



# Comparative evaluation of low-level light therapy and ethinyl estradiol and desogestrel combined oral contraceptive for clinical efficacy and regulation of serum biochemical parameters in primary dysmenorrhoea: a prospective randomised multicentre trial

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## Abstract

We aimed to compare low-level light therapy with oral contraceptive pills for pain relief and serum levels of nitric oxide and prostaglandin E<sub>2</sub> in patients with primary dysmenorrhoea. This was a randomised, active comparator-controlled, multicentre study. In total, 156 patients were randomised to receive either low-level light therapy with light-emitting diodes (LED) applying on two acupoints, namely, conception vessel 4 (CV4) and CV6 or conventional treatment with oral Marvelon, 30 µg of ethinyl estradiol and 150 µg of desogestrel (DSG/EE), for three consecutive menstrual cycles. The main outcome was the proportion of patients who achieved 33% or more decrease in pain scores measured using the visual analogue scale, which was deemed as efficient rate. Absolute changes in visual analogue scale scores, serum levels of nitric oxide (assessed by nitrites and nitrates reflecting nitric oxide metabolism) and prostaglandin E<sub>2</sub> (measured by enzyme-linked immunosorbent assay) were the secondary outcomes. A total of 135 patients completed the study (73 in the light therapy group and 62 in the DSG/EE group). The efficient rate at the end of treatment was comparable between the groups (73.6% vs. 85.7%,  $\chi^2 = 2.994$ ,  $p = 0.084$ ). A more significant reduction in pain scores was observed in the DSG/EE group (39.25% vs. 59.52%,  $p < 0.001$ ). Serum levels of prostaglandin E<sub>2</sub> significantly decreased from baseline but did not differ between groups ( $-109.57 \pm 3.99$  pg/mL vs.  $-118.11 \pm 12.93$  pg/mL,  $p = 0.51$ ). Nitric oxide concentration remained stable in both groups. Low-level light therapy with LED-based device applied on acupuncture points CV4 and CV6 demonstrated a similar level of dysmenorrhoea pain reduction to DSG/EE combined contraceptive. Both treatment modalities achieved clinically meaningful levels of pain reduction. Registration on ClinicalTrials.gov: TRN: NCT03953716, Date: April 04, 2019.

**Keywords** Dysmenorrhoea · Low-level light therapy · Visual analogue scale · Prostaglandin · Nitric oxide

## Introduction

Primary dysmenorrhoea (PD) is defined as cramping pain in the lower abdomen during menstruation in absence of any discernible pelvic pathology [1, 2]. Systemic symptoms usually associated with PD, such as sweating, headache, nausea, vomiting and diarrhoea [3]. Population surveys have suggested that the prevalence of PD varies between 16 and

93% [4, 5], and severe pain is associated with limited daily activity and compromised quality of life [6]. Overproduced prostaglandins are integral to the pathogenesis by causing myometrial hypercontractility and vasoconstriction, primarily resulting in the accumulation of anaerobic metabolites that stimulate the pain receptors [3, 7].

Oral contraceptive pills (OCPs), as one of the mainstays of treatment for PD, have yielded approximately 70–80% efficacy, but many still fail such pharmacological therapy [8, 9]. Current research has shown that the use of OCPs on a long-term basis is associated with an increased risk of venous thromboembolism [10]. Moreover, the dosing regimens of hormone therapy such as oral contraceptives may challenge compliance. Thus, numerous alternative treatments including herbal remedies, heat application,

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acupressure, exercises and dietary supplements have been investigated in recent years [3, 11].

Low-level light therapy (LLLT), also known as photobiomodulation, involves exposure of tissues to red or infrared light with low levels of energy densities [12]. In contrast to the laser beam used for cutting, ablation or thermal coagulation, LLLT causes no heat effect or structural changes in target tissue and has been developed into a sophisticated therapeutic procedure for a wide variety of ailments [13, 14]. Notably, LLLT is able to induce analgesic effect by stimulating the generation of endorphin, activating the circulation of blood and lymph flow and promoting healing of injured cells, especially for acute painful conditions [12]. Besides, it has been found to reduce serum levels of prostaglandin through superoxide dismutase hastening [15, 16]. These facts make it a potentially novel treatment for dysmenorrhoea. Meanwhile, evidence is growing that LLLT is effective in reducing menstrual pain compared with the placebo device [17, 18]. However, there is still a dearth of scientific data exploring the differences in management of PD between the conventional modality with hormonal agents and photobiomodulation. Herein, we conducted this pragmatic, multicentred, randomised, conventional drug-controlled study to assess the effectiveness and safety of LLLT for women with PD.

## Materials and methods

### Study design

This was a 12-week, prospective, randomised, multicentre, active comparator-controlled study that was compliant with standard guidelines and registered at ClinicalTrials.gov (NCT03953716). The study protocol was compliant with the ethical principles of the Declaration of Helsinki and was approved by the institutional review board at all study sites. Patients were recruited from June 2019 to June 2020 at eight hospitals in seven provinces. All subjects signed a written declaration of informed consent. The sample size of the study was not estimated because it is the first comparative evaluation between OCPs and LLLT in management of PD. To determine a reliable difference and standard deviation of clinical efficacy between groups, we included a much larger study population than previously reported.

