



Clinical efficacy of laser combined with menstrual regulation in the treatment of female melasma: a retrospective study

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Received: 2 July 2018 / Accepted: 27 November 2018 / Published online: 8 January 2019
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Abstract

The aim of this study was to evaluate the clinical efficacy of using a Medlite C6 Q-switch Nd:YAG laser combined with menstrual regulation-based traditional Chinese medicine (TCM) in the treatment of female melasma. Forty cases of female patients with melasma, who were treated between December 2013 and December 2015 at the Jiangsu Provincial Hospital of Traditional Chinese Medicine, were reviewed retrospectively. Twenty patients received Q-switch Nd:YAG 1064 nm laser treatments combined with menstrual regulation treatments (experimental group), and 20 patients were treated only with the laser (control group). All treatments lasted for 6 months. The patients' faces were photographed before, immediately, and 6 months after treatment. The therapeutic efficacy was assessed by the reduction in the Melasma Area and Severity Index (MASI) score and the total skin damage score, and this was then compared between the two groups. Immediately and 6 months after the treatment, both the MASI and total skin damage scores in the experimental group were significantly lower compared to those in the control group ($P < 0.001$). The experimental group had significantly higher basic recovery and effectiveness rates than the control group ($P = 0.020$ and $P = 0.008$, respectively) and had a significantly lower invalidity rate ($P < 0.001$). Results from Medlite C6 Q-switch Nd:YAG laser treatment combined with menstrual regulation are superior than those obtained using only a laser for the treatment of female melasma.

Keywords Female · Melasma · Menstrual regulation · Laser · Efficacy

Background

Melasma is a frequently acquired pigmentary disorder in women, which may be related to the female-specific

physiological characteristics (e.g., menstruation). Melasma is difficult to treat by different approaches, none of which show stable and satisfactory results. Conventionally, laser treatment has been effectively used for chloasma, significantly improving the symptoms, while high recurrence rates and uneven black and white depigmentation of the skin were often observed [1–7], suggesting that the laser alone is not sufficient for the treatment of melasma. Better treatment regimens are needed.

The combination of laser treatment with other techniques (such as medicine) can achieve good results [3, 8–11] and is superior to the laser alone. As a result, combined therapies such as laser treatment with oral tranexamic acid [12], traditional Chinese medicine (TCM) with photorejuvenation [13], and laser treatment with topical application of cream (e.g., azelaic acid cream) [11] have been increasingly used clinically.

The TCM-based menstruation regulation method has been used for the treatment of female-specific diseases (e.g., luteinized unruptured follicle syndrome and diminished ovarian reserve). For example, Yan-hua et al. combined menstrual

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regulation method with triptorelin acetate injections to treat patients with luteinized unruptured follicle syndrome, increasing the rates of ovulation and pregnancy rates [14]. Huang et al. employed menstrual regulation and hormone replacement therapy to treat diminished ovarian reserves [15]. However, the efficacy of menstrual regulation for melasma has not been evaluated yet.

We supposed that laser treatment combined with menstrual regulation would be more effective for female melasma. We evaluated the efficacy of the laser combined with menstrual regulation in the treatment of female melasma in comparison with treatment using only the laser.

Methods

Patients

Fifty-six female patients with melasma treated between December 2013 and December 2015 at the Department of Plastic Surgery, Jiangsu Provincial Hospital of Traditional Chinese Medicine (Nanjing, China) were retrospectively reviewed. Female premenopausal patients, aged 18–50 years and in accordance with the diagnostic standard of melasma, were included. Patients who (1) exhibited other pigmentary diseases (such as zygomaticofacial naevus fuscoceruleus, Riehl melanosis, and trauma-induced pigmentation) or mental disorders or behavioral disabilities, (2) refused to cooperate with the doctors to finish treatments, (3) received laser or medical treatment for melasma within 3 months prior to this study, (4) were over 65 years or younger than 18 years, (5) were pregnant or lactating women, or (6) were with irregular menstrual cycles were excluded from this study. Eventually, 40 cases of patients were analyzed. Twenty patients received Medlite C6 Q-switch Nd:YAG 1064 nm laser treatment with the menstrual regulation method (experimental group), and 20 patients were only treated with the Medlite C6 Q-switch Nd:YAG laser (control group). Patients' characteristics such as gender, age, and the course, classification, and distribution of the melasma were reviewed. This study was approved by the Ethics Committee of the Jiangsu Provincial Hospital of Traditional Chinese Medicine. Written informed consent was obtained from each participant.

