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The effect of non-ablative thermomechanical skin treatment (Tixel®) on dry eye disease: A prospective two centre open-label trial

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ABSTRACT

Purpose: To determine the effects of a thermo-mechanical action-based peri-orbital fractional skin treatment (Tixel®) on dry eye disease.

Methods: This prospective, controlled, open labelled study was conducted at two study centres: Midland Eye, Solihull, UK, and Vallmedic Vision, Andorra. Participants were screened at the baseline visit (visit-1), received three Tixel® treatments at 2-weeks intervals including further assessment (visits 2, 3 and 4). Participants were followed up for three months post-treatment (visit 5). Vision, intraocular pressure (IOP), dry eye symptomatology were assessed, including the Ocular Surface Disease Index (OSDI) questionnaire, non-invasive tear break-up time (NIBUT) and tear osmolarity as well as detailed ophthalmic assessments.

Results: Seventy-four participants (41 in Birmingham and 33 in Andorra) with periorbital wrinkles and moderate to severe dry eye disease (DED) were enrolled. The mean age was 59.3 ± 13.3 years and 57 were females. No adverse events, no change in vision ($p = 0.310$) or IOP ($p = 0.419$) were observed. Tixel treatment was associated with clinically and statistically significant improvement in the DED symptoms, which was supported by a reduction of 21.40 ± 15.08 ($P < 0.001$) of the OSDI index. Non-invasive tear break-up time improved by 2.10 ± 0.91 s ($p < 0.001$) in the Birmingham cohort and 6.60 ± 2.13 s ($p < 0.001$) in the Andorra cohort. Tear osmolarity reduced from 299.8 ± 13.3 mOsm/L to 298.8 ± 15.6 mOsm/L following the Tixel treatment ($p = 0.271$).

Conclusions: Thermo-mechanical action-based *peri*-orbital fractional skin treatment Tixel® could be an attractive, safe and effective treatment for DED. This treatment is associated with high clinical and statistically significant improvement in DED signs and symptoms with no adverse events.

1. Introduction

Dry eye disease (DED) is a common and potentially debilitating disease that has been characterised by loss of tear homeostasis associated with numerous symptoms, such as itchy, sore, gritty and red eyes [1]. The loss of tear stability is a hallmark of DED where hyperosmolarity, ocular surface inflammation and damage, neurosensory abnormalities contribute aetiological roles [1]. The severity of DED can vary person to person, but the incidence is higher with age, prolonged computer user, contact lens wearers and people who have undergone recent ocular surgery [2]. Evaporative type DED is the commonest aetiological subtype which is frequently caused by underlying meibomian gland dysfunction (MGD). MGD is marked by an increased viscosity and melting point of the meibomian gland secretions leading to blockage and inflammation of the ductal system. Thus, MGD can trigger the vicious circle of tear film hyperosmolarity, evaporation, instability and inflammation. It is this vicious circle that needs to be broken to manage dry eye by intervening at any stage in the circle.

It is estimated that DED currently affects more than 344 million people worldwide including over 30 million in the United States [1]. Studies conducted in Asia (China, Japan, South Korea), and Europe (England, France) demonstrated the prevalence ranged from 4.1 % to 23.7 % [3].

DED is expensive for the economy and for an individual. It costs approximately US$ 3.84 billion from a taxpayer's perspective and as much as US$55.4 billion to society within the United States [4].

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Similarly, the mean annual direct cost per patient due to DED in the UK has been estimated at £525, including a significant indirect loss of work productivity [5].

Thermo-mechanical action (TMA®) is a relatively new technique used until now for aesthetic indications (Fig. 1). Heat is transferred directly onto the skin by a matrix of tiny pyramid-shaped pins made of biocompatible materials covering a treatment area of 1 cm^2 for the large therapeutic element (the tip) and 0.3 cm^2 for the small tip one which is used for the treatment of the eyelids. The pins are heated to a temperature of 400 °C, which rapidly transfers thermal energy (0.16 millijoules/pin) upon brief contact with the skin which only lasts for a few milliseconds (the contact duration and extent of thermal resistance of the tip with the skin can be set by the user). TMA® delivers thermal energy creating localised tissue coagulation. It is indicated for treatment of actinic keratosis and has been demonstrated in clinical studies also for the treatment of ageing skin [6,7], *peri* orbital wrinkles [8] facial rejuvenation [9], rosacea [10] acne vulgaris [11] and hypertrophic scars [12].

