photonics

MDPI

Article

Bypassing the Heat Risk and Efficacy Limitations of Pulsed 630 nm LED Photobiomodulation Therapy for Anti-Primary Dysmenorrhea: A Prospective Randomized Cross-Over Trial

Qiqi Fu [1], Hui Jiang [2], Jiali Yang [1], Yafei Li [3], He Fei [4], Jianlong Huang [3], Yinghua Li [4,*] and Muqing Liu [1,5,*]

1 School of Information Science and Technology, Fudan University, Shanghai 200433, China
2 Academy for Engineering and Technology, Fudan University, Shanghai 200433, China
3 Traditional Chinese Medicine of Zhongshan, Affiliated Hospital of Guangzhou University of Chinese Medicine, Zhongshan 528400, China
4 The Fifth People's Hospital of Shanghai, Fudan University, Shanghai 200240, China
5 Zhongshan Fudan Joint Innovation Center, Zhongshan 528400, China
* Correspondence: zhulihan@fudan.edu.cn (Y.L.); mqliu@fudan.edu.cn (M.L.)

Abstract: In recent years, photobiomodulation (PBM) has attracted widespread attention for the treatment of various causes of pain and inflammation. Primary dysmenorrhea (PD) is a common gynecological condition characterized by severe menstrual pain, and the limited effectiveness and side effects of conventional treatments have highlighted the urgent need to develop and identify new adjunct therapeutic strategies. The present study from the perspective of light morphology aimed to bypass the heat risk limitation and evaluate the efficacy and safety of pulsed 630 nm PBM therapy for reducing pain associated with PD. The pulse light parameters were designed according to the transmittance of red light. In this randomized, cross-over design, sham-controlled study, 46 women with PD were included and randomly assigned to either pulsed 630 nm light therapy or white light sham control therapy. The intervention lasted for 20 min per day and was administered for 7 consecutive days before and during menstruation. The results showed that the pulsed 630 nm PBM treatment demonstrated a significant reduction in pain levels compared to the placebo treatment ($p < 0.001$), with 55.00% of active treatment participants experiencing a pain intensity differential concentration exceeding 50.00%. Moreover, participants reported an improved quality of life during the active treatment phase and generally preferred it as a more effective method for relieving PD. No adverse events or side effects were reported throughout the trial. Based on the results, pulsed 630 nm LED therapy showed significant relief of menstrual pain compared to white light placebo treatment and improved quality of life under certain circumstances. Therefore, this study proposes that pulsed red light PBM therapy may be a promising approach for future clinical treatment of PD.

Keywords: primary dysmenorrhea; 630 nm LED light; pulsed wavelength; pain; quality of life; global evaluation assessment

Citation: Fu, Q.; Jiang, H.; Yang, J.; Li, Y.; Fei, H.; Huang, J.; Li, Y.; Liu, M. Bypassing the Heat Risk and Efficacy Limitations of Pulsed 630 nm LED Photobiomodulation Therapy for Anti-Primary Dysmenorrhea: A Prospective Randomized Cross-Over Trial. *Photonics* **2024**, *11*, 136. https://doi.org/10.3390/photonics11020136

Received: 3 November 2023
Revised: 21 November 2023
Accepted: 24 November 2023
Published: 31 January 2024

1. Introduction

Primary dysmenorrhea (PD), characterized by painful menstrual cramps without any underlying pelvic pathology, is a common condition affecting a significant number of women globally [1,2]. The incidence of PD continues to increase after adolescence and affects nearly 90% of women [3]. Menstrual pain can have a profound impact on the quality of life and daily functioning of affected individuals [4]. The release of prostaglandins is believed to be responsible for the uterine muscle contractions and subsequent pain associated with PD [3,5]. The present management of PD typically encompasses pharmacological and non-pharmacological interventions. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed in clinical practice presently, but the failure rate in reducing dysmenorrhea can be as high as 30% [6]. Moreover, NSAIDs are associated with various adverse

effects such as indigestion, headache, and drowsiness and may present negative implications for women planning to conceive [7]. Heating pads, as a traditional physical therapy, have been substantiated to provide only modest pain reduction, approximately 20%, in randomized controlled trials [8]. The severity and duration of pain encountered by patients diagnosed with PD, alongside the adverse side effects and potential dependency associated with current pharmacological interventions, emphasize the imperative for developing a pioneering therapeutic strategy that effectively diminishes pain and enhances the quality of life for individuals afflicted with PD. The investigation of novel treatment modalities is critically significant for the clinical management of patients with this condition.

Photobiomodulation (PBM) therapy, also known as low-level light therapy (LLLT), is a non-thermal and non-invasive therapy that utilizes a specific spectrum of light (390–1100 nm) to modulate cellular activities and exert therapeutic effects [9]. In recent years, PBM therapy has been widely reported for treating wounds, musculoskeletal disorders, and neuropathic symptoms [10–12], for promoting tissue healing [13], and for relieving pain [14] and has attracted great attention in the field of biomedical research. LEDs have been widely applied in PBM therapy due to their advantages of high efficiency, long lifespan, flexible wavelength selection, and small size with low power consumption. At present, some clinical studies have shown that red light can reduce pain in women with PD. Hong et al. found that CW red light therapy (610 nm, 1.8 mW/cm^2, 20 min/day) for PD can reduce pain by 30.45% over two consecutive treatment cycles [6]. Zhu et al. showed that LLLT with an LED (light-emitting diode)-based device (630 nm, 2.5 mW/cm^2, 3 J/cm^2, 20 min/day) applied at acupuncture points CV4 and CV6 exhibited a similar effectiveness regarding dysmenorrheal pain reduction compared to a DSG/EE (30 μg of ethinyl estradiol and 150 μg of desogestrel) combined contraceptive [15]. Shin et al. also found statistically significant changes in VAS scores within 6 months of LLLT (610 nm, 1 mW/cm^2, 20 min/day) compared to a placebo control treatment [16]. Moreover, numerous studies have reported the safety of LED therapy for pain and inflammation within a specific range of light intensity, with no significant adverse reactions observed [14,17]. Consequently, within a specified light irradiance range, employing this methodology in clinical settings is deemed to be a secure approach for treating various types of pain and inflammation.

However, despite the growing body of evidence supporting the efficacy of PBM therapy for PD, the application of this therapy specifically remains relatively underexplored. The reason may be that most of these studies have used continuous wave (CW) light sources, and for PD, the main obstacle is to obtain effective light intensity, which in turn requires consideration of the balance between the tolerance of human epidermal tissue to temperature changes and effectiveness [18]. Pulsed light sources, on the other hand, have shown advantages in terms of depth penetration and efficiency.