Diagnosis of melasma

Melasma was diagnosed based on the Criteria for the Clinical Diagnosis and Therapeutic Effects of Melasma, revised in December 2003 by the group for pigmentary diseases of the Professional Board of Dermatology and Venereology of the Chinese Association of Integrated Chinese and Western Medicine [16].

Treatment for experimental group patients

The patients in the experimental group received TCM prescriptions for the premenstrual, menstrual, and postmenstrual periods and laser treatment.

The TCM prescription for the premenstrual period included a modified Wentu Liu Ling decoction containing 15 g morinda officinalis, 15 g raspberry, 15 g atractylodes rhizome, 10 g *Codonopsis pilosula*, 12 g Chinese yam, 10 g medicated leaven, 15 g schizonepeta tenuifolia, 10 g *Tribulus terrestris*, 10 g radix angelicae, 10 g white muscardine silkworm, 10 g white paeony root, 10 g cohosh, 10 g rhizoma cyperi, and 10 g radix aucklandiae.

The prescription for the menstrual period included modified Wu Wei Tiao Jing San decoction containing 10 g angelica sinensis, 10 g radix paeoniae rubra, 10 g trogopterus dung, 10 g folium artemisiae argyi, 30 g motherwort, 10 g atractylodes rhizome, 10 g rhizoma cyperi, 10 g cortex moutan, 10 g savia miltiorrhiza, 10 g herba lycopi, 10 g radix dipsaci, 10 g poria, and 10 g radix cyathulae.

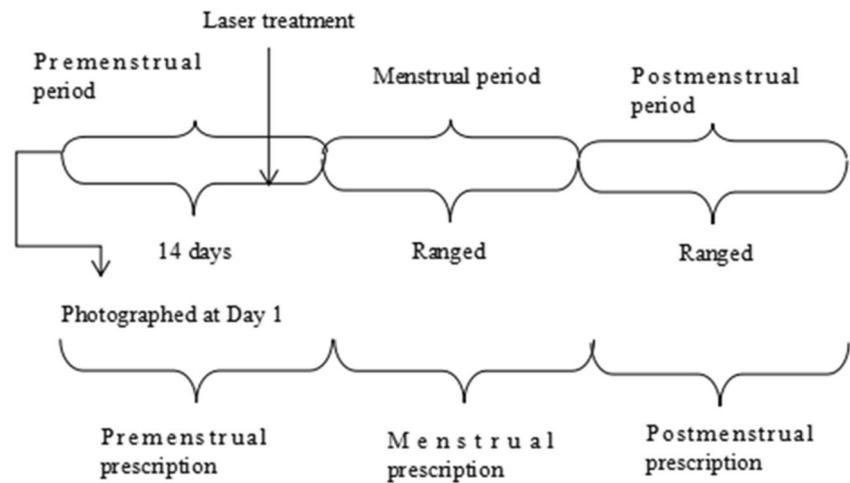
The prescription for the post-menstrual period included a modified Gui Shao Di Huang decoction containing 15 g radix rehmanniae, 15 g angelica sinensis, 15 g white paeony root, 10 g wolfberry, 10 g cortex moutan, 6 g rhizoma anemarrhenae, 10 g *Codonopsis pilosula*, 3 g radix glycyrrhizae preparata, 10 g cortex lycii radices, 15 g schizonepeta tenuifolia, 10 g *Tribulus terrestris*, 10 g radix angelicae, 10 g white muscardine silkworm, 10 g cohosh, 15 g atractylodes rhizome, and 15 g dogwood.

Each of the above prescriptions was decocted twice with water and mixed well with about 300 ml of water, which was orally administered 1 h after meals twice a day, 150 ml at 9 am, and 150 ml at 3 pm, respectively, continuously during the treatment period.