Many of the patients receiving TMA® based fractional skin treatment such as Tixel® for *peri*-orbital wrinkles are aged 50 years or older and suffer from DED. It was an observation by one of the co-authors (LH) that patients were experiencing a significant improvement of DED symptoms following aesthetic treatment sessions with Tixel®. This preliminary observation led to designing this prospective controlled open-label trial to characterise the effect of Tixel® treatment in alleviating DED and the associated signs and symptoms in those undergoing treatment for wrinkles.

2. Methods

2.1. Participants

A prospective, controlled open labelled study was conducted at two international sites: Midland Eye, UK, and Vallmedic Vision, Andorra. A total of 74 participants with DED were recruited. The study followed the declaration of Helsinki, received approval from the respective Institutional Human Ethics Committee and registered with ClinicalTrials.gov (NCT04730336). Written informed consent was received from all participants. Participants were provided with an emergency contact number for reporting any adverse event during the study, alternatively they were suggested to contact the clinical study centre for any emergency.

Strict inclusion criteria were employed prior to the recruitment of participants for this study. All participants were required to fulfil the following criteria: above 18 years of age; an Ocular Surface Dryness Index (OSDI) score of at least 23; a non-invasive tear break up point (NIBUT) <10 s; have *peri*-orbital wrinkles, no history of ocular surgery; no ocular medication and dry eye treatment other than artificial tears within the last 3 months; and able to attend for all five study visits. Presence of *peri*-orbital wrinkles was visually confirmed but was not measured in this study. The exclusion criteria for this study were: pregnant or lactating women; existing lesions or medication for the ocular or orbital area; acute ocular disease; significant blepharitis; outdoor or sunbed tanning with the last four weeks of participating the study; impaired immune system; history of bleeding coagulopathies; and use of anticoagulants. Blepharitis was graded followed Efron grading scale, anyone having blepharitis more than 3 was excluded.

2.2. Tixel treatment

Fractionated treatment of the eyelid skin was performed using Tixel® (Novoxel, Israel) equipped with the smaller Tixel tip consists of 24-pins (Fig. 1). The total surface of the tip which had 4 × 6 pyramids was 0.3 cm^2. Preorbital area including the upper and lower lid area as shown in the Fig. 1 were treated. The tip base temperature was maintained at 400 °C during treatment and superficial non-ablative tissue coagulation (250 μm deep, 300 μm diameter) induced by the quick protrusion and contact of the heated tip directly onto the periorbital skin surface. The contact duration in milliseconds and the extent of thermal matching (protrusion, in microns) is normally customised by the user. For the current study, the contact duration was standardised at all sites to 8 ms and protrusion was set to 400 μm as a single contact/shot (0.16 millijoules energy per point).

2.3. Study design

A total of 40 shots in the *peri*-orbital area during each treatment: 10 per eyelid, were placed directly on to the upper and lower eyelid skin. In one of the sites, Birmingham, the eye lids were anaesthetised with lignocaine 5 % cream for 15 min with a standard wrinkle treatment regime. In Andorra analgesic cream was not applied on any of the patients. Treatment required about 2 min for both eyes combined. Since the device does not emit radiation, eye shields were not required.

This study followed the tenets of good clinical practice. The activities and clinical assessment for each of the study visits are detailed in Table 1 and with a flow chat in Fig. 2. Three Tixel treatments were delivered at 2-weeks intervals. Participants were followed up over three months from last treatment with a total of five study visits, no additional maintenance therapy was adviced. Best corrected visual acuity was measured using a LogMAR visual acuity chart. Dry eye symptoms were assessed using the Ocular Surface Dry Index (OSDI) questionnaire, and participants were stratified for analysis by mild, moderate and severe dry eye symptoms based on criteria previously published.[13] The two sites performed