Therefore, to bypass the heat risk limitation and further explore the efficacy and safety of pulsed 630 nm PBM therapy for reducing pain associated with PD, we irradiated the female abdomen with the pulsed red light parameters displayed in Table 1. In this work, we preliminarily determined the transmittance of 630 nm light through fresh pork belly to determine the pulsed light parameters. Based on this, we then evaluated the pain suppression rate of pulsed 630 nm LED therapy compared to white light placebo treatment in women with PD as well as the quality of life of women with dysmenorrhea; additionally, a global evaluation assessment was performed.

Table 1. Pulsed 630 nm PBM parameters for the trial.

Mode	Pulsed
Wavelength (nm)	630
Duration (s)	1200
Average irradiance (mW/cm^2)	10
Dose (J/cm^2)	12
Duty cycle	40%
Peak irradiance (mW/cm^2)	25
Frequency (Hz)	50

Dose (J/cm^2) = irradiance (mW/cm^2) × duration (s)/1000. Average irradiance = peak irradiance × duty cycle (results are quoted to two decimal places).

2. Materials and Methods

2.1. Study Design

This was a randomized, double-blind placebo-controlled study with a cross-over design. The study protocol was compliant with the ethical principles of the Declaration of Helsinki. Participants were adolescent and adult women with more than moderate PD, recruited from June 2022 to February 2023 at Shanghai Fifth People's Hospital (Shanghai, China), and provided informed consent prior to participation. The study was prospectively registered with the Clinical Trial Registry, China (ChiCTR-ERC-17012528).

2.2. Participant Selection

Female participants who met the study inclusion and exclusion criteria were included. Healthy female participants aged 14 to 39 years with regular menstrual cycles, a self-reported history of PD, at least moderate pain due to menstrual cramps (based on the VAS, with scores of 0–10, where scores of 4–7 and 7–10 represented moderate and severe pain, respectively), and a body mass index (BMI) of less than 24 were recruited for this study.

The exclusion criteria were as follows: patients with serious medical or psychiatric disorders; patients who had received a positive prescreening pregnancy test result; patients who had used oral contraceptives within the last month; patients with a history of phototherapy allergy; and patients who had been treated for PD within one month prior to recruitment. Participants were not allowed to self-administer drugs that might interfere with the study. For participants who suffered unbearable pain, the researchers prescribed painkillers for relief, and this was then recorded on the case report form.

Prior to the first cycle study of each woman's menstrual period, a medical history was taken, and the participant underwent an obstetric and gynecological examination that included ultrasonography and clinical laboratory testing. The women were required to employ physical methods of contraception throughout the treatment. It was announced to all potential study participants that the study was confidential and that participant privacy would be maintained.

2.3. Study Intervention

Qualified participants were randomized to a pulsed 630 nm PBM therapy group or a placebo treatment group in a 1:1 ratio. Either the placebo treatment device or the active treatment device was worn for 20 min daily for 7 days before and during the menstrual cycle (Figure 1, CV6, located 1.97 inches below the navel; CV4, located 3.94 inches below the navel). The specific LED irradiation parameters are shown in Table 1. Blinding was achieved by using a white light placebo control with identical electrical power (3W) and appearance to exclude the influence of heat on the participants and the results. Both the researchers and participants were unaware of the assigned outcomes.

A spectral irradiance meter (SPIC-200, Everfine, Hangzhou, China) was exploited to measure the light spectrum, peak wavelength, and color temperature. Irradiance was measured using a photodiode power sensor (S170C, Thorlabs, Newtown, CT, USA) with a digital optical power meter (PM100D, Thorlabs, Newton, NJ, USA).

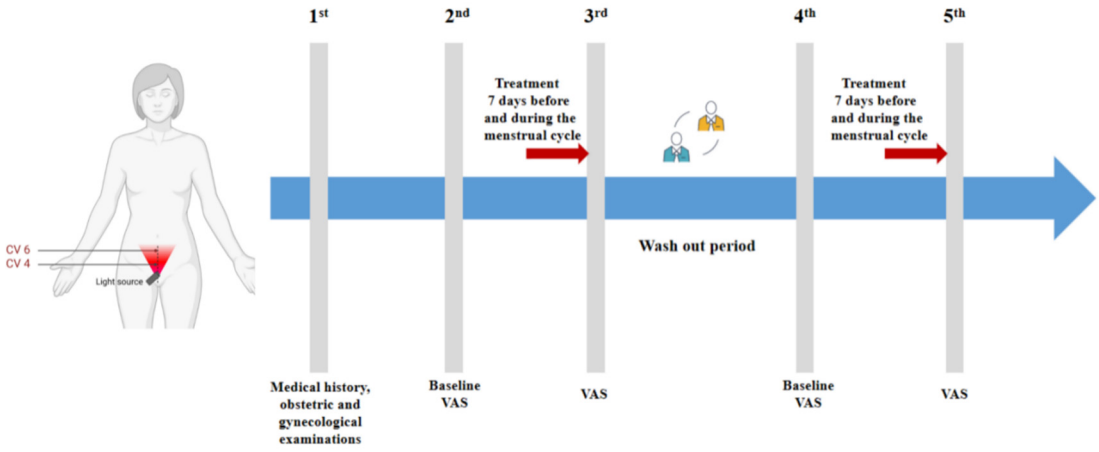

Figure 1. Flow chart of the study protocol.

2.4. Randomization Procedures

Participants were randomly assigned to one of two groups using a computer-generated randomization sequence. The randomization was performed by an independent statistician who had no involvement in the recruitment or assessment of participants. The randomization sequence was securely stored and accessible only by the independent statistician responsible for generating the allocation sequence.

2.5. Pain Assessment

2.5.1. VAS for Pain

The VAS is an 11-point scale, with 0 representing "no pain" and 10 representing the most severe pain. Participants were instructed to rate their pain intensity on a scale ranging from 0 to 10. Following the intervention, participants provided daily ratings of their pain intensity at its most severe point during the menstrual period in order to assess the total sum of pain intensity differences.

2.5.2. Quality of Life

Quality of life assessments were conducted through the completion of a survey questionnaire to evaluate various indicators, including period regularity, blood clotting, muscle soreness, abdominal distension and pain, breast tenderness, joint pain, lumbago, diarrhea, constipation, appetite, diet, headache, agitation, insomnia, nausea sensation, and any reported adverse events or side effects.

2.5.3. Global Evaluation Assessment

Participants were asked to rate the effectiveness of the intervention in alleviating menstrual pain using an absolute scale ranging from 0 to 4, with 0 representing "poor", 1 representing "fair", 2 representing "good", 3 representing "very good", and 4 representing "excellent" [19].

2.6. Evaluation of Safety

Adverse events were assessed as treatment-emergent adverse events throughout the entire study period. They were collected during the screening phase of the entire treatment period and included adverse events that started or worsened after the first intervention in the treatment phase.