### Study patients

A total of 156 women aged 16–35 years, with clinical diagnosis of PD but otherwise in good health, were recruited. All patients were screened for a normal pelvic condition based on both ultrasonography and physical examination. They were required to use a condom or diaphragm as methods

of contraception during the treatment course. Patients with irregular menstrual cycles, ongoing or history of pelvic inflammatory disease, adnexal masses or cysts, endometriosis, adenomyosis, uterine fibromas or endometrial polyps were not eligible for this survey. Participants who were addicted to alcohol or cigarettes, had received regular treatment for PD within 3 months prior to recruitment or had contraindications to study modalities were also excluded. The contraindications of LLLT are as follows: (1) had serious medical or psychiatric disorders; (2) with a positive screening test of pregnancy and (3) had experienced hypersensitivity to phototherapy.

### Study treatments

A computerised random number was generated using SAS (Cary, NC) with a ratio of allocation 1:1. Patients were randomly assigned to the treatment modality of either contraceptive pills or LLLT. Marvelon (N.V. Organon, NL) is a monophasic OCP formulation containing 30 µg of ethinyl estradiol and 150 µg of desogestrel (DSG/EE) in each tablet. Participants in DSG/EE group were instructed to take one tablet per day from 5th day of the menstrual cycle for 21 days every 28 days.

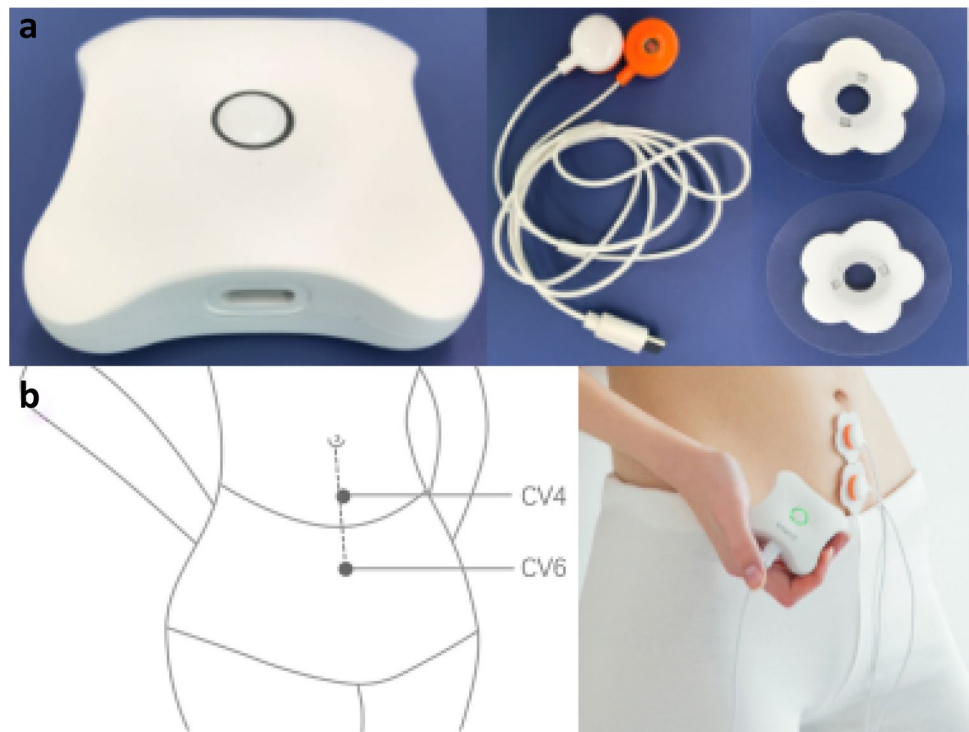
The light exposure was applied to the experimental group with LLLT device of 630 nm wavelength (red light). This small and portable device, called Eospal (BEST Biotech Inc., CN), is specifically designed for self-management of dysmenorrhoeic pain, approved by the China Food and Drug Administration (Registration No. 20182090168); it has entered the market in recent years. The device specifications are displayed in Table 1. As depicted in Fig. 1, the light was generated from a microprocessor-controlled light-emitting diode (LED) and was transmitted through lines to skin-adhesive pads that were attached to two acupoints: conception vessel 4 (CV4, Guanyuan) and CV6 (Qihai). Technically, a power of 2.5 mW was applied on 1 cm<sup>2</sup> skin surface (0.5 cm<sup>2</sup> per pad) over the two acupressure points with a peak fluence dose of 3 J/cm<sup>2</sup>. Patients in the LLLT group were required

**Table 1** Illumination parameters of the LED-based low-level light therapy device

Items	Values
Rated voltage	3.7 VDC
Rated current	300 mA
Power density	1.0–2.5 mW cm <sup>-2</sup>
Energy	3.0 J cm <sup>-2</sup>
Wavelength (spectrum)	630 ± 20 nm (red)
Irradiation time	20 min
Device weight	32 g ± 10%

VDC, voltage direct current

**Fig. 1** The component of low-intensity level light device and related acupuncture points. **a** The low-level light therapy device consists of the controller, lines and skin-adhesive pads; **b** The location of the two acupoints where the pads should be positioned to: conception vessel 4 (CV4, also known as Guanyuan) which located at two fingerbreadths below the umbilicus and conception vessel 6 (CV6, Qihai) which located at two fingerbreadths below the CV4



to perform each light irradiation 20 min once per day for 5 consecutive days every 7 days. Phototherapy should be suspended during menstruation. Professional instructions were provided to guarantee that the patients could use the device correctly. Both interventions were continued for 12 weeks. Individual adherence was confirmed at each cycle by video check for LLLT group or pill counts for DSG/EE group.

