

# Effect of a Novel Thermostatic Device on Meibomian Gland Dysfunction: A Randomized Controlled Trial in Chinese Patients

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## Research Article

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# Abstract

## Background

As a chronic disease, meibomian gland dysfunction (MGD) which causes excessive evaporation of tears by changing the tear film composition, is considered a leading cause of dry eye. Although a variety of physical therapy equipment, there is currently no economical and effective treatment for MGD. The aim of this study was to evaluate the effectiveness and safety of the MiBoFlo Thermoflo® (Mibo Medical, Dallas, TX, USA), a new thermostatic device, on both objective symptoms and subjective signs in Chinese MGD patients.

## Methods

This was a prospective, randomized, controlled clinical trial. 108 eyes of 54 MGD patients in Beijing Tongren Hospital were recruited and randomized 1:1 to MiBoFlo (n = 54 eyes) or LipiFlow® (TearScience, Morrisville, NC, USA) (n = 54 eyes) treatment group. In the MiBoFlo group, treatment for each eye took 10 minutes and proceeded every two weeks for a total of three times. Patients in the LipiFlow group received a single 12-minute treatment. Main Outcome Measures: The primary outcomes include changes in Ocular Surface Disease Index (OSDI) score, Meibomian Glands Yielding Liquid Secretion (MGYLS) score and Meibomian Glands Secretion (MGS) score from baseline to 2 months. The secondary outcomes include Tear Meniscus Height (TMH), Non-invasive Keratograph Break-up Time (NIKBUT), Corneal Fluorescein Staining (CFS) and Meibomian Glands (MG) loss from baseline to 2 months. Safety outcomes include visual acuity (VA), intraocular pressure (IOP), anterior segment and facial skin.

## Results

The OSDI score, MGYLS score and MGS score all improved from baseline to 1 month in both MiBoFlo and LipiFlow group, and these improvements were maintained at 2 months. CFS score, NIKBUT and MG loss had no significant change in both groups. CFS score improvement in MiBoFlo group were significantly more obvious than in LipiFlow group in the follow-up visit ( $p < 0.01$ ).

## Conclusion

As a portable and comfortable device, MiBoFlo treatment can offer an advancement for the treatment of MGD and a course of treatment results in at least two months of sustained improvement in both symptoms and meibomian gland function.

## Introduction

As a chronic disease, dry eye disease (DED) is no longer just a condition of old age, and its prevalence in teenagers has increased year by year.<sup>1,2</sup> Meibomian gland dysfunction (MGD), which causes excessive evaporation of tears by changing the tear film composition, is considered a leading cause of DED.<sup>3,4,5</sup>

Characterized by the meibomian gland obstruction, MGD currently has two main types of treatments, pharmacotherapy and physical therapy.<sup>6</sup> It was proved that warm compresses had been an effective way for relieving eye discomfort,<sup>4</sup> however, patient adherence is often poor due to the time used and the difficulty in maintain the temperature of the warm compresses for an extended period of time. In addition to this, the temperature passed by warm compresses are not enough for completely melting obstructive material within the meibomian gland excretory duct.<sup>7</sup> In recent years, LipiFlow Thermal Pulsation System® (TearScience, Morrisville, NC, USA) has developed as a new type of MGD therapy device, which clears the blocked meibomian glands by simultaneously applying controlling heat and graded pulsatile pressure to the outer and inner surface of the eyelids.<sup>8</sup> It was first described by Korb and Blackie in 2010<sup>9</sup> and its clinical effects have been proved by a number of studies.<sup>10</sup>

MiBoFlo Thermoflo® (Mibo Medical, Dallas, TX, USA), a new thermostatic device for MGD treatment, is composed of a small embedded computer and a handheld probe connected to it. It applied heat thermoelectrically through a silver pressure plate to the outer eyelid, which keep the temperature constant at 42°C.<sup>11</sup> Practitioner-administered manual massage by reciprocating and rotating probe is carried out at the same time. There are a few reports about the MiBoFlo at present. Kenrick measured the palpebral conjunctiva temperature before and after MiBoFlo therapy by a non-contact infrared thermometer, however, they did not involve its clinical effects.<sup>12</sup>

Thus, the aim of our randomized prospective preliminary clinical study was to evaluate the effectiveness and safety of treatment with the MiBoFlo on both objective symptoms and subjective signs of MGD patients in China.