2.7. Study Procedure

This study involved a disease screening phase, where eligible participants were randomly assigned to one of two sequences—treatment or placebo.

To minimize the potential impact of the guiding language used on the experimental results, caution was exercised in designing and delivering the instructions and prompts. The language used was carefully chosen to be neutral, unbiased, and devoid of any potential influence on the participants' responses or behaviors. Additionally, the instructions were tested and refined through pilot studies to ensure clarity and comprehensibility.

2.7.1. Screening Phase

Qualified female participants were selected during the screening phase. Prior to randomization, participants were assessed for the severity of menstrual pain. This study included participants with pain scores above three on the pain intensity scale. Upon completion of the screening, participants were randomly assigned to one of two groups. Additionally, each participant received guidance on the usage of the designated device and underwent training on how to utilize the study documentation prior to the commencement of the experiment.

2.7.2. Baseline VAS Scores

After completion of screening and randomization, participants entered the baseline data collection phase at the onset of their menstrual cycle. Baseline VAS scores were obtained from all participants at the beginning of the study. Participants were instructed to rate the intensity of their pain on a continuous scale ranging from 0 to 10. The VAS scores served as a baseline measure of pain severity and provided a starting point for evaluating the efficacy of the intervention. The duration of this phase varied among participants depending on the length of their menstrual cycles and the randomness of cycle initiation.

2.7.3. Treatment Phase 1

Participants wore the treatment or placebo device for 20 min each day for the first 7 days of the next menstrual cycle and during menstruation. VAS scores were recorded, and the three most severe days during menstruation were selected as the first post-treatment VAS score. Participants also completed an assessment of quality of life and a global evaluation assessment of the intervention approach for this study.

2.7.4. Baseline VAS Scores after a Wash-Out Period

During the study, participants were mandated to abstain from any form of intervention or treatment for a designated period of time in order to mitigate any residual effects and revert back to their pre-intervention baseline state.

2.7.5. Treatment Phase 2

During the seven days preceding the next menstrual cycle and throughout the duration of menstruation, participants were instructed to wear a therapeutic or placebo device (different from the methods of intervention used in the initial treatment) for 20 min each day. The recording metrics were the same as in the first trial session.

2.8. Statistical Analysis

Participants who completed the entire treatment and all study assessments were included in the statistical analysis. All results are expressed as the mean ± standard error of the mean (s.e.m.) and were analyzed using GraphPad Prism version 9.4.1 software (GraphPad, San Diego, CA, USA). Statistical analysis was performed using paired t-tests to compare the mean VAS scores before and after each treatment session within each group. Repeated measures ANOVA was used to compare the differences in pain reduction between the active treatment and placebo treatment groups. A p-value of less than 0.05 was significant. ANOVA analysis was used to evaluate the overall perception of the investigators or patients regarding the treatment condition changes.

3. Results

3.1. Light Transmittance Assay and PBM Intervention Parameters

Primarily, CW 630 nm is effective at an intensity of at least 0.14 mW/cm^2 for normal or prostaglandin-$F_{2\alpha}$-induced human uterine smooth muscle cells (according to another study by our research group); however, the uterus is approximately 2.5 cm from the human surface [20], and the attenuation of 630 nm light at this depth is about 98.5–99.3% (Figure 2, Table S1). Accordingly, 630 nm light at an intensity of 25 mW/cm^2 (with a mean light transmittance of about 1%) is required to achieve such an effect. Nevertheless, when the illumination intensity was above 25 mW/cm^2, the surface temperature of the skin was approximately 40°C (the lighting device was close to the skin for 3 min), which is nearly the tolerance temperature of the human body; thus, this strategy achieved less practical clinical significance. Based on this, we designed pulsed light for the trial (Figure 3, Table 1), with a luminous area of 9π cm^2.

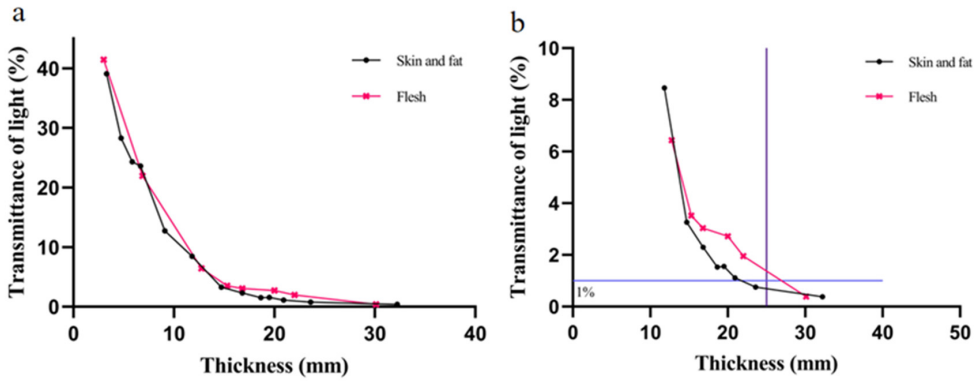

Figure 2. Transmittance from a 630 nm LED light source through the abdominal skin of a pig. The thickness was (**a**) 3.3–33.23 mm and (**b**) 12.75–33.23 mm. Black line, skin and fat; trend line, $y = 0.6121^{e-1.794x}$ ($R^2 = 0.9661$). Red line, flesh; trend line, $y = 0.6215^{e-1.677x}$ ($R^2 = 0.9813$). Test methods used before each test initially used the optical power meter to probe a quartz sheet and test the intensity of ambient light; then, a certain thickness of tissue on the quartz sheet was used, with a peak light intensity of 25 mW/cm^2 of pulsed light at 630 nm in close proximity to the test-light intensity.

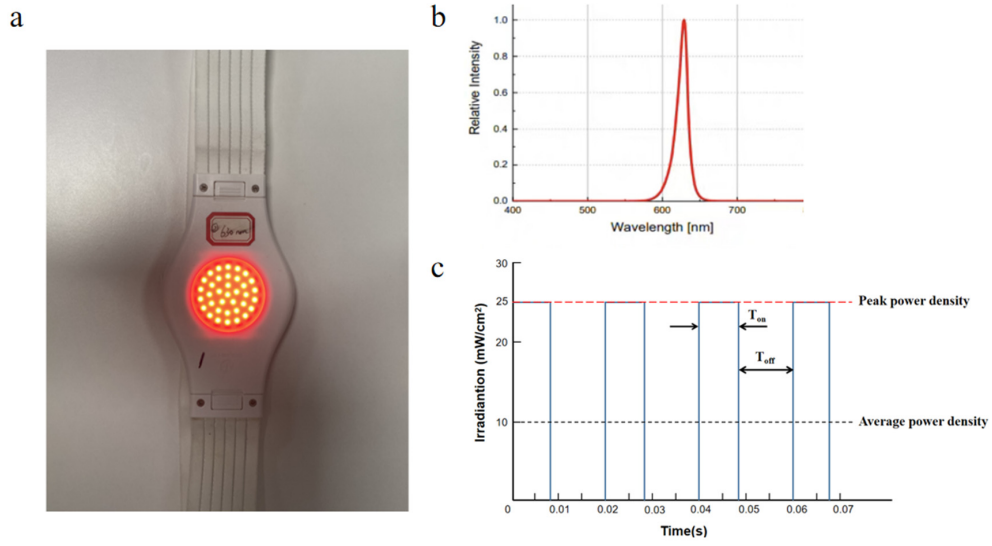

Figure 3. Experimental equipment for PBM treatment. (**a**) The irradiation device for PD participants. (**b**) Normalized spectral power distributions of 630 nm LED modules. (**c**) Conceptual diagram comparing the CW and PW.