During the study period, private use of drugs or self-administer therapy that may interfere with or mask the effects of the study modalities was not permitted. For participants suffered unbearable pain, the rescue painkillers (ibuprofen, 0.3 g/capsule, Sino-GlaxoSmithKline, CN) were prescribed by investigators. The quantity of painkillers that the subjects requested was documented in the case report form.

### Parameters and assessments

Pain intensity was evaluated using a 10-cm visual analogue scale (VAS) ranging from 0 (no pain) to 10 (worst pain) at 10 a.m. on the first or second day of menstruation at each cycle (week 0, 4, 8, 12), in which mild pain was scored as 1–3, moderate pain 4–6 and severe pain 7–10. Previous study reported a 33% or more reduction in the VAS score indicated clinically significant regression [19]. As primary endpoint, the proportion of women who achieved significant pain relief (> 33% reduction from basal VAS pain score) after the treatment was defined as the therapeutic efficiency. The second outcomes were absolute changes from baseline in VAS

scores, levels of serum nitric oxide (NO) and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>). The safety profile was assessed by routine blood and urine tests and functional tests of liver and kidney.

Blood samples were taken on the second day of menstrual cycle at screening visit and week 12. Samples were centrifuged at 3000 revolutions per minute for 20 min, and the supernatants were stored at –80 °C. The serum was thawed at room temperature to examine the levels of PGE<sub>2</sub> using an enzyme-linked immunosorbent assay kit according to the manufacturer's instructions (RJ13649, RENJIE Biotech Inc., CN). The colour reaction was measured at 450 nm using a colorimetric microplate reader (Infinite® F50, Tecan, CH). The NO concentration in the plasma was determined by the total nitrite and nitrate levels. Briefly, a mixture of 50 µL of supernatant and 50 µL of Griess reagent (RJ-W-A804, RENJIE Biotech Inc., CN) was incubated for 10 min. Standard curves were prepared with known concentrations (1–100 µmol/L) of sodium nitrite. Absorbance was measured at 540 nm. The sensitivity of the assay for PGE<sub>2</sub> and NO was 1.0 pg/mL and 1 µmol/L, respectively.

### Statistical analysis

Patients who completed the entire treatment and all post-intervention assessments were included in the per-protocol analysis. In addition, for primary outcome, an intention-to-treat analysis (ITT) with missing values replaced by last observation carried forward (LOCF) was also performed. Data are presented as mean ± standard error of the mean

(SEM). Basic characteristics, changes in serum levels of PGE<sub>2</sub> and NO between groups were compared using an independent sample *t*-test. The therapeutic efficiency (proportion of patients who achieved > 33% reduction in pain scores) in each visit was compared by chi-squared test, and so was the proportion of patients who benefited from an improved pain severity. Repeated measures were used to analyse the changes in VAS scores between the groups. Age at recruitment, age at menarche, days of menstrual cycle, bleeding days and body mass index were all considered as covariates. A paired *t*-test was used to determine the intra-group differences in longitude comparison. Statistical analysis was conducted using SPSS version 26.0 (IBM, Armonk, NY, USA). Statistical significance was set at  $p < 0.05$ .