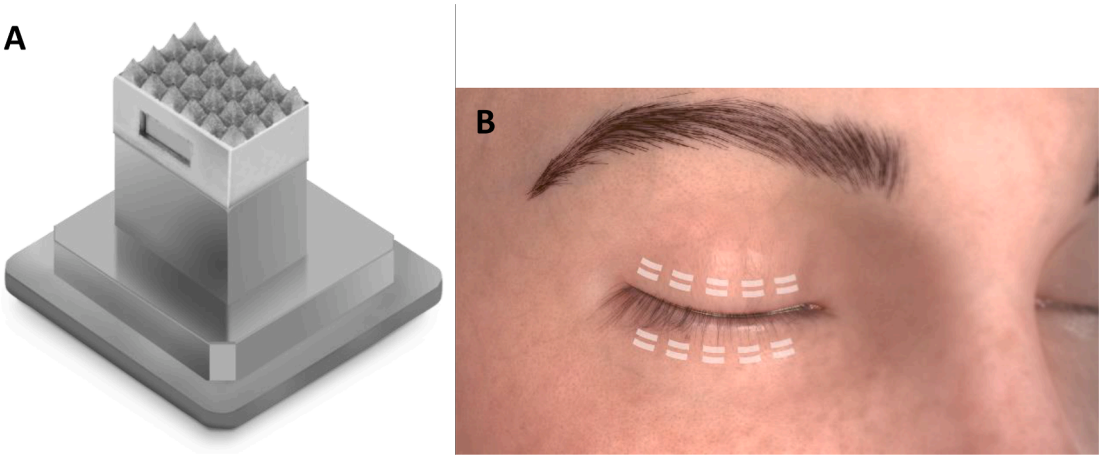

Fig. 1. (A) Titanium 24-pin Tip used for thermomechanical heat transfer to tissue. (B) Area of upper and lower lid for Tixel treatment shown in an animation.

Table 1
Details of the sequential clinical assessments and activities for each study visits.

Procedure	Visit 1 Treatment 1 T_0	Visit 2 Follow-up 1 followed by Treatment 2 $T_0 + 2w$ (±5days)	Visit 3 Follow-up 2 followed by Treatment 3 $T_0 + 4w$ (±5days)	Visit 4 Follow-up 3 $T_0 + 6w$ (±5days)	Visit 5 Follow-up 4 $T_0 + 18w$ (±5days)
Maximum duration for follow up	–	2 weeks± 5 days	4 weeks± 10 days	6w± 15 days	18w± 20 days
Participant screening, informed consent, detailed history, enrolment based on inclusion/ exclusion criteria, detailed ophthalmic examination	X				
For females - verbal Inquiry regarding pregnancy	X	X	X	X	X
OSDI questionnaire	X	X	X	X	X
Non-invasive tear break up time	X	X	X	X	X
Tear Osmolarity	X	X	X	X	X
Slit lamp examination, including lid margin profile	X	X	X	X	X
Intraocular pressure measurement	X	X	X	X	X
Concomitant therapy/medication (including ocular)	X	X	X	X	X
Periorbital general skin examination prior to treatment or follow up	X	X	X	X	X
Tixel® Treatment	X	X	X		
Post treatment care	X	X	X	X	X