3.2. Screening of Samples

This study screened a total of 46 women and ultimately included 40 eligible participants. They were randomly assigned to two groups, with 20 participants in each group (Figure 4). There were no deviations or violations from the protocol observed throughout the study. All participants showed good adherence to the treatment. Direct observation of the participants was conducted during the study, and evaluations were performed during each menstrual cycle. All participants completed pain surveys during their menstrual periods, with a high rate of adherence to the questionnaire at each time point. No adverse events were reported in this study, and there were no dropouts. Participants in the study did not receive any rescue medication during the study period.

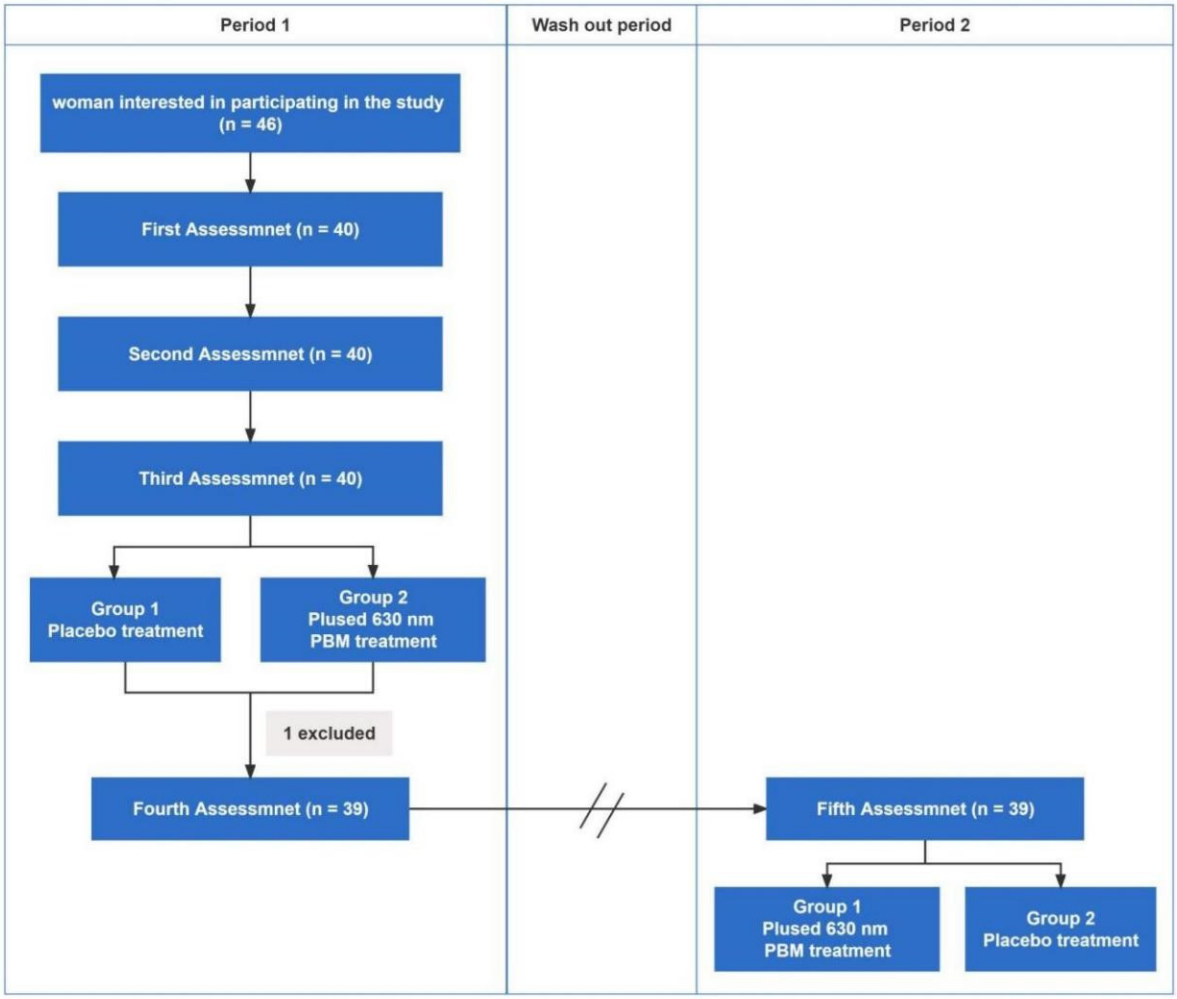

Figure 4. Sample flow chart of participants at each stage.

3.3. Baseline Characteristics

The mean age of the participants was 25 years (Figure 5a), ranging from 18 to 39 years, and the mean dysmenorrhea time was 6 years (Figure 5b). At baseline, most participants (92.50%) reported experiencing moderate to severe pain according to the VAS score (Figure 5c). There were no significant differences observed in baseline characteristics between the active treatment and placebo treatment groups, ensuring comparability between the two groups (Figure 5d). Other baseline characteristics assessed include menstrual cycle regularity and previous treatment history for PD. These characteristics were similar in both the active treatment and placebo treatment groups, further strengthening the comparability between the groups.