## Methods

### Study design

This was a prospective, randomized, observer-masked clinical trial, aim to evaluate the effectiveness and safety of treatment with the MiBoFlo on both objective symptoms and subjective signs of MGD patients and compare the therapeutic effects and the superiority differences between the MiBoFlo and the LipiFlow therapy. All patients were given a full explanation of the study, and written informed consent was obtained from all participants. This study conformed to the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Review Committee of Beijing Tongren Hospital. The trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) as NCT04310969 first posted at 17/03/2020.

### Study Population

Patients who must meet the following criterion at the same time were included: 18 years of age or older; meet the diagnostic criteria for dry eye developed by DEWS II: Ocular Surface Disease Index (OSDI) score  $\geq 15$  points, Tear film Break-up Time (TBUT)  $\leq 10$  seconds; meet the signs of MGD: presence of lid margin abnormalities, orifice abnormalities and meibum abnormalities.

Patients with one of the following conditions were excluded from the group: used artificial tears other than aqueous supplementation; used non-steroidal anti-inflammatory drugs, topical glucocorticoids, immunomodulators; had skin allergies or inflammation; had history of ocular surgery, eyelid surgery or neurological paralysis within 6 months; had active ocular infection or inflammation; had history of systemic disease affecting ocular surface function, such as Stevens-Johnson syndrome, Sjögren syndrome etc.

## **Treatment**

54 subjects (108 eyes) who met inclusion criteria in clinics at Beijing Tongren Hospital were enrolled for this study in June 2020. The MiBoFlo treatment group was set as experiment group, and the LipiFlow group was set as positive control group. The subjects were randomized 1:1 to the MiBoFlo treatment group (54 eyes) and LipiFlow treatment group (54 eyes) using the randomized digital table by the randomization manager.

In the MiBoFlo group, treatment for each eye took 10 minutes and proceeded every two weeks for a total of three times. And patients in the LipiFlow group received a single 12-minute treatment. The medication before and after treatment in both groups remained unchanged.

In the MiBoFlo group, first used the security key to start and preheated the machine to 42.5°C. Keep patients in supine position, cleaned the eyelids and smeared with a small amount of ultrasound gel in order to reduce friction between the device and eyelid skin. Then massage the outer skin of the upper and lower eyelids by reciprocating and rotating the handheld probe for a period of 10 minutes. Same procedure for another eye. Eyes keep closed during therapy.

The treatment of the LipiFlow group was performed on the same day as the first treatment of patients in the MiBoFlo group. Keep patients in fowler position and administered a drop of tropical anesthetic into patient's both eyes. Placed the sterile eye cup into conjunctival sac and fixed it on the skin with surgical tape. Then the program started with heat up, apply constant pressure, apply increasing pressure and apply alternating pressure in turn. After 12-minute treatment, removed eye cups from both eyes slightly.

## **Effectiveness outcomes**

The evaluation data of each patients before the first treatment was used as the baseline, and the follow-up examinations were scheduled at 1 month and 2 months after the first treatment. The evaluator was blinded for the grouping situation. The parameters used to evaluate the effectiveness and safety of both treatment groups were as follows.

## **Primary outcomes**

OSDI questionnaire was chosen to assess subjective symptoms of dry eye, which can demonstrate sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease.

Meibomian Glands Yielding Liquid Secretion (MGYLS) was standardized using Meibomian Gland Evaluator. A total of 30 glands were evaluated along eyelid margin, consisting of 5 consecutive glands located in each of the nasal, central and temporal regions of the upper and lower eyelids respectively. For each of 5 consecutive glands, MGYLS was scored using the following grading system: 0 indicated all 5 glands have secretory capacity, 1 indicated 3–4 glands have secretory capacity, 2 indicated 1–2 gland(s) has(have) secretory capacity, 3 indicated no gland has secretory capacity. The total MGYLS score (range 0–18) was calculated as the sum of the grades for 6 areas of each eye.

Meibomian Glands Secretion (MGS) was standardized using Meibomian Gland Evaluator, either. For each of 5 consecutive glands, MGS was scored using the following grading system: 0 indicated clear liquid secretion, 1 indicated cloudy liquid secretion, 2 indicated granular secretion, 3 indicated toothpaste-like opaque secretion.

### **Secondary outcomes**

The lower eyelid tear meniscus was photographed under a white light source by Oculus Keratograph 5M® (Oculus Optikgeräte GmbH, Wetzlar, Germany), and Tear Meniscus Height (TMH) was measured with the built-in ruler in order to estimate tear secretion.