Laser therapy was performed through a nanosecond laser using a Medlite C6 Q-switch Nd:YAG laser (Aokang, USA) with a wavelength of 1064 nm. In brief, before the treatment, the patients' faces were washed and photographed for filing. During the laser treatment, the patients were required to wear goggles. A laser treatment head was positioned perpendicular to the skin and focused on irradiating lesions individually. The emitted light spot, with a diameter of 6 mm, frequency of 10 Hz, and energy density of 2.5–3.5 J/cm², evenly and slowly irradiated back and forth in parallel to cover lesions two to three times until the skin became slightly red. According to the previous treatment response, the patients received laser treatment with gradually increasing energy. The treatment was stopped upon the occurrence of slightly reddish skin. After the therapy, sterile surgical masks were used to calm the patients.

As shown in Fig. 1, each patient underwent the treatment six times, with an interval of a menstrual cycle. The day for the first laser treatment was referred to as Day 1 of the first

Fig. 1 Treatment flow chart



premenstrual period since the treatment (i.e., 14 days before the first menstruation day or the first day to take the prescribed medicine for the premenstrual period). The faces were photographed on the first treatment day using a digital camera (DSC-RX100 M3, Sony, Japan) from the front and lateral positions. The 2nd, 3rd, 4th, 5th, and 6th laser treatments were on the first day of the 2nd, 3rd, 4th, 5th, and 6th premenstrual periods, respectively. After six laser treatments, the patients' faces were photographed again on the first day of the next premenstrual period for the evaluation of the curative effect. All the patients were banned from the oral or external administration of melasma agents as well as sunlight exposure.

Treatment for control group patients

The patients in the control group received only laser treatments. The protocol was similar to that in the laser treatment section for the experimental group patients.

Efficacy evaluation

After the treatment and 6-month follow-up, two dermatologists analyzed the photos of skin lesions on the patients' faces. If there was substantial difference in the judgment between the two dermatologists, a third dermatologist would join in and the result closer to that of any of the first two dermatologists was determined as the final result. The melasma area and severity index (MASI) [17] and total skin damage scores [16] were used to evaluate the curative effect. The total skin damage score is the skin damage area score plus the skin color score [16]. In particular, skin damage scores of 0, 1, 2, and 3 represented skin damage areas of 0, < 2, 2–4, and > 4 cm², respectively. Skin color scores of 0, 1, 2, and 3 showed normal, light-brown, brown, and dark-brown skin colors, respectively. A drop index of the total skin damage score was defined as (pre-treatment score – post-treatment score)/pre-treatment score × 100%. Basic recovery was defined as over 90%

of the area of the visible stain faded away, the skin color nearly changed, and a post-treatment efficacy index of ≥ 0.8 . Obvious effectiveness was defined as 60–90% of the area of the visible stain faded away, apparently fainter skin color, and a post-treatment efficacy index of 0.5–0.8. Improvement was defined as 30–60% of the area of the visible stain faded away, fainter skin color, and a post-treatment efficacy index of 0.3–0.5. Invalidity was defined as $\leq 30\%$ of the area of the visible stain faded away, no obvious change in the skin color, and a post-treatment efficacy index of < 0.3.

Statistical analysis

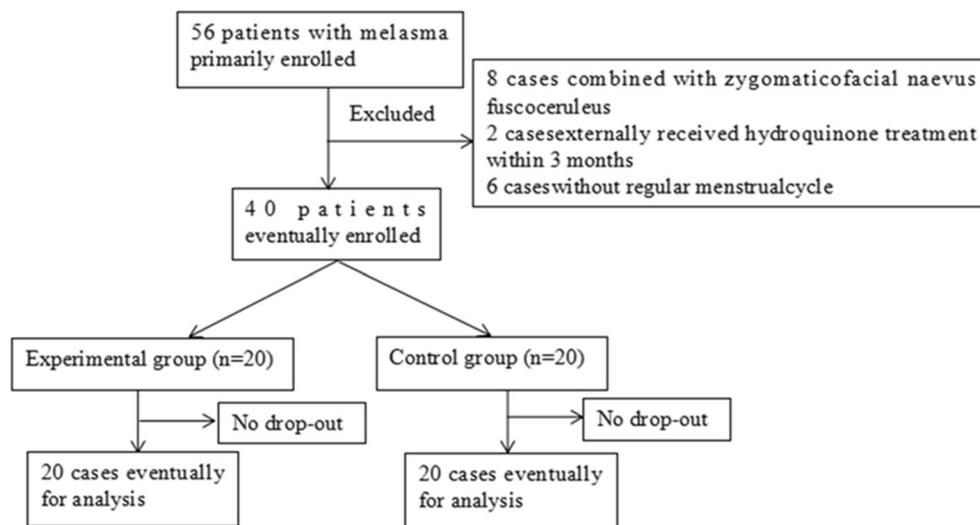
All the data were analyzed with SPSS 20.0 (SPSS Inc. Chicago, IL, USA) or Stata 13.0. (STATA Corp., College Station, TX). The measurement data were expressed as mean \pm standard deviation; data with a normal distribution were compared between the experimental and control groups using the *t* test, and those with abnormal distributions were compared using a nonparametric test. Enumeration data were compared using the chi-squared test or Fisher's exact test. $P < 0.05$ represents a statistical difference, and $P < 0.01$ represents a significant statistical difference.