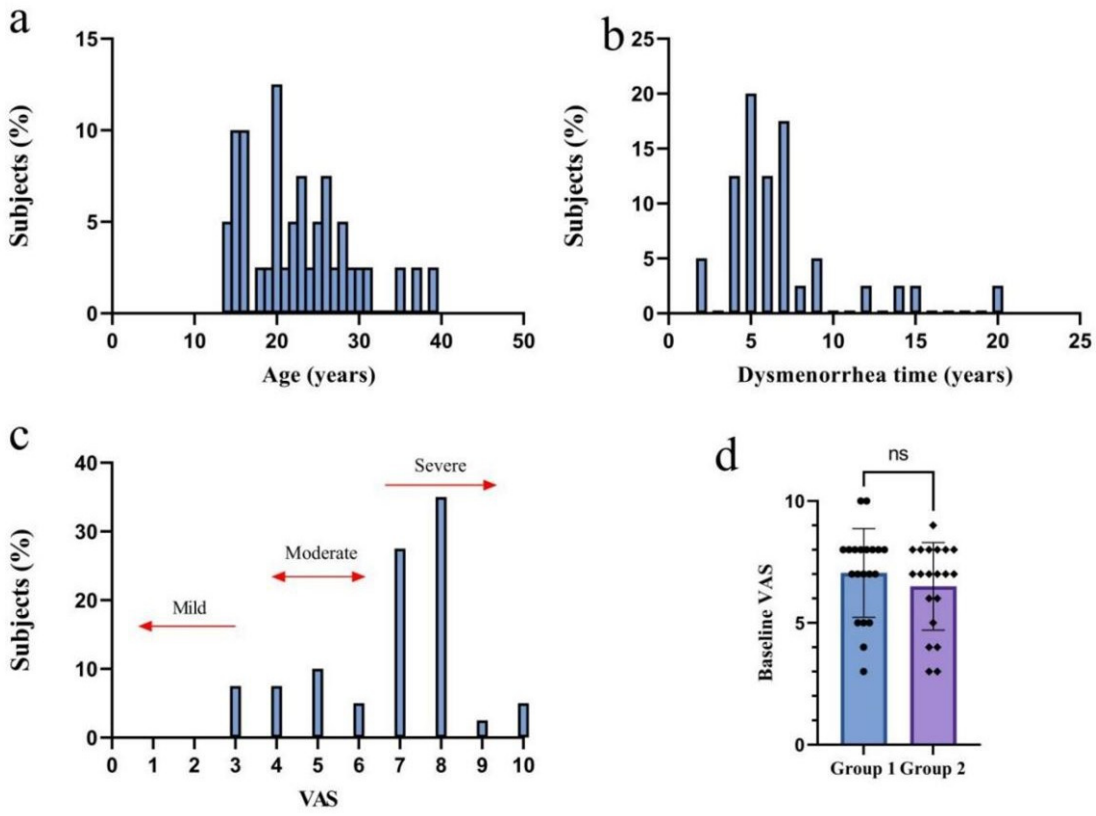

Figure 5. Baseline characteristics of the participants. (**a**) Age distribution of study patients. (**b**) Dysmenorrhea time in study patients. (**c**) Distribution of dysmenorrhea severity among participants. (**d**) Initial VAS scores of the two randomly assigned groups of participants. ns, not significant by one-way ANOVA; mean + s.e.m. in bar graphs.

3.4. Pain Severity

In the first treatment session, 80.00% of participants had a baseline VAS score of more than 7.00. After the intervention, there was little change in the placebo group's VAS score, and all participants in the pulsed 630 nm PBM therapy group had a VAS score of less than 7.0, with scores of 3–4 reported by 80.00% of participants (Figure 6a). In addition, the mean baseline pain score was 6.63 in the active treatment group, indicating a high level of pain experienced by the participants. After receiving the pulsed 630 nm PBM treatment, the mean pain score decreased to 3.63, representing a statistically significant reduction in pain severity ($p < 0.0001$). In contrast, the placebo group exhibited a mean baseline pain score of 7.30. However, after receiving the placebo treatment, the mean pain score decreased only slightly to 6.75, which was not statistically significant ($p > 0.05$). This suggested that the placebo intervention did not provide significant pain relief for PD. Furthermore, when comparing the changes in pain severity between the active treatment and placebo treatment groups, there was a statistically significant difference ($p < 0.0001$). Participants in the active treatment group experienced a greater reduction in pain severity than those in the placebo treatment group (Figure 6b). After the wash-out phase, the second phase of treatment, the two groups were crossed over, showing the same results (Figure 6c,d).