The non-invasive keratograph break-up time (NIK BUT) was used to evaluate tear film stability and also assessed by Oculus Keratograph 5M. The average NIK BUT was recorded into the statistical result.

Fluorescein was applied in the lower conjunctival sac of each eye with a fluorescein sodium ophthalmic strip (Jingming New Technological Development Co., Ltd, Tianjin, China), and corneal erosion assessed by Corneal Fluorescein Staining (CFS) was scored using the following grading system: grade 0 indicated no corneal erosion, grade 1 indicated 1–5 punctate epithelial erosions seen inferiorly, grade 2 indicated 6–30 punctate epithelial erosions, grade 3 indicated more than 30 punctate epithelial erosions.<sup>13</sup>

Meibography was performed using Meibo-Scan attached to the Oculus Keratograph 5M. Structural changes of meibomian were observed with infrared light source. The area of MG loss was measured with the ImageJ software and its relation to the total area was noted as percentage.<sup>14</sup>

### **Safety index**

Visual acuity (VA), intraocular pressure (IOP), anterior segment and facial skin were observed at every follow-up, in order to ensure the safety of treatment.

### **Statistical analysis**

Statistical analysis was performed using SPSS software (IBM Corp, Somers, NY) and GraphPad Prism version 9. Two-way ANOVA were used to assess the effects of the MiBoFlo and LipiFlow treatment on the main and secondary outcomes assessed at baseline, 1 month and 2 months. A statistically significant difference was based on the level  $\alpha=0.05$ .

We estimated that the primary outcome would have to be analyzed in 44 subjects (22 subjects in each group) to achieve the study power of  $\geq 80\%$  for a significant P value of 0.05 with two-tailed test.<sup>15</sup>

## Results

This study enrolled 54 subjects (108 eyes), aged 22 to 78 years. In the end, there were 22 subjects in MiBoFlo group who completed the final follow-up, and 20 subjects in LipiFlow group in total. The MiBoFlo group, with an average  $43.95 (\pm 11.40)$  years of ages, includes 17 females and 5 males. The LipiFlow group, with an average  $41.90 (\pm 11.03)$  years of ages, includes 15 females and 5 males.

The baseline of each evaluating parameters of two devices were compared before the treatment. It was showed that the there was no statistically significant difference in the baseline level of OSDI score, MGYLS score, CFS score, NIKBUT, TMH and area of MG loss in both groups. However, a significant intergroup difference found in the baseline level of MGS score. (Table 1)

The symptoms of dry eye patients were assessed by OSDI questionnaire. In MiBoFlo group, the OSDI score decreased from  $44.31 \pm 1.03$  at baseline to  $34.00 \pm 13.84$  at 1 month ( $p < 0.01$ ), and to  $28.65 \pm 18.20$  at 2 months ( $p < 0.0001$ ). In LipiFlow group, the OSDI score decreased from  $46.10 \pm 17.70$  at baseline to  $33.28 \pm 21.41$  at 1 month ( $p < 0.001$ ), and changed to  $30.63 \pm 19.86$  at 2 months ( $p < 0.0001$ ) (Figure 1). OSDI improvement had no significant intergroup difference at 2-month follow up ( $p = 0.84$ ).

The secretory capacity of meibomian gland were assessed by MGYLS score. In MiBoFlo group, the MGYLS score decreased from  $8.68 \pm 3.64$  at baseline to  $7.32 \pm 3.25$  at 1 month ( $p < 0.0001$ ), and to  $5.07 \pm 2.26$  at 2 months ( $p < 0.0001$ ). In LipiFlow group, the MGYLS score decreased from  $8.43 \pm 3.67$  at baseline to  $5.15 \pm 3.30$  at 1 month ( $p < 0.0001$ ), and to  $2.98 \pm 2.78$  at 2 months ( $p < 0.0001$ ) (Figure 2). MGYLS improvement had no significant intergroup difference at 2-month follow up ( $p = 0.09$ ).

The meibum were assessed by MGS score. In MiBoFlo group, the MGS score decreased from  $9.20 \pm 3.70$  at baseline to  $7.18 \pm 2.86$  at 1 month ( $p < 0.05$ ), and to  $4.86 \pm 2.18$  at 2 months ( $p < 0.001$ ). In LipiFlow group, the MGS score decreased from  $10.98 \pm 3.78$  at baseline to  $8.00 \pm 2.09$  at 1 month ( $p < 0.001$ ), and to  $4.78 \pm 2.22$  at 2 months ( $p < 0.001$ ) (Figure 3). MGS improvement had no significant intergroup difference at 2-month follow up ( $p = 0.13$ ).