The Minimum Standards of Reporting Checklist contains details of the experimental design, statistics, and resources used in this study.

Results

Patient basic characteristics

Forty patients with melasma were eventually reviewed, 20 in each experimental and control groups (Fig. 2). There were no significant differences in age, disease course, classification of skin damage, and Fitzpatrick types of melasma between the experimental and control groups at the baseline (Table 1).

Fig. 2 Flow chart for patient selection

Variation of MASI score

As shown in Table 2, before the treatment, there was no significant difference in the MASI scores between the groups. Both immediately after the treatment and after 6 months during the follow-up, the experimental group had significantly lower MASI scores than the control group ($P < 0.001$ and $P = 0.001$, respectively).

Variation in total skin damage score

Before treatment, there was no significant difference in the total skin damage scores between the groups ($P = 0.732$). After treatment, both the total skin damage scores and the decrease (reflected by the drop index) were significantly lower in the experimental group than that in the control group (both $P < 0.001$; Table 3). Greater recovery and obvious effectiveness rates were found in the experimental group ($P = 0.020$ and 0.008 , respectively; Table 3).

Typical photos of melasma on the faces of the patients are shown in Fig. 3. For a typical patient (44 years old) in the experimental group, the melasma became evidently lighter after the treatment, acne improved, and the skin appeared bright and fine. During the follow-up, no melasma recurred, and the acne disappeared. In contrast, for a patient (37 years old) in the control group, no obvious lightening of the melasma was observed after the treatment, and a new skin lesion occurred under the eye corner during the follow-up.

Discussion

The TCM methods such as soothing the liver and relieving depression, invigorating the kidney, strengthening the spleen and eliminating dampness, and activating the blood and removing stasis have been used for the treatment of melasma, without obvious side effects [18–20]. However, these methods need a long treatment course, and more than one dialectical method is often needed. In addition, many female melasma

Table 1 Patient basic characteristics

	Experimental group (n = 20)	Control group (n = 20)	P value
Age (years)	42.8 ± 7.8	41.3 ± 7.2	0.544
Disease course (years)	5.1 ± 3.7	4.1 ± 2.7	0.340
Classification of skin lesion			
Butterfly type, n (%)	5 (25)	6 (30)	0.723
Upper face type, n (%)	6 (30)	7 (35)	0.736
Lower face type, n (%)	1 (5)	0 (0)	1.000
Generalized type, n (%)	8 (40)	7 (35)	0.744
Fitzpatrick type			
III type, n (%)	14 (70)	15 (75)	0.723
IV type, n (%)	5 (25)	5 (25)	1.000
V type, n (%)	1 (5)	0 (0)	1.000

Table 2 Variation of MASI score between the experimental and control groups

	Experimental group (n = 20)	Control group (n = 20)	P value
Before the treatment	21.64 ± 9.06	16.78 ± 10.12	0.118
After the treatment	4.49 ± 2.76	10.83 ± 6.84	<0.001
At 6 months during the follow-up	6.37 ± 4.43	14.84 ± 9.76	0.001

patients are diagnosed with menstrual and endocrine disorders and often simultaneously take other drugs, which is ideal for TCM-based treatments. Therefore, we combined the laser therapy with a suitable TCM-based menstruation regulation method to treat melasma, in an attempt to make use of the advantages of the TCM and western medicine treatments and to avoid disadvantages such as shortening treatment course, which has not been previously reported.