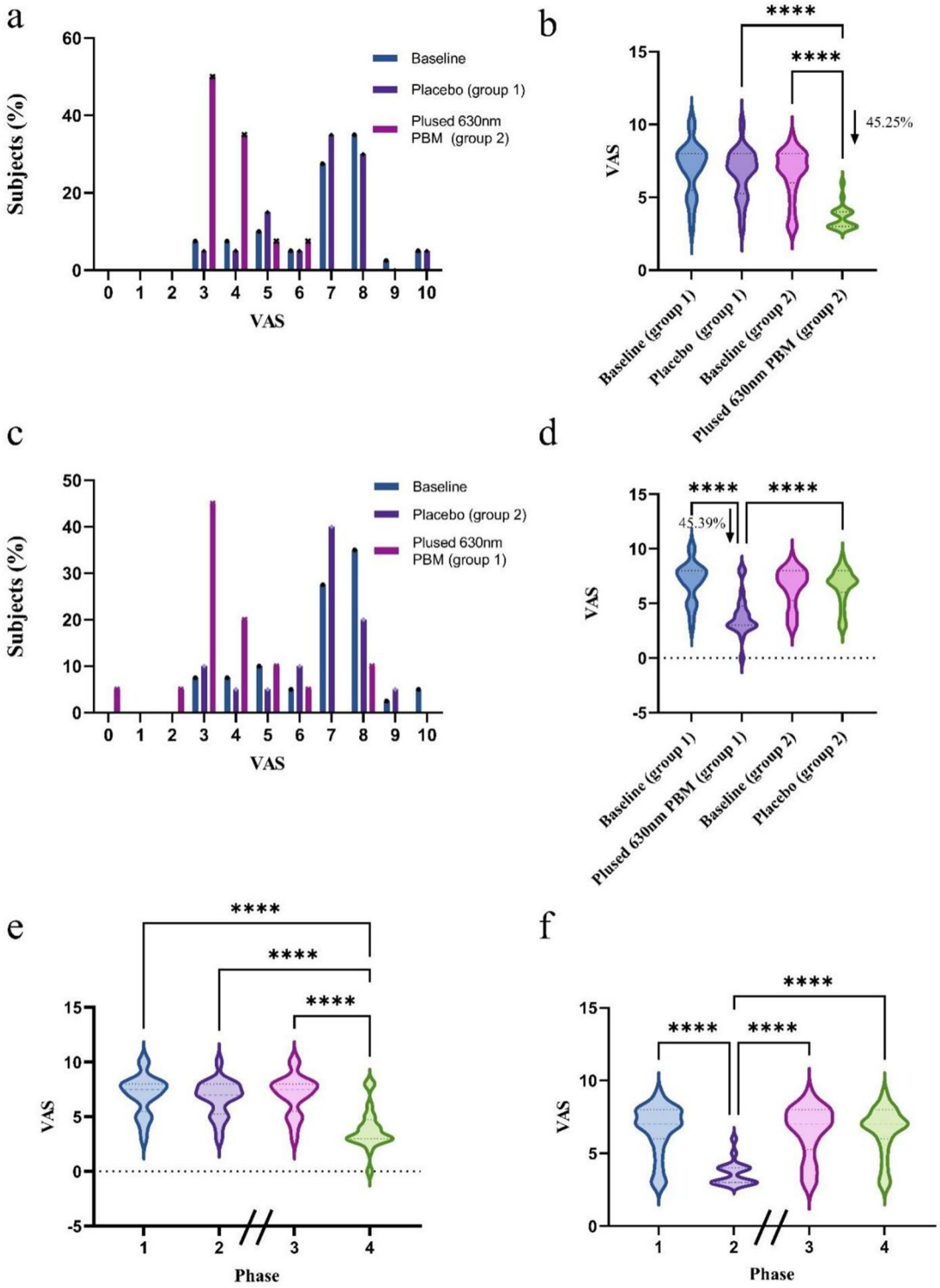

Figure 6. Pulsed 630 nm PBM therapy for pain relief in participants with PD. VAS score distribution (**a**) and significance analysis (**b**) of participants before and after the first treatment session. After the wash-out period, the VAS score distribution (**c**) and significance analysis (**d**) of participants before and after the second treatment period. VAS scores of participants in Group 1 (**e**) and Group 2 (**f**) throughout the study, where in Group 1, 1—Baseline, 2—Placebo, 3—Baseline after the wash-out period, and 4—Pulsed 630 nm PBM and in Group 2, 1—Baseline, 2—Pulsed 630 nm PBM, 3—Baseline after wash-out period, and 4—Placebo. (n = 20). **** $p < 0.0001$ by one-way ANOVA; mean + s.e.m. in bar graphs.

The scores of the two groups randomly separated according to Figure 6e,f were consistent at the two baseline points (stage 1 and 3) throughout the whole study period, which excluded the error caused by individual differences in the subjects and provided a reference value for evaluating the research results of different intervention methods for the same group of participants. Neither the placebo device intervention phase of Figure 6e nor that of Figure 6f was significantly different for participants, with a 45.32% reduction in pain rates following the pulsed 630 nm PBM intervention.

In this study, it was observed that 55.00% of participants receiving the active treatment exhibited a maximum sum of pain intensity difference concentration exceeding 50.00%. Conversely, the sum of differences in the maximum pain intensity for all participants in the placebo group was less than 30% (Table 2). These findings indicate that pulsed 630 nm PBM therapy is effective for reducing the pain severity of PD.

Table 2. Global Evaluation Assessment.

Category	Placebo, n (%)	Pulsed 630 nm PBM, n (%)
<30	40 (100.00%)	10 (25.00%)
30–49	0	8 (20.00%)
50–69	0	19 (47.50%)
≥70	0	3 (7.50%)

3.5. Quality of Life

Additionally, apart from its efficacy in alleviating dysmenorrhea, the majority of participants reported that pulsed 630 nm PBM therapy also improved symptoms related to blood clotting and muscle soreness. Moreover, a subset of participants indicated that pulsed 630 nm PBM was effective for enhancing period regularity, reducing abdominal distension and pain, relieving breast tenderness, alleviating lumbago, regulating diet, mitigating headaches, and reducing feelings of agitation. A few participants reported experiencing the positive effects of pulsed 630 nm PBM on joint pains, diarrhea, constipation, and appetite (Table 3).

Table 3. Improvements in quality of life and adverse effects during treatment with pulsed 630 nm PBM in PD participants.

Symptom	Numbers of Improved Volunteers	Numbers of Adverse Reactions	Corresponding Number
Period regularity	12	0	/
Blood clotting	23	0	/
Muscle soreness	24	0	/
Abdominal distension and pain	16	0	/
Breast tenderness	12	0	/
Joint pain	3	0	/
Lumbago	13	1	28
Diarrhea	6	0	/
Constipation	1	0	/
Appetite	2	0	/
Diet	11	0	/
Headache	12	1	28
Agitation	14	0	/
Insomnia	0	0	/
Nausea sensation	0	0	/

Although no serious adverse events or complications were reported in either group, during the active treatment period, Case 28 presented with both headache and abdominal discomfort, characterized by temporary episodes of mild pain and swelling. Volunteers

provided feedback suggesting that these symptoms may be attributed to excessive workload, although the exact cause remains unclear at present. Overall, the incidence of adverse events was low and the reported side effects were mild and transient. The safety evaluation suggests that pulsed 630 nm PBM treatment is well-tolerated and does not pose any significant risks or safety concerns for individuals.

3.6. Global Evaluation Assessment

Based on the global evaluation assessment, 73.30% of participants reported that the pulsed 630 nm PBM treatment was a better way to relieve dysmenorrhea, while 83.30% of participants reported a less effective pain relief outcome with the placebo device (Table 4).

Table 4. Global Evaluation Assessment.

	Placebo, n (%)	**Pulsed 630 nm PBM, n (%)**
Poor (=0)	34 (85.00%)	0
Fair (=1)	4 (10.00%)	2 (5.00%)
Good (=2)	2 (5.00%)	5 (12.50%)
Very good (=3)	0	7 (17.50%)
Excellent (=4)	0	26 (65.00%)
Mean ± SD	0.20 ± 1.80	3.43 ± 1.43
Mean difference ± SE	3.23 ± 0.16	
p-Value	<0.0001	

4. Discussion

PD, characterized by painful menstrual cramps, affects a significant proportion of women worldwide and often requires medical intervention [21]. The significant factors contributing to the occurrence of dysmenorrhea, a common menstrual disorder, encompass hormonal imbalances [8], uterine abnormalities [22], prostaglandin release [23], psychological stress [24], and lifestyle factors. NSAIDs and hormonal contraceptives are the mainstay of treatment for PD, but they are not without limitations. And a significant proportion of women who suffer from dysmenorrhea obtain no relief from NSAIDs (reviewed by Oladosu et al. 2018) [25], highlighting the need for extensive research and comprehensive intervention approaches. In recent years, complementary and alternative medicine (CAM) approaches have gained attention for the management of PD. These include acupuncture, transcutaneous electrical nerve stimulation (TENS), PBM therapy, herbal medicine, and mind-body techniques like yoga and meditation [19,26]. However, the evidence supporting the efficacy of these CAM therapies is limited, and further research is required to establish their safety and effectiveness.