In MiBoFlo group, the TMH changed from  $0.23 \pm 0.08$  mm at baseline to  $0.24 \pm 0.07$  mm at 1 month ( $p = 0.21$ ), and to  $0.27 \pm 0.13$  mm at 2 months ( $p = 0.09$ ). In LipiFlow group, the THM changed from  $0.25 \pm 0.12$  mm at baseline to  $0.24 \pm 0.10$  mm at 1 month ( $p = 0.90$ ), and to  $0.24 \pm 0.08$  mm at 2 months ( $p < 0.99$ ).

In MiBoFlo group, the NIKBUT changed from  $6.44 \pm 3.46$  seconds at baseline to  $6.44 \pm 2.13$  seconds at 1 month ( $p < 0.99$ ), and to  $5.99 \pm 2.67$  seconds at 2 months ( $p = 0.79$ ). In LipiFlow group, the NIKBUT changed from  $5.78 \pm 2.95$  seconds at baseline to  $5.33 \pm 2.62$  seconds at 1 month ( $p = 0.81$ ), and to  $5.86 \pm 2.69$  seconds at 2 months ( $p < 0.99$ ).

CFS was used for assessing corneal epithelium. In MiBoFlo group, the CFS score decreased from  $0.16\pm 0.43$  at baseline to  $0.05\pm 0.21$  at 1 month ( $p=0.07$ ), and to  $0.02\pm 0.15$  at 2 months ( $p=0.10$ ). In LipiFlow group, the CFS score decreased from  $0.38\pm 0.63$  at baseline to  $0.30\pm 0.56$  at 1 month ( $p=0.99$ ), and to  $0.18\pm 0.50$  at 2 months ( $p=0.48$ ). CFS score improvement in MiBoFlo group were significantly more obvious than in LipiFlow group in the follow-up visit ( $p=0.01$ ).

The area of meibomian glands loss was evaluated by Meibo-Scan and ImageJ software. In MiBoFlo group, the area of meibomian glands loss changed from  $0.27\pm 0.17$  at baseline to  $0.27\pm 0.18$  at 2 months ( $p=0.05$ ). In LipiFlow group, the area of meibomian glands loss changed from  $0.22\pm 0.11$  at baseline to  $0.22\pm 0.10$  at 2 months ( $p=0.05$ ).

No subject in either group experienced any device-related adverse events that involved changes in VA, IOP, anterior segment and facial skin. Only one case in the LipiFlow group encountered difficulties in the process of installing the eye cup because of small palpebral fissure.

## Discussion

At present, the therapeutic effect and maintenance time of LipiFlow are relatively clear, however, there are few studies on the efficacy of MiBoFlo. The purpose of this study is to explore the short-term therapeutic effects of MiBoFlo on MGD patients in China.

The OSDI score observed in both groups improved significantly at the first visit. There was no significant change in 2-month follow-up, however, compared with baseline level, the changes were still clinically meaningful.

A study published by Kimberly L recruited 310 subjects in order to assess the minimal clinically important difference (MCID) for the OSDI, which is defined as “the smallest difference in score in that domain of interest which subjects perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient’s management.”<sup>16</sup> It found that the MCID ranged from 4.5 to 7.3 for mild or moderate disease and from 7.3 to 13.4 for severe disease,<sup>17</sup> and it suggested that the response to treatment among patients with severe symptoms should be set higher than the response to treatment among patients with moderate symptoms. Thus, in our study, by calculating the difference of OSDI score between baseline and 2-month follow-up for each patient, we found that in MiBoFlo group, the mean improvement for severe patients was 11.3, and for mild to moderate patients was 5.5, and in LipiFlow group, the mean improvement for severe patients was 10.7, and for mild to moderate patients was 5.1, which indicated that both devices were meaningful for the improvement of DED patients’ unpleasant symptoms.

It is a remarkable fact that due to the feature of the separation of dry eye symptoms and signs,<sup>18</sup> the patient’s “severe” OSDI score cannot indicate that he/she is a patient with severe dry eye. The severity of DED is to be comprehensively evaluated with symptoms and signs.