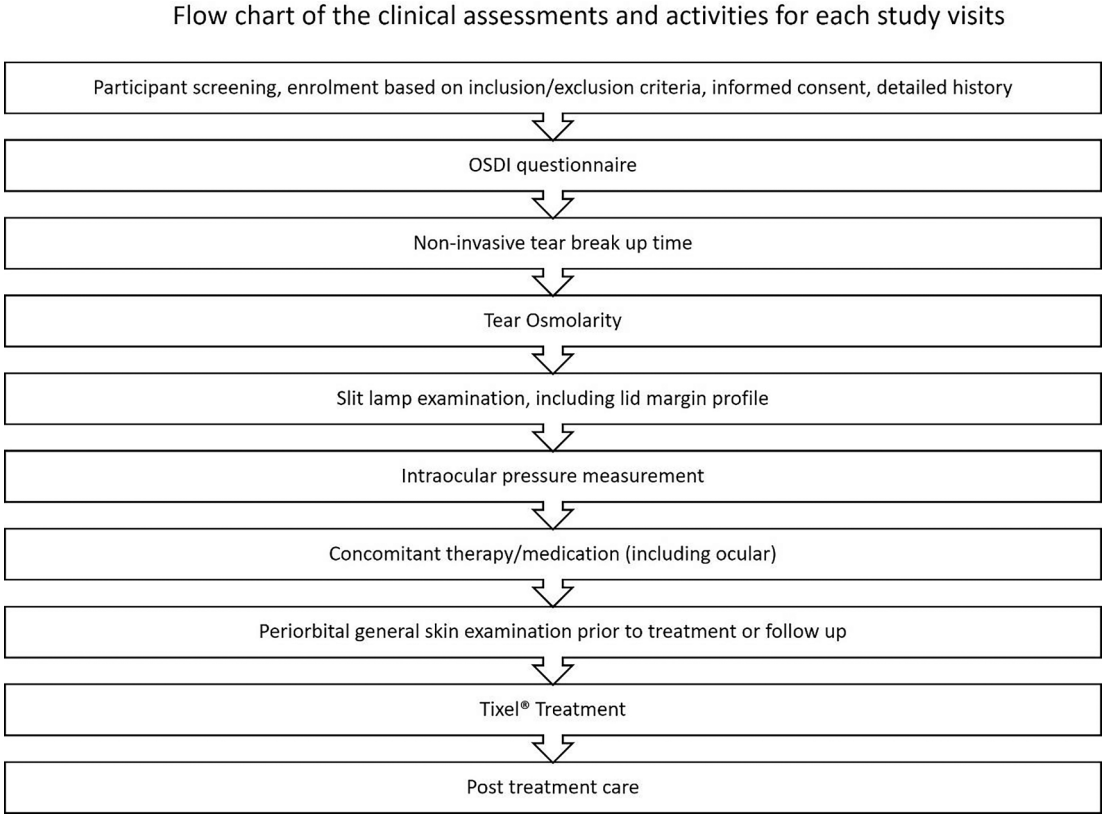

Fig. 2. Flow chart of the clinical assessments and activities for each study visits.

NITBUT and with the equipment available. Three measurements were taken, the average NIBUT was assessed using Oculus® Keratograph 5 M (Oculus®, Arlington, WA, USA) at the UK centre and automatic measurement by Sirius (CSO Costruzione Strumenti Oftalmici, Florence, Italy) at the Andorra centre. Tear osmolarity (TearLab, California, USA) was measured from the lower lateral canthal tear meniscus as per the Tearlab protocol. Detailed slit-lamp examination and measurement of intraocular pressure (IOP) by Goldmann applanation tonometry were also performed.

2.4. Statistical analysis

All data were analysed using Excel (Microsoft Office, Redmond, WA, USA), Graph Pad Prism version 8.01 (California, USA), or Statistical Package for Social Sciences (SPSS) for Windows software version 23.0 (IBM SPSS NY, USA). Sample size was calculated using G*Power version 3.1.9.4, which determined a total of 68 participants were required for the desired study power. The effect size dz was determined to be 0.446 based on a pilot study where NIBUT was the designated outcome to detect a clinically significant difference of 5.0 s following treatment at 80 % power ($\beta = 0.2$) and statistical significance level of 5 % ($\alpha = 0.05$),

with the standard deviation estimated to be approximately 5.5 s.

Results are presented as mean ± standard deviation (SD) including their descriptive statistics. Clinical data were collected from both the eyes, however, data that were randomly selected from one eye, right eye, in this case, were analysed in this study. A two-way mixed model analysis of variance (ANOVA) testing was conducted to determine the significance of treatment, followed by confirmation of normal distribution by Kolmogorov-Smirnov test. Categorical data were analysed with using chi-squared or Fisher's exact test based on the variable.

3. Results

Sixty-eight participants were required to determine clinically and statistically significant difference. A total of 74 participants (57 females and 17 males) were included in this study. 74, 74, 71, and 63 participants completed visit 2, 3, 4 and 5 respectively. Each study visit was about 45 min to one hour.

The mean age of all the participants was 59.3 ± 13.3 years (range 23 to 79 years). At Midland Eye, UK 41 participants were recruited: 41, 41, 38, and 34 participants completed visits 2, 3, 4 and 5 respectively. At the Andorra study centre, 33 participants were recruited, all the participants completed visit 2, 3, and 4, and 29 participants completed visit 5. Recruitment was within periods of COVID lockdown explaining some of the later dropouts.