During the late 19th century, Nobel laureate Niels Ryberg Finsen extensively documented the therapeutic use of red light for the management of smallpox, in addition to the application of ultraviolet light for treating lupus vulgaris [27]. In recent years, there has been a growing body of research uncovering the pivotal therapeutic potential of light across various light parameters in the management of superficial diseases. Furthermore, these studies have revealed significant inhibitory effects for a wide range of pain and inflammatory conditions [28]. In recent research, Di et al. [10] discovered that red light therapy exhibited potential in diminishing the progression of hypersensitivity while simultaneously facilitating sensorimotor advancements subsequent to spinal cord injury. Costa and his colleagues showed that 630 nm LED modulate inflammatory process and increase the vascularity [29]. However, despite its long-standing presence in the medical field, the clinical application of PBM has remained relatively limited. One of the primary obstacles lies in achieving an adequate irradiance of light for effective PBM therapy, that is, the balance between effectiveness and the tolerance of human epidermal tissue to temperature [30,31]. Given the depth of dysmenorrhea lesions, there is still a lack of scientific data to fully explore the efficacy and safety of PBM in the treatment of PD. Studies have shown that the targeted delivery of energy with pulsed light allows for precise control and

minimization of adverse effects [32]. Furthermore, the pulsed nature of the light can reduce the risk of thermal damage to the surrounding tissues, making it a safer option in certain medical procedures. Piccolo et al. demonstrated that the red intense pulsed light (595 nm, 25 J/cm^2, and pulse duration ranging from 3 to 24 ms) represents an effective and safe treatment for the most common superficial vascular alterations and could be suggested as a first choice therapy for facial telangiectasias [33]. Therefore, in this experiment, we carefully considered the light intensity adopted for PBM treatment, optimized the balance between temperature tolerance and treatment effectiveness of PBM, and determined the light parameters according to the transmittance of red light. This pulsed-light strategy operated at a peak intensity of 25 mW/cm^2 with a duty ratio of 40%. Then, we explored the influence of pulsed 630 nm central wavelength LED on anti-primary dysmenorrhea, investigated the quality of life of women with dysmenorrhea, and performed a global evaluation assessment.

The findings of our study revealed a substantial alleviation of primary dysmenorrhea pain through the intervention of 630 nm pulsed PBM therapy. This result is consistent with, and even superior to, the previous research on CW [16] and supports the hypothesis that pulsed red LED light PBM therapy can be an effective approach for managing primary dysmenorrhea pain. One possible explanation for the superior pain relief achieved through the use of pulsed PBM therapy is the pulsatile nature of the intervention, which could result in improved penetration of light into the targeted tissues [34]. This increased tissue penetration could facilitate the activation of photoreceptors and the subsequent modulation of cellular processes involved in pain perception and inflammation [9]. Furthermore, unlike CW light, pulsed light has the unique temporal characteristic of allowing the modulation of the duration and frequency of light exposure, potentially leading to more precise and targeted effects [35]. This temporal specificity may enhance the therapeutic efficacy of PBM by optimizing the activation of specific cellular processes involved in pain modulation [36]. Another potential reason for the enhanced effectiveness of pulsed PBM is the possibility of avoiding desensitization or adaptation of the targeted tissues. Continuous exposure to a particular stimulus, such as CW PBM, can lead to cellular adaptation and diminished response over time [37]. By utilizing pulsed light, we may have circumvented this issue, ensuring that the tissues remain responsive and receptive to the PBM intervention, thereby maximizing its therapeutic impact.

This pain reduction could potentially be attributed to the enhancement of local blood circulation and improved tissue oxygenation within the affected region. Increased angiogenesis induced by PBM therapy may lead to the formation of new blood vessels, further improving blood flow and reducing pain [38]. Moreover, PBM has been shown to modulate the activity of nociceptive fibers and the transmission of pain signals. By inhibiting the firing of nociceptive neurons and decreasing the transmission of pain signals, pulsed 630 nm PBM may reduce pain sensitivity in those with PD [39]. It is well-established that dysmenorrhea is associated with an increased release of pro-inflammatory cytokines, such as prostaglandins, leukotrienes, and tumor necrosis factor-alpha (TNF-α) [40,41]. These inflammatory mediators contribute to increased uterine contractility and heightened pain perception [42]. PBM has been shown to have anti-inflammatory properties, including the downregulation of pro-inflammatory cytokines and the inhibition of inflammatory signaling pathways [43,44]. Therefore, it is plausible that pulsed 630 nm may reduce the release of pro-inflammatory mediators, leading to a decrease in uterine contractility and subsequent pain relief in those with PD [45].

In this work, quality of life, including changes in blood clotting and muscle soreness, were also assessed. It was observed that participants receiving active treatment reported improvements in these domains compared to those receiving the placebo intervention. The improvement in blood clotting is noteworthy, as excessive clot formation during menstruation can lead to increased pain and discomfort [46]. By reducing the clot size or frequency, pulsed PBM therapy may contribute to a more comfortable and less painful menstrual experience. The precise mechanisms underlying this effect warrant further investigation.

Furthermore, the observed reduction in muscle soreness is a significant finding, as it is a common symptom experienced by individuals with primary dysmenorrhea [47]. Pulsed PBM therapy may attenuate muscle soreness through its potential influence on cellular metabolism, inflammation, and pain perception, and similar results were reported by Marchi et al. [48]. By targeting these mechanisms, PBM therapy could potentially alleviate the muscular discomfort associated with dysmenorrhea, leading to improved physical comfort and overall well-being. The overall positive impact of pulsed 630 nm PBM therapy on menstrual symptomatology and quality of life suggests that this intervention has the potential to be a comprehensive approach to managing primary dysmenorrhea. The safety evaluation conducted throughout the trial revealed no significant adverse events or side effects associated with the treatment. This suggests that pulsed 630 nm PBM therapy is well-tolerated and safe for use in individuals with PD.

Despite the promising findings reported here, several limitations should be acknowledged. Firstly, the sample size of this trial was relatively small; thus, future studies with larger sample sizes are warranted to validate these findings. Secondly, longer-term studies are needed to assess the sustainability and long-term effects of pulsed 630 nm PBM therapy. Furthermore, the relationship between light dose and therapeutic effect in human studies as well as the understanding of the molecular mechanisms is incomplete. Hence, further exploration is required to fully investigate the potential of pulsed red light PBM as a promising therapeutic strategy for PD before its successful application in clinical treatment of dysmenorrhea patients can be achieved.

5. Conclusions

In the present study, we designed pulsed red LED parameters based on light transmittance and found that these parameters conferred a pain suppression effect in women with PD. The differences in pain intensity and global assessment of pain relief evaluated through pain relief scores indicated that PBM is significantly superior to white light placebo. The potential of this treatment modality was further supported by improvements in menstrual symptoms and quality of life. This study will provide a certain experimental basis for research on PBM therapy as an anti-primary dysmenorrhea strategy.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/photonics11020136/s1, Table S1. Transmittance of 630 nm LED light source in different models.