## Results

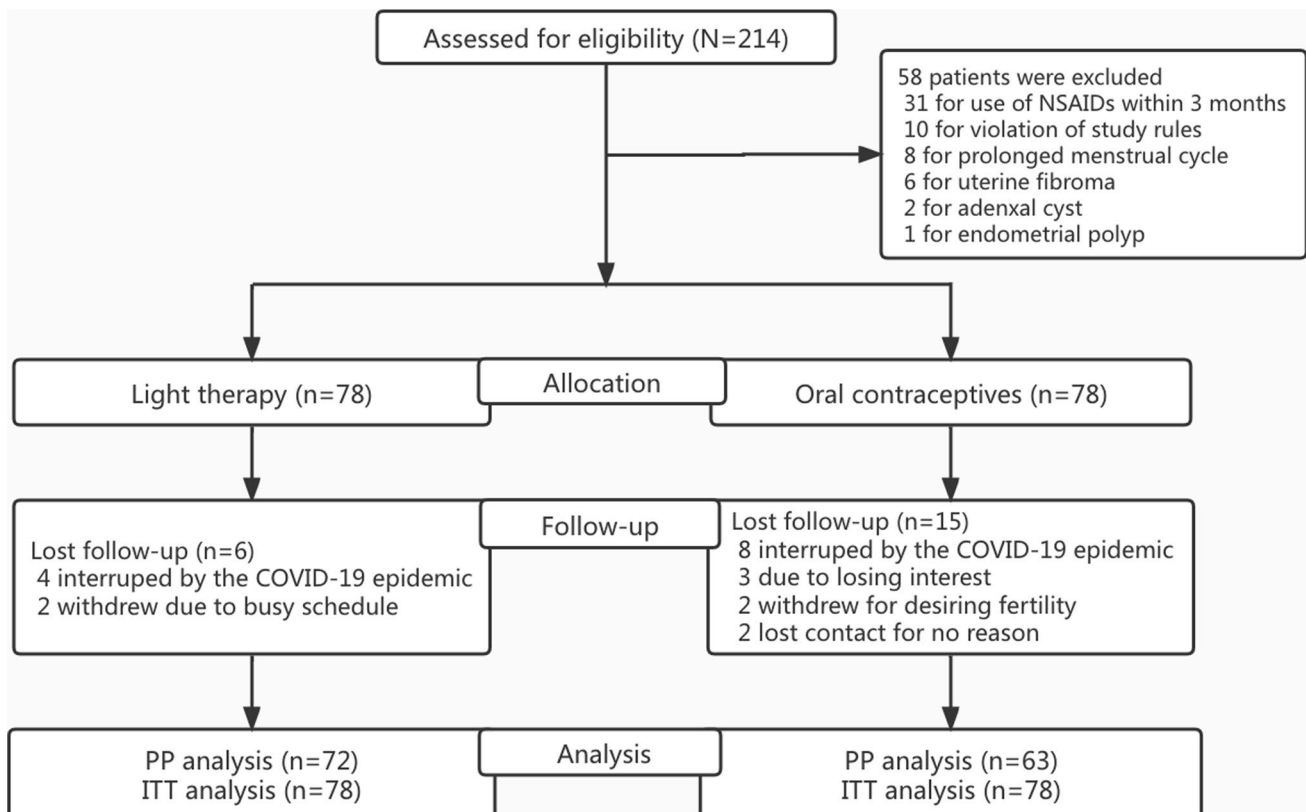
### Baseline characteristics

A total of 156 participants enrolled in the current study, of whom 135 completed all the study process (72 in the LLLT group and 63 in the DSG/EE group). As illustrated in Fig. 2, there were 21 (13.5%) cases lost to follow-up mainly

due to the interruption of coronavirus disease pandemic. As shown in Table 2, the basal characteristics in terms of blood tests and physical examinations were well-balanced between groups.

### Pain severity

Results regarding the therapeutic efficacy and changes in VAS scores are presented in Fig. 3. Pain intensity in both groups significantly decreased from basal values ( $p < 0.001$ ). At the 4th week, the photobiomodulation group demonstrated a lower clinical efficacy than the DSG/EE group. Nevertheless, this inter-group difference narrowed over time and became comparable at the 8th ( $p = 0.053$ ) and 12th week ( $p = 0.084$ ). Besides, categorised by the pain intensity, the percentage of different severity at each visit is shown in Table 3. While a larger reduction in VAS scores was noted in the DSG/EE group ( $59.5 \pm 4.2\%$  vs.  $39.3 \pm 2.6\%$ ,  $p < 0.001$ ), the proportion of patients who benefited from an improved pain severity did not differ between groups as well ( $66.7\%$  vs.  $79.4\%$ ,  $p = 0.099$ ). The ITT analysis meanwhile revealed similar results of a comparable efficacy ( $p = 0.216$  at 8th week,  $p = 0.447$  at 12th week) between the experimental group and the drug control group, with DSG/EE more