The menstruation regulation method is mainly used to adjust the menstrual cycle of infertile female patients and help them release dominant follicles during the ovulatory period, which increases the probability of pregnancy. Menstrual regulation prescriptions include menstrual cycle-regulating decoctions, kidney tonification, and ovulation-promoting decoctions. As this study focused on treating melasma through adjusting the menstrual cycle without the requirement of ovulation, the kidney tonification and ovulation-promoting decoction used in the menstruation regulation prescriptions were removed. The decoction in the study was used in the pre-, post-, and menstrual periods.

The abnormal levels of β -estradiol and progesterone are the main cause of melasma through the induction of melanin from melanocytes. It has been shown that estrogen and progesterone stimulate the melanocytes to secrete melanin [21]. β -Estradiol incubation for 24 h increased the tyrosine enzyme activity of melanocyte by 145–213% of the base activity [22]. Melasma patients complained of the worst state during the premenstrual period and felt slightly better after menstruation. Therefore, we started the treatment during the premenstrual period.

According to the premenstrual physiological characteristics, we used the Wen Tu Liu Ling decoction to enhance and maintain a state of overabundant Yang, reinforce the spleen and strengthen and regulate Qi flow (G2), and activate the blood

circulation, which enhance the transition to the menstruation period. Percutaneous relieving drugs, such as schizonepeta tenuifolia, radix angelicae, *Tribulus terrestris*, white muscardine silkworm, white paeony root, and cohosh, in favor of medicines absorbed by the face, were added in this period. The prescription for the premenstrual period can improve the inherent metabolism of the drugs via the skin, enhance self-metabolism, and provide kinetic energy for metabolizing turbid Qi and congestion during the menstruation period.

The menstrual cycle of the patients in this study was 28 ± 7 days, which is normal. Therefore, any day within the 7 days before the menstrual period is suitable for the laser treatment; thus, the melanin is shattered by the laser, engulfed by macrophages, and then adequately excreted by the circulation in the menstruation period.

The Wu Wei Tiao Jing prescription used during the menstruation period can activate the blood and warm meridians and promote extravasated blood flow downward. If the relieving drugs are added in this period, the efficacy would be uneven without completely cleaning the extravasated blood. Thus, removing extravasated blood and dampness is the main goal during the menstruation period.

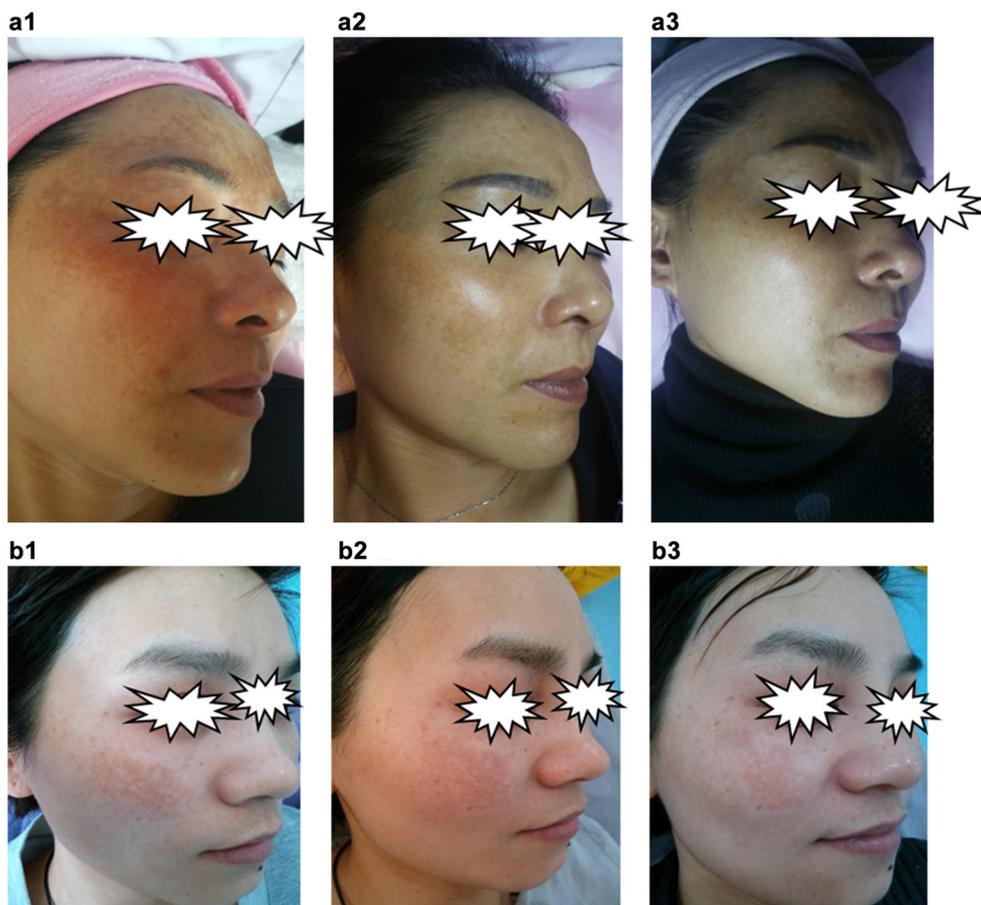
During the post-menstruation period, the sea of blood is empty such that Yin and Yang need to be nourished and tonified, respectively. Therefore, the Gui Shao Di Huang decoction should be used. For patients with melasma after menstruation, the dampness is removed, the face color recovers to the ideal state, and the melasma becomes lightest, which is the proper time to induce gas and blood flow up to face. Therefore, for nourishing the Yin and slightly tonifying the Yang, a relieving drug was added on the face to further reduce the melasma.