There were no serious adverse events associated with the Tixel® treatment to the skin of the eyelids during this trial. No other safety-related event was observed.

Table 2 shows the results for the clinical measurements that were conducted during each visit. No major change with the visual acuity ($p = 0.310$) and IOP ($p = 0.419$) were observed during this study (Table 2).

3.1. Tear break-up time

Following three Tixel treatments, the NIBUT significantly improved for the groups of participants recruited at both sites ($p < 0.05$). For the UK cohort, NIBUT improved from 5.0 ± 2.6 s to 7.1 ± 1.3 s ($p < 0.001$, Fig. 3A), for the Andorra cohort it improved from 6.5 ± 3.1 to 13.2 ± 3.2 s ($p < 0.001$; Fig. 3B). It should be noted that the severity of initial NIBUT was different at the 2 sites.

3.2. Osmolarity

The combined tear osmolarity changed from 299.8 ± 13.3 mOsm/L at the start of this study to, 299.8 ± 12.8, 300.0 ± 11.7, 299.7 ± 10.1, and 298.8 ± 13.4 mOsm/L at visits 2, 3, 4 and 5 respectively. The overall improvement (reduction) of tear osmolarity was 1.0 ± 0.5 mOsm/L, which was not statistically significant ($p = 0.271$).

3.3. OSDI scores

A total of 80 % of participants had severe symptoms (33–100 OSDI index score), out of the rest 20 % had moderate (23–32 OSDI index score) symptoms at the baseline visit. By the end of the study, this proportion had changed to 36 %, 8 %, and 26 % having reported severe, moderate and mild dry eye symptoms respectively with 30 % reporting no dry eye symptoms. The OSDI index for the UK and Andorra cohort was 49.81 ± 16.44 and 45.49 ± 17.05 respectively, the difference was not statistically significant ($p = 0.318$).

The mean DED symptoms at visits 1, 2, 3, 4 and 5 were recorded as 47.47 ± 18.62, 35.76 ± 16.40, 32.02 ± 15.53, 28.00 ± 13.87 and 26.04 ± 13.69 respectively by the OSDI index score (Fig. 4). Overall, the results demonstrated a mean 21.43 ± 13.07 OSDI index score improvement during this study for all participants ($p < 0.001$). Results also showed clinically significant improvements with dry eye symptoms when a sub-analysis was performed as characterised by 18.0 ± 6.7 and 33.4 ± 9.2 OSDI index improvement for patients with moderate and severe dry eye symptoms at baseline respectively, indicating a larger improvement for more severe symptoms. Fig. 5 details the improvement of the OSDI index scores during the study stratified by the severity of DED.

4. Discussion

This prospective multicentre clinical trial reports the effect on DED symptoms of TMA® based fractional skin treatment around the *peri*-orbital area. It shows that Tixel can significantly improve DED signs and symptoms when followed for three months after treatment.

Tixel® is a radiation-free treatment, that has been deemed safe on the *peri*-orbital skin earlier [14]. There were no serious adverse events reported during the study.

The treatment did not affect the visual acuity and IOP. It was well accepted by patients and was very easy and quick to perform. Improvement in skin wrinkles was not an outcome measure for this study but the parameters used were the ones that are used for wrinkle treatments.

The study design for this proof-of-concept study was to perform 3 Tixel treatments at 2-week intervals (similar to a possible treatment protocol for DED patients undergoing treatment with intense pulsed light (IPL). The trend with DED signs and symptoms observed in this study confirms three Tixel treatment as an effective strategy for alleviating DED related signs and symptoms.

The improvements observed with DED symptoms were clinically significant. This was characterised by an improvement of 18.0 ± 6.7 (for moderate dry eye) and 33.4 ± 9.2 (for severe dry eye) OSDI index score for DED participants. The minimum clinically important difference (MCID) suggested by the Tear Film Ocular Surface Dry Eye Workshop (TFOS DEWS II) subcommittee for the same is up to 7.3 and 13.4 OSDI index scores respectively [2]. The mean improvement with symptoms recorded in this study was an OSDI index score of 21.4 which is higher than previously observed by Xue et al. [15] with IPL treatment and similar to reported by Tauber et al. [16] with iLux (Alcon, Fort Worth, TX, USA) treatment.

