly superior patient satisfaction and treatment compliance. The improved treatment of blepharitis by means of Blephapad Combo might therefore help the performance and success of cataract surgery.

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