Based on the pathogenesis, observing the orifice and meibum is the easiest and most direct way for objective signs evaluation. Thus, MGYLS and MGS were chosen as main outcome parameters for meibomian gland assessment. From this study, we can see that the MGYLS and MGS observed in MiBoFlo group improved significantly in both 1-month and 2-month follow-up visit. It was worth noting that the results of LipiFlow group revealed a more obviously trend of continued improvement in 1-month follow-up period.

From the comparison of two groups, the LipiFlow treatment was more like a “one-step process”, and the MiBoFlo treatment seemed to be “layer by layer”. For the difference of treatment effects between two groups, there could be following reasons through analysis. First of all, although both MiBoFlo and LipiFlow achieve the therapeutic effect by transferring heat from the device to the meibomian glands, the difference is the actual temperature reaching the meibomian glands. MiBoFlo is an external eyelid-warming device, heat must pass through the eyelid tissue to reach the meibomian glands. Overheating is not advisable in order to ensure security of the skin and cornea. Thus, heat loss is inevitable. LipiFlow is an internal eyelid-warming device and a lid warmer designed to rest on the sclera to transfer heat directly to the palpebral conjunctiva. A research reported by Kenrick CJ showed that the upper palpebral conjunctival temperatures had increased from 37.0°C to 42.0°C after 12 minutes LipiFlow treatment, however, after 10 minutes MiBoFlo treatment, the temperatures increased minimally.<sup>12</sup>

Secondly, the pressure applied to meibomian gland is different either. The pressure of a deliberate blink is about 0.3 psi. As for MGD patients, Korb reported that the pressure required for obtaining the nonliquid meibum varied from 5–40 psi, however, with moderate to significant discomfort.<sup>19</sup> During LipiFlow treatment, the eyelids were compressed between the bladder and the lid warmer at 6 psi simultaneously combined with the inserted eye cup. In MiBoFlo group, the method of discharging meibum is to artificially gently massage the outer eyelid during treatment and followed by physical force compression and the applying pressure is human controlled.

Summing up the above, we hypothesize that LipiFlow covered and squeezed the lower 2/3 meibomian glands while uniformly heating, and had the ability to empty abnormal meibum at once. And in MiBoFlo group, the result tended to be the superimposed effect of multiple treatments. The clearing of the obstruction might restore individual glands to a more normal state, manifesting improvement of MGYLS and MGS. The smooth discharge of normal meibum is beneficial to the recovery of tear film homeostasis. Enhanced lubrication from improved aqueous retention led to epithelial cell regeneration. Thus, following the tear film stability improvement, the other objective signs would get better, such as TMH, NIKBUT and CFS in this study.

In addition, it was showed that CFS score improvement in MiBoFlo group were significantly more obvious than in LipiFlow group in this study. It may be due to the small palpebral fissure in Chinese, which may cause damage to the ocular surface during LipiFlow treatment.

In this study, Image J was used in analyzing area of MG loss in two groups. Like evaluating MGYLS and MGS score, all MGs of the lower eyelid were analyzed, not just the central MGs, because of the wide range of massage. In the final analysis, it is found that there was no statistical difference in both groups before and after treatment. However, in the study of Arjan et al., it was indicated that the meibomian gland structure might increase after LipiFlow treatment relative to untreated controls.<sup>20</sup> The discrepancy between the two studies could be related to the follow-up time and evaluation methods.

Throughout the treatment, no subject in either group experienced any device-related adverse events that involved changes in VA, IOP, anterior segment and facial skin. Only one case in the LipiFlow group encountered difficulties in the process of installing the eye cup because of small palpebral fissure.

Such improvements in subjective symptoms and tear film stability following a painless, relaxing and safe therapy, stand in contrast to the most common treatments for DED patients currently in use, for example, pharmacotherapy. Pharmacological approaches require patient adherence to a dosing regimen that typically involves single or multiple daily doses, often for extended periods of time. Considering that the aqueous supplementation would count for little at the treatment efficacy, we allow patients to continue to use the same eye drops as before, but the medication must remain unchanged during the follow-up.

This is our preliminary study, and our report is not without limitations. Firstly, in this study, it was difficult for us to mask patients and operators, so only the observers could be masked in order to avoid bias as much as possible. Secondly, insufficient number of enrolled patients and follow-up time might cause deviations in the results. In the future clinical management on MGD, clinicians might consider adopting multiple-dose MiBoFlo therapy, or combination therapy with LipiFlow.