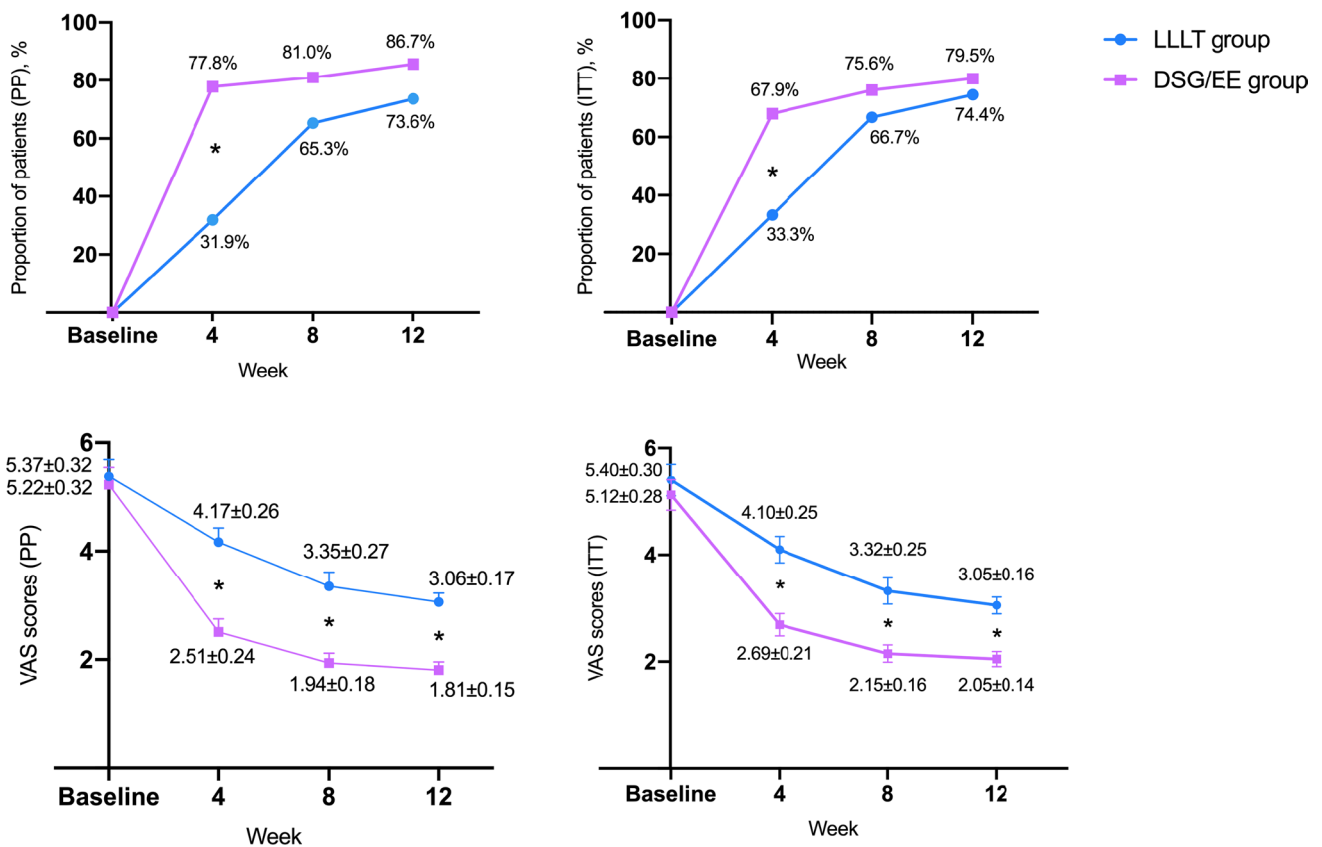
**Fig. 2** The study flow chart. NSAIDs, non-steroid anti-inflammatory drugs; COVID-19, coronavirus disease 2019; PP, per protocol analysis; ITT, intention to treat analysis

**Table 2** Basal characteristics of the participants

Characteristic	LLLT group (n = 72)	DSG/EE group (n = 63)	p value
Age, years	25.99 ± 0.49	25.63 ± 0.59	0.64
Menarche age, years	12.89 ± 0.13	12.97 ± 0.16	0.711
Gravidity	0.25 ± 0.08	0.29 ± 0.11	0.742
Parity	0.11 ± 0.04	0.21 ± 0.07	0.22
Height, cm	162.01 ± 0.63	162.02 ± 0.62	0.993
Weight, cm	52.92 ± 0.88	52.37 ± 0.71	0.639
BMI, kg/m <sup>2</sup>	20.18 ± 0.34	19.95 ± 0.24	0.589
Systolic pressure, mmHg	108.79 ± 1.22	105.48 ± 1.26	0.062
Diastolic pressure, mmHg	70.12 ± 0.92	67.74 ± 1.09	0.096
Heart rate, times/min	78.15 ± 1.67	78.71 ± 1.37	0.755
Menstrual cycle, days	29.52 ± 0.29	29.50 ± 0.36	0.971
Menstrual bleeding, days	6.14 ± 0.15	6.13 ± 0.15	0.964
PGE <sub>2</sub> , pg/mL	572.27 ± 18.19	587.10 ± 19.45	0.579
NO, μmol/L	8.26 ± 0.33	8.12 ± 0.32	0.772
VAS scores	5.37 ± 0.32	5.22 ± 0.32	0.737

LLLT, low-level light therapy; DSG/EE, desogestrel and ethinyl estradiol; BMI, body mass index; PGE<sub>2</sub>, prostaglandin E<sub>2</sub>; NO, nitric oxide; VAS, visual analog scale

Quantitative variables are described as mean ± SEM



**Fig. 3** Proportion of women who achieved significant pain relief and mean changes in visual analogue scale scores over time. Data were expressed as percentage or mean ± SEM; intergroup significance between groups at each visit, \* $p < 0.001$