Significant improvement of NIBUT 2.1 and 6.6 s observed at the two trial centres [2]. This is higher than previously reported with IPL treatment [15], and iLux treatment [16]. This study could be improved by using the same instruments for measurement of NIBUT at each site, however, as a proof of concept study, this clearly shows improvements in both sites albeit with some variations. Andorra cohort had NIBUT baseline 1.5 s higher than the UK cohort, which could be due to higher relative humidity in Andorra compared to Birmingham (UK centre). Due to Covid restrictions, several participants towards the end of the study were recruited more than six months after the first-batch of participants. There are a number of other potential causes for the difference in the two sites – different instrumentation for measurements, different patient mix, different climate eg Andorra is at high altitude.

Osmolarity has been regarded to be the best single objective test for

Table 2
Clinical measurements conducted at baseline (visit-1), and during visit-2, visit-3, visit-4, and visit-5. P-value represents statistical significance. Asterisks* denotes statistically significant difference.

Measurement	Baseline (Visit-1)	Visit-2	Visit-3	Visit-4	Visit-5	Overall change	P-value (statistical significance)
Best corrected visual acuity (log MAR)	0.47 ± 0.21	0.03 ± 0.11	0.02 ± 0.10	0.04 ± 0.13	0.56 ± 0.19	0.00 ± 0.00	0.310
Intraocular pressure (mm of Hg)	14.6 ± 3.4	14.8 ± 3.5	14.1 ± 3.5	14.5 ± 3.1	14.0 ± 3.5	0.6 ± 0.1	0.419