## Conclusion

As a portable and comfortable externally heat applied source, MiBoFlo treatment can offer an advancement for the treatment of MGD and a course of treatment results in at least two months of sustained improvement in both symptoms and meibomian gland function. We believed that MiboFlo could be used as the treatment options of MGD patients, or as a combined treatment option with the thermal pulsation system treatment.

## Abbreviations And Acronyms

CFS = Corneal Fluorescein Staining; IOP = intraocular pressure; MG = Meibomian Glands; MGD = meibomian gland dysfunction; MGS = Meibomian Glands Secretion; MGYLS = Meibomian Glands Yielding Liquid Secretion; NIKBUT = Non-invasive Keratograph Break-up Time; OSDI = Ocular Surface Disease Index; TBUT = Tear film Break-up Time; VA = Visual Acuity

## Declarations

**Ethics approval and consent to participate**

This study conformed to the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Review Committee of Beijing Tongren Hospital. The trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) as NCT04310969. All patients were given a full explanation of the study, and written informed consent was obtained from all participants.

### **Consent for publication**

Written informed consent for publication was obtained from all participants.

### **Availability of data and materials**

The datasets generated during and analyzed during the current study are not publicly available due to the need for further research but are available from the corresponding author on reasonable request.

### **Competing interest**

The authors declare that they have no competing interests

### **Funding**

Not applicable.

### **Authors' contributions**

Ying Jie and Lei Tian are the main persons in charge of this clinical trial and responsible for subjects enrolled. Siyuan Li and Ke Yang are responsible for designing the trial. Siyuan Li, Jingyi Wang, Lei Zhu and Jun Feng are responsible for the treatment and follow-up of the trial. Siyuan Li and Ke Yang wrote the main manuscript text. All authors reviewed the manuscript.