**Table 3** Number (percentage%) of patients presenting with none, mild, moderate or severe pain during the treatment

Severity	None		Mild		Moderate		Severe	
	LLLT	DSG/EE	LLLT	DSG/EE	LLLT	DSG/EE	LLLT	DSG/EE
PP analysis								
Baseline	0	0	21 (29.2)	21 (33.3)	25 (34.7)	20 (31.8)	26 (36.1)	22 (34.9)
4th week	0	7 (11.1)	33 (45.8)	37 (58.7)	26 (36.1)	16 (25.4)	13 (18.1)	3 (4.8)
8th week	6 (8.3)	10 (15.9)	34 (47.3)	43 (68.3)	26 (36.1)	9 (14.3)	6 (8.3)	1 (1.6)
12th week	6 (8.3)	13 (20.6)	41 (57)	46 (73.0)	25 (34.7)	4 (6.4)	0	0
ITT analysis								
Baseline	0	0	21 (26.9)	25 (32.1)	30 (38.5)	28 (35.8)	27 (34.6)	25 (32.1)
4th week	0	7 (9.0)	36 (46.2)	47 (60.3)	29 (37.2)	20 (25.6)	13 (16.6)	4 (5.1)
8th week	6 (7.7)	10 (12.8)	38 (48.7)	55 (70.5)	28 (35.9)	12 (15.4)	6 (7.7)	1 (1.3)
12th week	6 (7.7)	13 (16.6)	41 (52.6)	58 (74.4)	30 (38.4)	7 (9.0)	1 (1.3)	0

LLLT, low-level light therapy; DSG/EE, desogestrel and ethinyl estradiol; PP, per protocol; ITT, intention to treat

potent in pain score reduction ( $54.0 \pm 3.7\%$  vs.  $39.6 \pm 2.5\%$ ,  $p = 0.002$ ). There were 75.6% of women on DSG/EE experienced amelioration in pain severity compared to 62.8% in the LLLT group ( $p = 0.083$ ).

In addition, 9 participants in LLLT group and 2 in DSG/EE group requested painkillers at the 4th week. In the 8th week, the number of patients took analgesics decreased to 4 in experimental group and 1 in drug control. There was no woman that needs extra painkillers at the end of treatment.

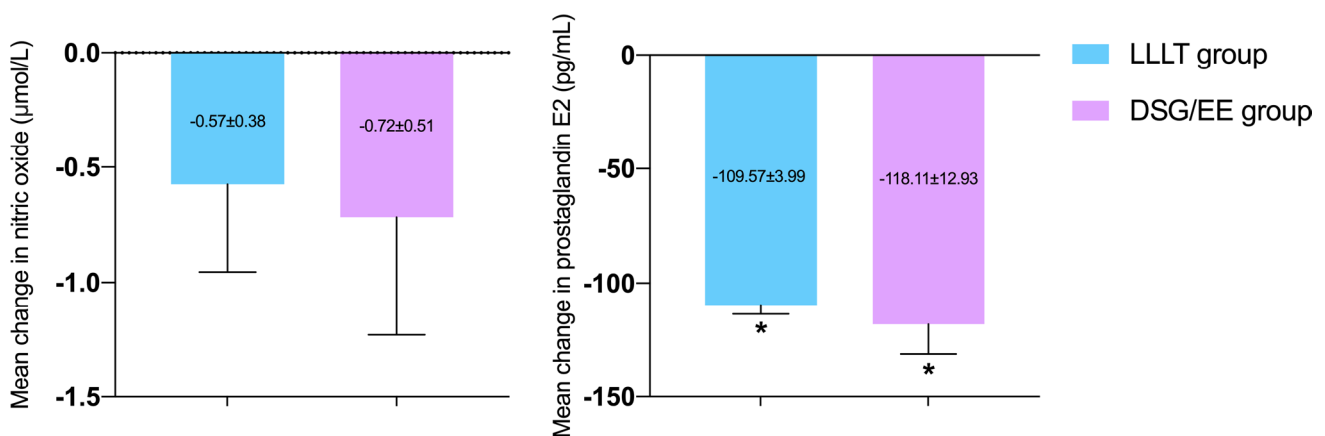
### Serum level of PGE<sub>2</sub> and NO

As shown in Fig. 4, the serum levels of PGE<sub>2</sub> decreased to  $462.70 \pm 17.09$  pg/mL in the LLLT group and  $468.99 \pm 18.87$  pg/mL in the DSG/EE group, whereas the NO concentrations remained stable corresponding to  $7.55 \pm 0.28$  pg/mL and  $7.54 \pm 0.34$  pg/mL respectively. Interestingly, despite the decline in the mean level of PGE<sub>2</sub>

was statistically significant in both groups ( $p < 0.001$ ), this effect did not differ between the two treatment modalities.

### Safety evaluation

Twelve patients reported adverse effects, three from the LLLT group presenting with transient skin rash along with slight itching and the other nine on DSG/EE complaining of decreased appetite with little impact on body weight. Since all side-effects were minor and disappeared after the treatment, none of these twelve participants discontinued the intervention. No serious adverse effect was observed. Changes in regular blood and urine tests and liver and kidney function are shown in Table 4. No meaningful abnormality was identified.