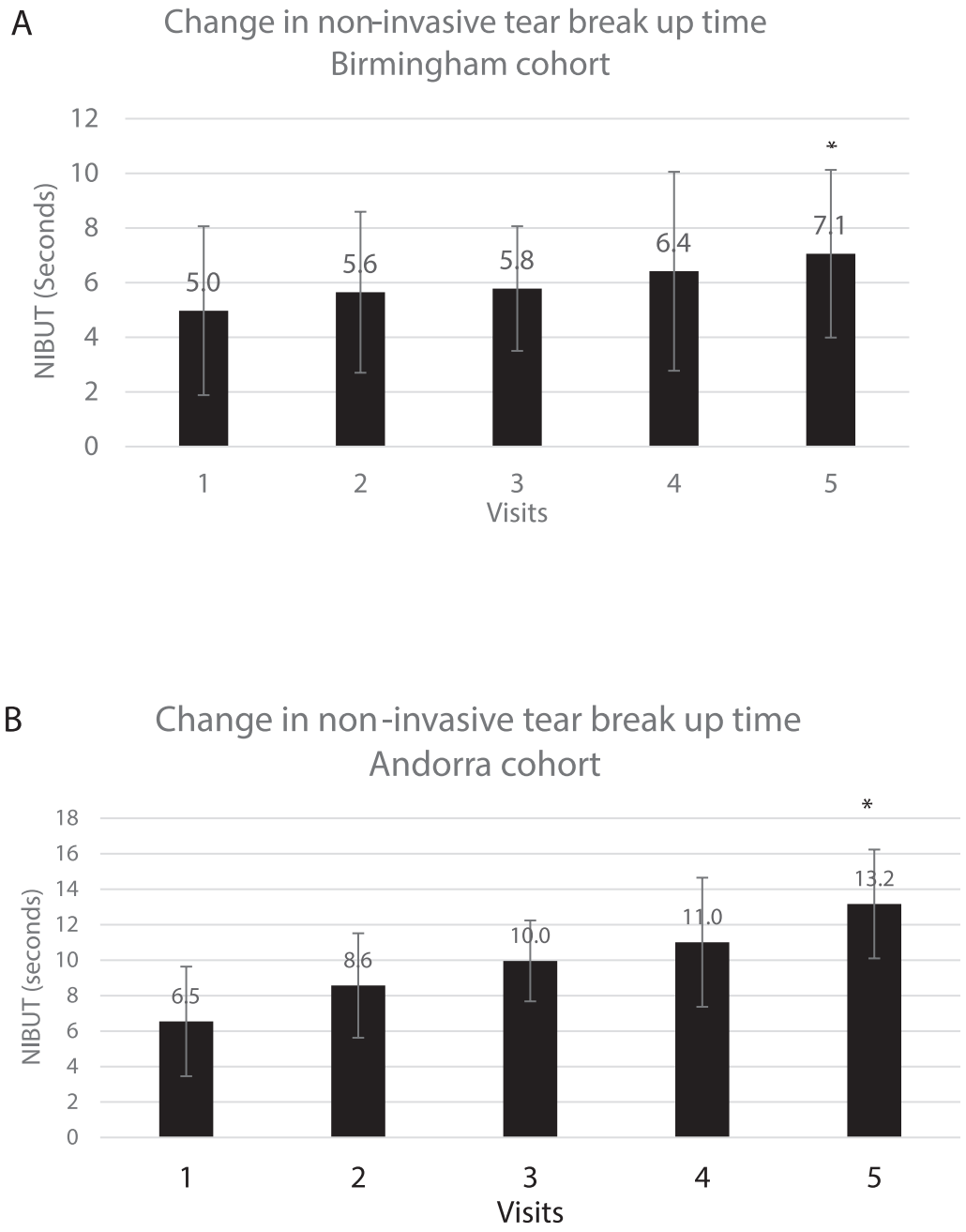

Fig. 3. Change of average non-invasive tear break up time during the study; (A) observation made in Birmingham cohort, the change was statistically significant compared to baseline visit-1 (*), (B) observation made in Andorra cohort; the change was statistically significant compared to baseline visit-1 (*).

the assessment of DED [17–19]. Following Tixel, mean tear osmolarity changed from 299.8 ± 13.3 mOsm/L before treatment to 298.8 ± 10.7 mOsm/L after treatment, indicating a minor reduction of tear osmolarity by 1.0 mOsm/L. This change was not statistically significant and fell short of the suggested MCID of 5.0 mOsm/L as suggested by TFOS DEWS II, it is a larger reduction than previously reported with IPL and LipiFlow [15,20,21].

The mechanisms of action of Tixel® treatment that underpin clinical improvements in DED patients are still under investigation. Several possible hypotheses can be tabled. Firstly, thermal energy transferred by Tixel® could help liquefy the inspissated meibum. This may open ductal obstruction and promote the release of liquid of meibum further improving quality of tear film lipid layer and shielding aqueous tear from undue evaporation. It is possible that Tixel reduces the microbial load of the periorbital and periocular area, thus can alter host immune and inflammatory responses. Other possible mechanisms may include reduction of epithelial turnover, fibroblast activation and modification of pro-inflammatory cascades leading to reduced ocular surface inflammation or that modification of growth factors from healing from the skin. It is likely more than one mechanism is involved following Tixel® in reducing DED signs and symptoms. Further research is ongoing to investigate these hypotheses.

There are limitations to this study. It started participant recruitment prior to the SARS-CoV-2 pandemic and faced challenges with following up research participants, particularly for the 3-months follow up (visit 5). Given the multinational nature of this study, the travel restrictions of different nations varied considerably which influenced the visit 5 attendance: in particular, this affected Andorra, where there were several cross-border patients. The NIBUT was measured in different study centres using different instruments, in Andorra without analgesia,