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## Tables

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

## Figures

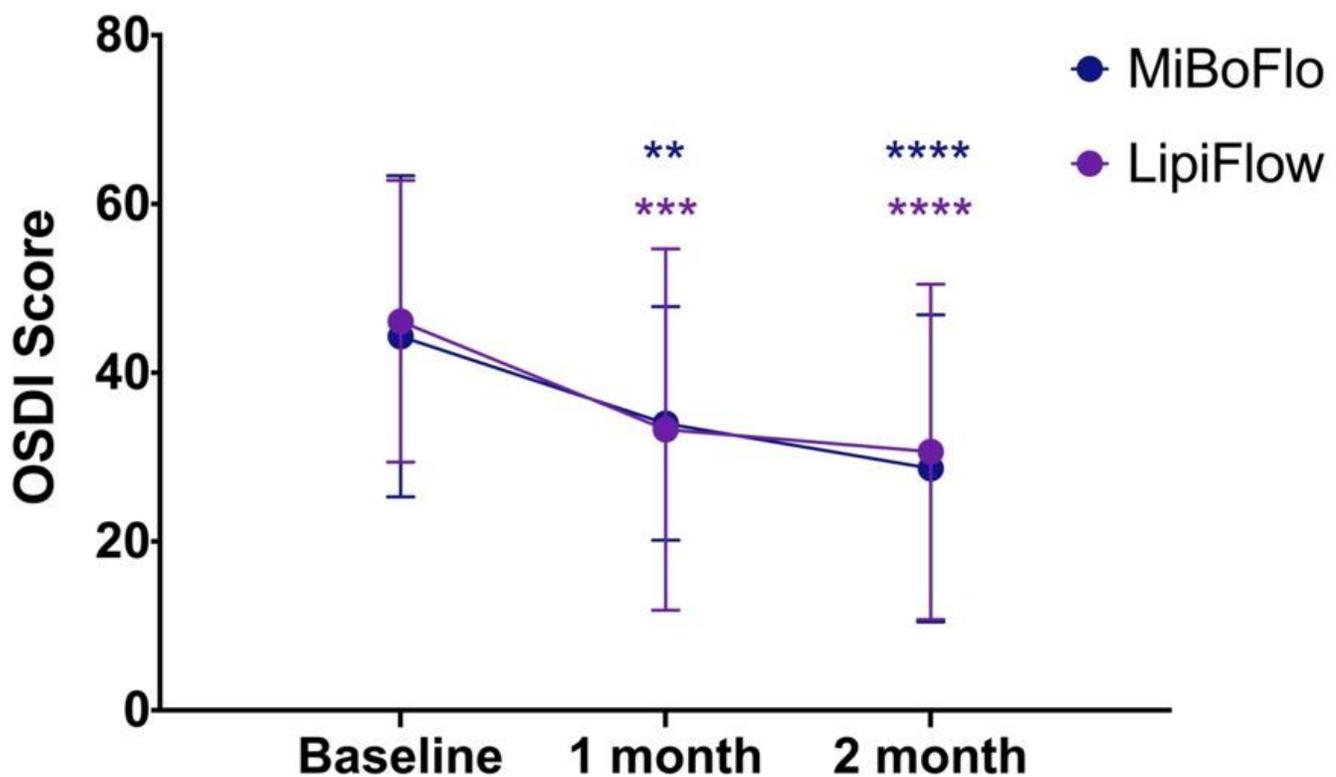


Figure 1

The mean OSDI score of the MiBoFlo group and the LipiFlow group measured at baseline, at 1 month and at 2 months. \*\*Values are significantly different from their respective baseline level ( $p \leq 0.01$ ). \*\*\*Values are significantly different from their respective baseline level ( $p \leq 0.001$ ). \*\*\*\*Values are significantly different from their respective baseline level ( $p \leq 0.0001$ ).