In our study, the laser treatment was used only six times, which is less than that in some previous studies involving only

Table 3 Variation of total skin damage score between the experimental and control groups

	Experimental group (n = 20)	Control group (n = 20)	P value
Total score before treatment	4.55 ± 0.89	4.45 ± 0.94	0.732
Total score after treatment	1.50 ± 0.61	3.70 ± 1.17	<0.001
Drop index of total score	0.67 ± 0.14	0.16 ± 0.22	<0.001
Efficacy, n (%)			
Basic recovery	8 (40)	1 (5)	0.020
Obvious effectiveness	12 (60)	3 (15)	0.008
Improvement	0 (0)	5 (25)	0.047
Invalidity	0 (0)	11 (55)	<0.001

Fig. 3 Melasma observations before, immediately, and 6 months after the treatment. A: A 44-year-old female patient with an upper face type and type-III Fitzpatrick of melasma and a disease course of 7 years in the experimental group. A1: a relatively large and dark melasma area before the treatment, with scattered acne; A2: evidently lighter melasma after the treatment with obvious acne improvement and bright and fine skin; A3: no melasma recurred, the skin appears bright and fine, and acne disappeared during the follow-up. B: A 37-year-old female patient with an upper-face-type and type-III Fitzpatrick of melasma and a four-year disease course in the control group. B1: a relatively dark melasma before the treatment; B2: insignificantly lighter melasma after the treatment; B3: a new skin lesion occurring under the eye corner during the follow-up



the laser treatment, such as ten [23] and 15 times [24]. This suggests that the laser treatment in combination with the menstrual regulation can not only achieve a better treatment efficacy for female melasma but also simultaneously decrease the laser treatment times to reduce laser-associated complications.

There are some limitations in this study. The sample size is relatively small, and the follow-up time is only 6 months. Next, we will recruit more patients and have a longer follow up time to further verify the efficacy of the laser treatment combined with the menstruation regulation method for melasma. In addition, thus far, the formulae of components of prescriptions are largely unclear. Identifying the detailed formulae, physiological functions, indications, etc. will improve and strengthen the application of the TCM in clinics, which is an important goal for the TCM treatment in the future.

Conclusions

In summary, laser treatment with menstrual regulation achieves a greater efficacy, and it is superior to laser-only treatment for melasma, as the former requires significantly reduced laser treatment. This study suggests a novel, effective technique for the treatment of female melasma.

Compliance with ethical standards

Ethics approval This study was approved by the Ethics Committee of the Jiangsu Provincial Hospital of Traditional Chinese Medicine. All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all the participants included in the study.

Competing interests The authors declare that they have no conflict of interest.

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