**Fig. 4** Mean changes in serum nitric oxide (left) and prostaglandin E<sub>2</sub> (right). Data are presented as mean ± SEM; intra-group significance before and after the treatment, \* $p < 0.001$

**Table 4** Safety evaluation of LLLT and DSG/EE

	LLLТ group (n = 72)			DSG/EE group (n = 63)		
	Month 0	Month 3	p value	Month 0	Month 3	p value
WBC, 10 <sup>9</sup> /L	5.93 ± 0.24	5.60 ± 0.19	0.171	5.65 ± 0.21	5.68 ± 0.20	0.884
HBG, g/L	128.93 ± 1.29	127.84 ± 1.37	0.354	128.96 ± 1.45	129.71 ± 1.45	0.479
PLT, 10 <sup>9</sup> /L	245.87 ± 6.95	246.17 ± 6.61	0.949	242.95 ± 6.65	252.18 ± 6.74	0.018
N, %	58.07 ± 1.08	57.91 ± 1.06	0.899	57.91 ± 1.19	55.70 ± 1.24	0.093
U-WBC	0 ± 0	0 ± 0	–	0 ± 0	0 ± 0	–
U-PRO	0 ± 0	0 ± 0	–	0 ± 0	0 ± 0	–
ALT, IU/L	12.19 ± 0.62	11.49 ± 0.74	0.215	12.17 ± 0.79	13.17 ± 0.98	0.288
AST, IU/L	15.59 ± 0.40	16.58 ± 0.54	0.046	16.17 ± 0.57	16.83 ± 0.52	0.167
Cr, μmol/L	59.02 ± 1.18	56.18 ± 1.09	<0.001	59.31 ± 1.55	59.96 ± 1.75	0.564
UA, μmol/L	268.23 ± 6.34	268.84 ± 6.49	0.914	271.28 ± 9.23	260.36 ± 6.51	0.101
BUN, mmol/L	4.14 ± 0.11	4.10 ± 0.13	0.724	4.17 ± 0.20	4.21 ± 0.18	0.775

LLLТ, low-level light therapy; DSG/EE, desogestrel and ethinyl estradiol; RBC, red blood cell; HB, haemoglobin; WBC, white blood cell; PLT, platelet; N, neutrophil; ALT, serum alanine aminotransferase; AST, serum aspartate aminotransferase; Cr, creatinine; UA, uric acid; BUN, urea nitrogen

Quantitative variables are described as mean ± SEM

## Discussion

Both LLLТ and DSG/EE treatment groups reached the primary endpoint of significant pain reduction. Given the similar proportion of patients who reached significant pain regression (> 33% reduction in VAS score), the efficient rate of LLLТ did not differ from that of DSG/EE, with DSG/EE more potent in pain score reduction. Both treatment modalities had similar extent of decreasing serum PGE<sub>2</sub> levels. Safety evaluation suggested that LED-based phototherapy had little negative effect on health.

In recent decades, LLLТ has a wide variety of applications ranging from pain suppression to facilitating the recovery of tissue repair [12, 14]. However, only two clinical trials have investigated its effect on dysmenorrhoea [17, 18]. A placebo-controlled, double-blinded study found that LLLТ could produce remarkable decline in pain scores for severe dysmenorrhoea, in which over half of the participants achieved great pain alleviation and improvement in quality of life after 3 cycles of application [17]. These findings are consistent with ours, but we included cases with a wider spectrum of pain intensity (scored no less than 2 points) and adopted a stricter criterion of > 33% reduction in pain scores to define meaningful improvement. Intriguingly, we observed an increasing benefit in the LLLТ group over time, inferring that photodynamic therapy with low-level energy was more likely to show therapeutic advantage under circumstances of persistent application. These findings are in consonance with those of an earlier placebo-controlled study revealing a more pronounced pain reduction after 6 cycles of light treatment [18].

The molecular mechanism underlying the therapeutic effect of LLLТ on cells and tissues has been investigated

by multiple studies. It has been proposed that cells undergo photochemical reactions to light radiation, which promotes adenosine triphosphate (ATP) production, favours modulation of reactive oxygen species and induces activation of some transcription factors that consequently upregulate the respiration of cells [12]. Dysmenorrhoeic women usually have increased activity in smooth muscle of both vessels and uterus, leading to uncoordinated contractions that contribute to hypoxia and ischaemia of local tissue [20]. In our survey, the LLLТ group yielded 73.6% of effective rate, implying a possible spasmolytic effect on smooth muscle constriction. Despite no study has ever addressed its impact on uterus, the LLLТ has been found to potentiate the relaxation on the smooth muscle in aorta and trachea [21, 22]. Clearly, further investigation is needed to disclose the structural changes behind the pain attenuation induced by photobiomodulation.

Generally, light-induced vasodilation has been regarded as the main therapeutic effect of LLLТ, in which the increased release of nitric oxide (NO) after photo-stimulation is hypothesised to facilitate the photodissociation of NO from cytochrome c oxidase, abolishing the inhibition of cellular respiration and ATP production [23]. On microscopic perception, Lohr et al. found that laser radiation at 670 nm could facilitate the release of NO from nitrosyl heme proteins and further enhance the cardio-protection from ischaemia and reperfusion [24]. As well, the investigation into vasodilatory effect on the coronary artery delineated that the photorelaxation effect on vessels was closely associated with intracellular NO levels and varied with different energy densities (maximum 56.8 ± 1.2% at 10 J/cm<sup>2</sup>) [25]. However, our data indicated that neither LED-based LLLТ nor DSG/EE had a notable regulation of NO concentration at serum level. Since the effect of NO is

primarily dominated by autocrine and paracrine signalling, we presumed that further test of NO concentration with tissue in endometrium or myometrium might reveal the changes in a more intuitionistic manner.