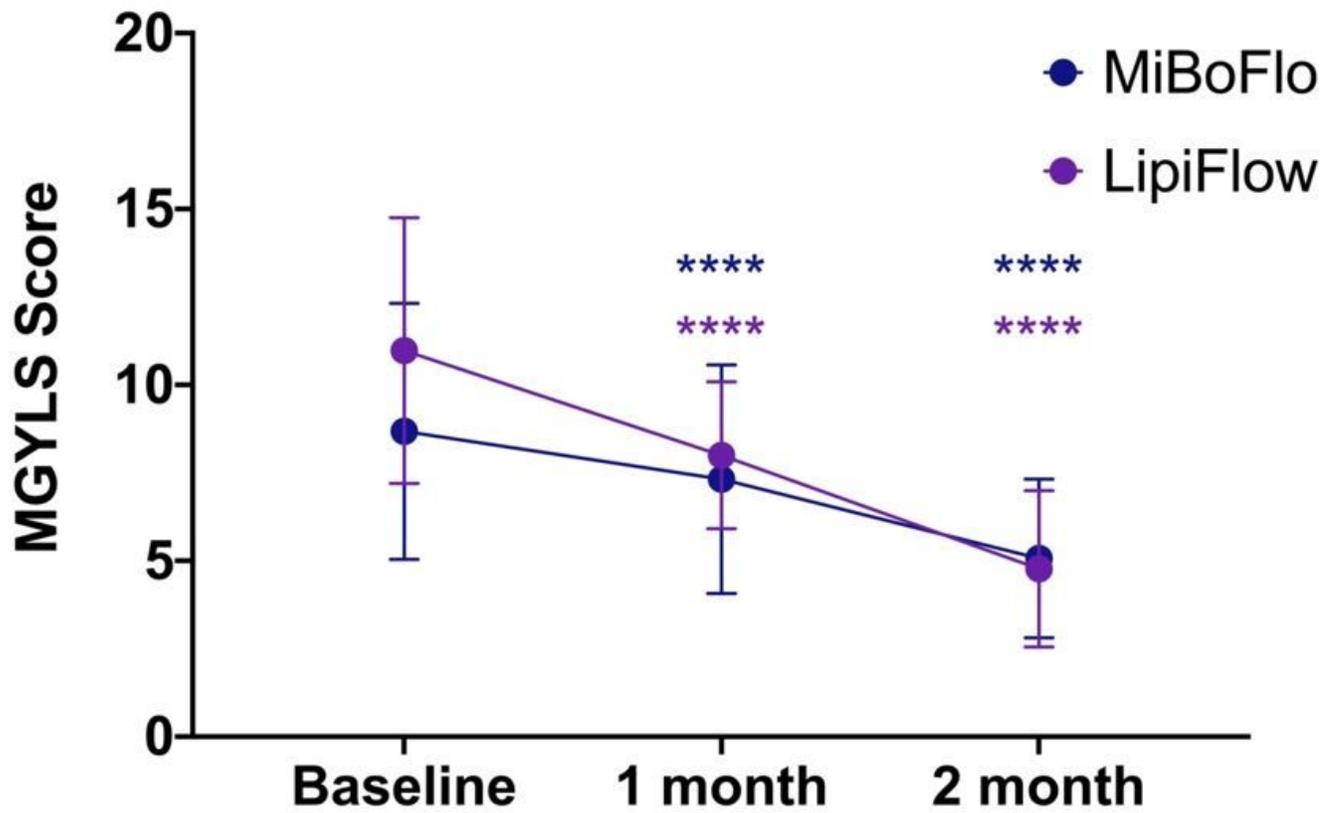


Figure 2

The mean MGYLS score of the MiBoFlo group and the LipiFlow group measured at baseline, at 1 month and at 2 months. \*\*\*\*Values are significantly different from their respective baseline level ( $p < 0.0001$ ).

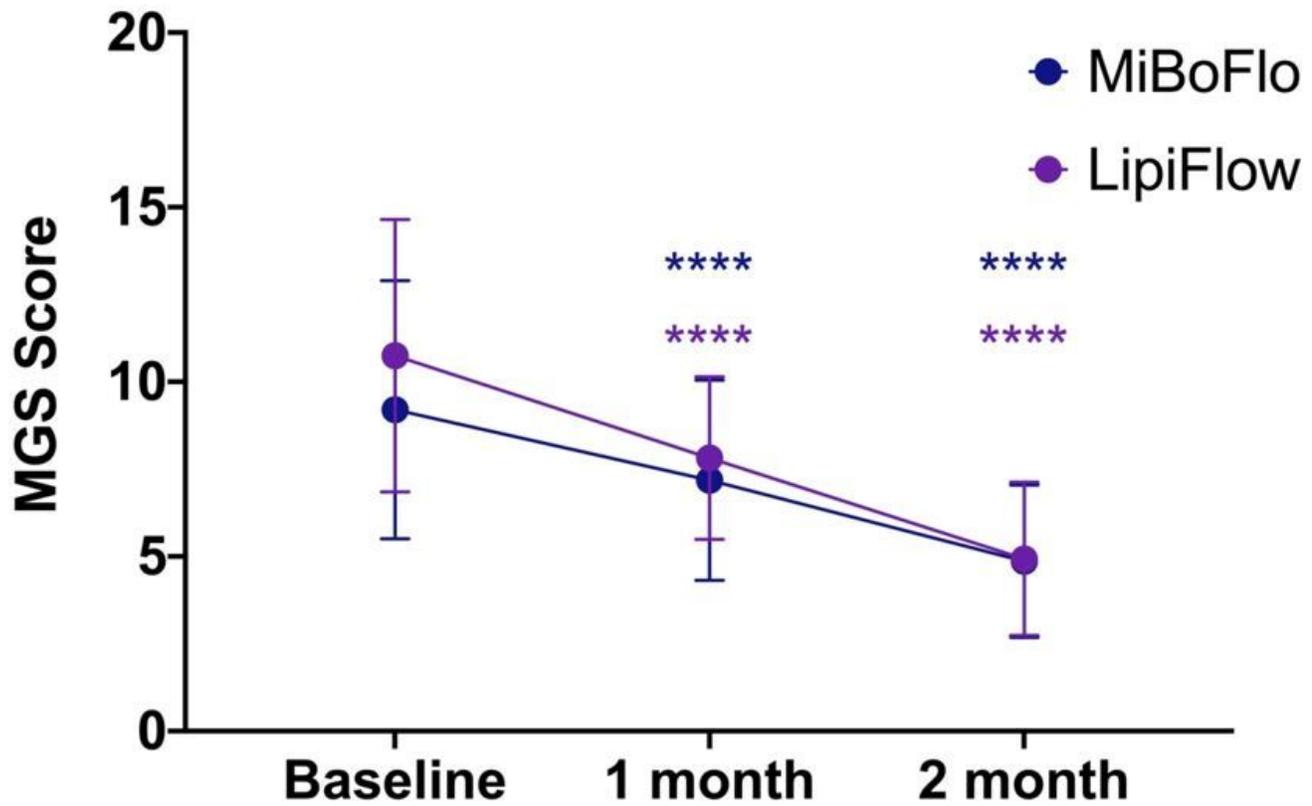


Figure 3

The mean MGS score of the MiBoFlo group and the LipiFlow group measured at baseline, at 1 month and at 2 months. \*\*\*\*Values are significantly different from their respective baseline level ( $p \leq 0.0001$ ).

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.jpg](#)