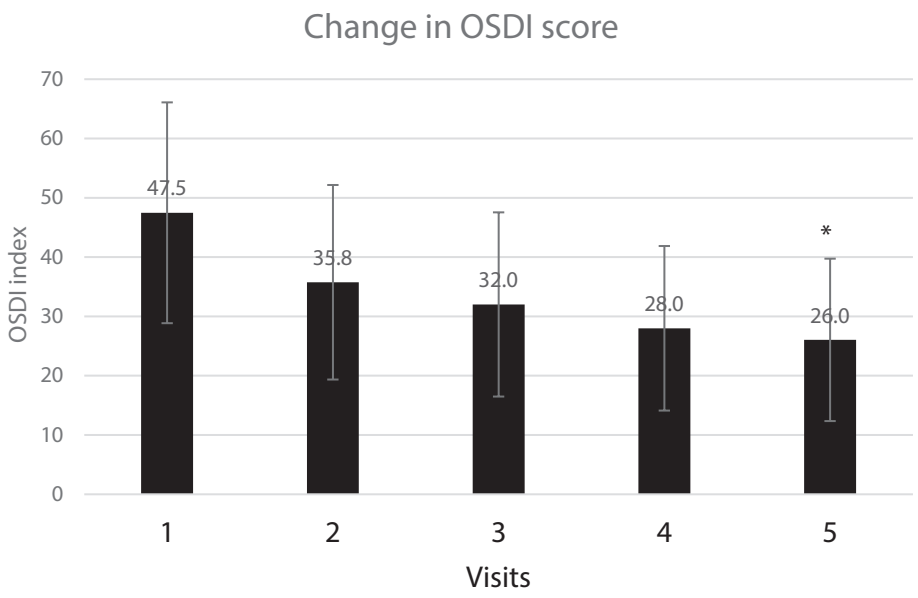

Fig. 4. Change of ocular symptoms measured by the ocular Surface Disease Index (OSDI) questionnaire during the study period; the change was statistically significant compared to baseline visit-1 (*).

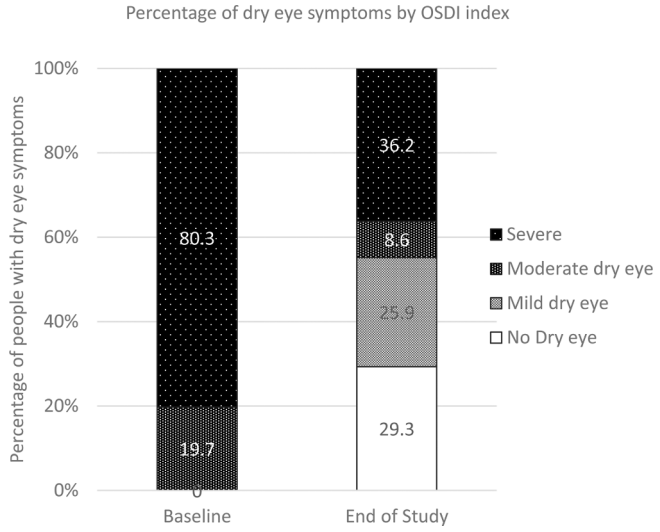

Fig. 5. Improvement of dryness stratified by the severity of ocular symptoms, measured by OSDI questionnaires during the study period.

in Birmingham lignocaine 5 % cream was applied. These factors may have had an influence on the results. Tixel treatment include heating sensation in the treatment area such as ocular adnexa and lid margin, which makes it is challenging to add a placebo group or employ double masking. However, participants recruited at all the study centres observed significant improvement with the measurement of tear break uptime. In addition, this study did not include assessments corneal staining and meibomian gland dysfunction such as meibomian gland scoring and assessment of meibum quality. It is expected that this treatment will improve the meibomian gland secretions and the authors are currently running further studies to characterise this.

The treatment protocol of 3 consecutive Tixel treatments was based on similar studies with IPL. It is not known whether more Tixel treatments would be beneficial and the period between treatments that would give the best results. The duration of benefit also needs to be investigated and whether a further treatment 6 or 12 months later as a 'top up' would be beneficial, given the chronic nature of MGD and DED.

In conclusion, Tixel treatment offered significant improvement in DED symptomatology, tear break up time, and most importantly improved tear homeostasis in this prospective two centre trial. The findings confirm that three Tixel treatments, each with a two-week interval provide encouraging clinical outcomes. These results appear to show at least comparable, and in many cases, superior results to other commercially available DED treatments and management regimes, making it a highly attractive treatment for DED.

5. Funding source

Novoxel partly funded the clinical trial in Andorra site. Both the authors Ludger Hanneken and Sunil Shah are the advisors of Novoxel.

6. Conflict of interest and disclosure

This work is original, has not been published and is not being considered for publication elsewhere. The authors received part funding from Novoxel to run this prospective study, However Novoxel was not involved in designing the study protocol, collecting or analysing the data, nor the writing of the paper.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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