Notably, there was a significant decrease in serum PGE<sub>2</sub> levels in both groups during the treatment. The excessive production of PG has been clearly tied to myometrial hypercontractility, leading to uterine hypoxia–ischemia and greater pain sensitivity [2, 7]. As a critical factor of pain signals, PGE<sub>2</sub> has been implicated in the aetiology of PD [26]. It has been suggested that hormonal contraceptives could lower PG levels in menstrual fluid by inhibiting ovulation and endometrial proliferation [7]. Likewise, animal studies have reported a significant reduction in serum PGE<sub>2</sub> levels after laser irradiation [27]. Lim et al. found that photoirradiation at 635 nm *in vitro* had an anti-inflammatory effect by decreasing PGE<sub>2</sub> in gingival crevicular fluid [28]. Moreover, a clinical study involving 83 female patients suggested that the analgesic effect of LLLT was positively correlated with reduced PGE<sub>2</sub> levels [15]. On deeper investigation, it has been proposed that the dissociation of reactive oxygen species induced by photobiomodulation seemed to inhibit the expression of cyclooxygenase, and thus lower the synthesis of PGE<sub>2</sub> [16]. The present study indicated that the LLLT may exert antinociceptive effect on menstrual pain by lowering the peripheral levels of PGE<sub>2</sub>.

It is been denoted that the clinical application of LLLT has been limited to superficial tissues due to the finite depth of light penetration [29]. Researchers have found the therapeutic irradiance of red light (630–700 nm) from LED only penetrated 2–3 mm beneath the tissue, which makes it unlikely that LLLT has a direct effect on intrapelvic organ concerning the inaccessible distance [30]. Studies have demonstrated that long-term menstrual cramps are closely associated with structural and functional modifications in pain processing mode of central nervous system [31]. In this regard, it is possible that LED-based photo-stimulation on CV4 and CV6 exerts the therapeutic efficacy like acupuncture via delivering a holistic regulation of pain perception. Acupuncture-mediated analgesia in dysmenorrhoea has been well-established in recent years, suggesting acupoint stimuli can modulate the neuroendocrine activities and receptor expression of hypothalamus-pituitary-ovary axis [32]. Similarly, laser acupuncture has been found to elicit activation in specific brain areas [33], which supports the assumption that the analgesia of LLLT for PD might extend from direct action on target organ to central reflex that affect cerebral function and activities. However, only limited number of studies have assessed the photobioactive effects on specific acupoints, as to dysmenorrhoeic pain, available data remain extremely sparse. Further research is needed to test these hypotheses.

Several limitations should be noted in the current study. First, the analgesic response to psychological effects could not be ruled out since we used subjective scales to measure the pain intensity in this open-label and active comparator-controlled study. Despite it may compromise the credibility, the pragmatic design helps medical providers to find out the efficacy of LLLT as alternative therapy in a real-world environment. Besides, it is impossible to perform the double-blindness as the two treatment modalities were absolutely different. Second, it's been suggested that the therapeutic effect of LLLT substantially relied on illumination parameters, such as wavelength, energy density, irradiation time and treatment interval [12]. Recent data suggested high-intensity laser therapy (HILT) is also effective in pain control for PD. Randomised trials revealed that HILT with 3 kW of peak power and 880 J of total energy exhibited superiority over the pulsed electromagnetic field [34], whereas no significant difference was detected between the HILT and LLLT [35]. Given the open-labelled features and limited indicators in available literatures, larger, double-blinded, placebo-controlled trials are still warranted to explore the mechanism of photobiomodulation in treatment of PD with high-quality evidence. Third, even though the outcomes by ITT analysis are essentially consistent to PP assessment in this study, the high rate of missing follow-up in the DSG/EE group might to some extent affect the reliability in interpretation of results. Forth, DSG/EE were chosen to represent OCPs in our study. This may limit the generalisation of these findings to all OCP regimens as different combination of progestogenic types and oestrogen doses may influence the effectiveness.

In conclusion, our data show that LLLT with LED-based device applying on acupuncture points CV4 and CV6 exhibited a similar effectiveness of dysmenorrhoeic pain reduction to DSG/EE combined contraceptive. Both treatment modalities achieved meaningful levels of pain reduction as well as notable suppression of serum PGE<sub>2</sub> concentrations in women with PD. Thus, for PD patients who are contraindicated with hormonal agents or prefer non-pharmacological treatment, LED-based LLLT may be offered as a non-invasive, convenient and drug-free alternative with fewer adverse effects for personal use at home.

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**Author contribution** SY Zhu: data collection, data analysis and manuscript drafting.

X Ma: protocol development and data interpretation.

XS Ding and JW Gan: data collection and management.

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**Data availability** The dataset supporting the conclusions of this article is included within the article and the additional data are available from the corresponding author upon request.

**Code availability** Not applicable.

## Declarations

**Ethics approval** This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Peking Union Medical College Hospital (date March 26, 2019; No. ZS-1913).

**Consent to participate** All individual subjects signed a written declaration of informed consent to participate the current study.

**Consent for publication** Not applicable.

**Conflict of interest** The authors declare no competing interest.

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