Author Contributions: Conceptualization, Q.F., H.J. and J.Y.; validation, Q.F. and Y.L. (Yinghua Li); formal analysis, H.F. and J.H.; investigation, Q.F. and J.H.; writing-original draft preparation, Q.F.; writing-review and editing, H.J., J.Y. and Y.L. (Yafei Li); project administration, M.L.; and funding acquisition, M.L. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the National Key Research and Development Program of China (Grant No. 2017YFB0403805) and the Zhongshan Science and Technology Bureau Program (Grant No. 2019AG038).

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Fifth People's Hospital of Shanghai, Fudan University (protocol code (2022) Ethics Approval No. (133) and date of approval, 21 September 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments: We are grateful to all the women who participated in our study and appreciate the arduous work performed by the clinicians and nurses in cooperating hospitals, namely, Minhang Branch of Cancer Hospital, Fudan University (Lei Zhang) and the Fifth People's Hospital of Shanghai.

Conflicts of Interest: The authors declare that they have no competing interests.

References

1. Elizabeth, F.; Elizabeth, C.; Johanna, S. Primary Dysmenorrhea: Diagnosis and Therapy. *Obstet. Gynecol.* **2020**, *136*, 1047–1058. [CrossRef]
2. Dawood, M. Primary dysmenorrhea: Advances in pathogenesis and management. *Obstet. Gynecol.* **2006**, *108*, 428–441. [CrossRef]
3. Ma, B.; Yang, S.; Tan, T.; Li, J.; Zhang, X.; Ouyang, H.; He, M.; Feng, Y. An integrated study of metabolomics and transcriptomics to reveal the anti-primary dysmenorrhea mechanism of Akebiae Fructus. *J. Ethnopharmacol.* **2021**, *270*, 113763. [CrossRef] [PubMed]
4. Iacovides, S.; Avidon, I.; Baker, F.C. What we know about primary dysmenorrhea today: A critical review. *Hum. Reprod. Update* **2015**, *21*, 762–778. [CrossRef] [PubMed]
5. Bi, W.; Zhou, J.; Zhao, L.; Wang, C.; Wu, W.; Zhang, L.; Ji, B.; Zhang, N.; Zhou, F. Preventive effect of different citrus essential oils on primary dysmenorrhea: In vivo and in vitro study. *Food Biosci.* **2021**, *42*, 101135. [CrossRef]
6. Hong, G.; Shin, B.; Park, S.; Gu, Y.; Kim, N.; Park, K.; Kim, S.; Shin, Y. Randomized controlled trial of the efficacy and safety of self-adhesive low-level light therapy in women with primary dysmenorrhea. *Int. J. Gynaecol. Obstet.* **2016**, *133*, 37–42. [CrossRef]
7. Chiang, Y.-F.; Hung, H.-C.; Chen, H.-Y.; Huang, K.-C.; Lin, P.-H.; Chang, J.-Y.; Huang, T.-C.; Hsia, S.-M. The Inhibitory Effect of Extra Virgin Olive Oil and Its Active Compound Oleocanthal on Prostaglandin-Induced Uterine Hypercontraction and Pain-Ex Vivo and In Vivo Study. *Nutrients* **2020**, *12*, 3012. [CrossRef]
8. Jo, J.; Lee, S. Heat therapy for primary dysmenorrhea: A systematic review and meta-analysis of its effects on pain relief and quality of life. *Sci. Rep.* **2018**, *8*, 16252. [CrossRef] [PubMed]
9. Yang, J.; Fu, Q.; Jiang, H.; Li, Y.; Liu, M. Progress of phototherapy for osteosarcoma and application prospect of blue light photobiomodulation therapy. *Front. Oncol.* **2022**, *12*, 1022973. [CrossRef] [PubMed]
10. Cheng, K.; Martin, L.F.; Slepian, M.J.; Patwardhan, A.M.; Ibrahim, M.M. Mechanisms and Pathways of Pain Photobiomodulation: A Narrative Review. *J. Pain* **2021**, *22*, 763–777. [CrossRef]
11. Hu, D.; Zhu, S.; Potas, J.R. Red LED photobiomodulation reduces pain hypersensitivity and improves sensorimotor function following mild T10 hemicontusion spinal cord injury. *J. Neuroinflamm.* **2016**, *13*, 200. [CrossRef] [PubMed]
12. Khanna, R.; Patwardhan, A.; Yang, X.; Li, W.; Cai, S.; Ji, Y.; Chew, L.A.; Dorame, A.; Bellampalli, S.S.; Schmoll, R.W.; et al. Development and Characterization of An Injury-free Model of Functional Pain in Rats by Exposure to Red Light. *J. Pain* **2019**, *20*, 1293–1306. [CrossRef] [PubMed]
13. Ezzati, K.; Fekrazad, R.; Raoufi, Z. The Effects of Photobiomodulation Therapy on Post-Surgical Pain. *J. Lasers Med. Sci.* **2019**, *10*, 79–85. [CrossRef] [PubMed]
14. Chung, H.; Dai, T.; Sharma, S.K.; Huang, Y.-Y.; Carroll, J.D.; Hamblin, M.R. The nuts and bolts of low-level laser (light) therapy. *Ann. Biomed. Eng.* **2012**, *40*, 516–533. [CrossRef] [PubMed]
15. Zhu, S.; Ma, X.; Ding, X.; Gan, X.; Deng, Y.; Wang, Y.; Sun, A. 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. *Lasers Med. Sci.* **2022**, *37*, 2239–2248. [CrossRef] [PubMed]
16. Shin, Y.; Kim, N.; Park, K.; Kim, D.; Hong, G.; Shin, B. Skin adhesive low-level light therapy for dysmenorrhoea: A randomized, double-blind, placebo-controlled, pilot trial. *Arch. Gynecol. Obstet.* **2012**, *286*, 947–952. [CrossRef] [PubMed]
17. Clement, M.; Daniel, G.; Trelles, M. Optimising the design of a broad-band light source for the treatment of skin. *J. Cosmet. Laser Ther.* **2005**, *7*, 177–189. [CrossRef] [PubMed]
18. Chen, Z.; Li, W.; Hu, X.; Liu, M. Irradiance plays a significant role in photobiomodulation of B16F10 melanoma cells by increasing reactive oxygen species and inhibiting mitochondrial function. *Biomed. Opt. Express* **2020**, *11*, 27–39. [CrossRef]
19. Agarwal, D.; Chaudhary, P. Effect of Turmeric-Boswellia-Sesame Formulation in Menstrual Cramp Pain Associated with Primary Dysmenorrhea-A Double-Blind, Randomized, Placebo-Controlled Study. *J. Clin. Med.* **2023**, *12*, 3968. [CrossRef]
20. Shaw, C.J.; Civale, J.; Botting, K.J.; Niu, Y.; Ter Haar, G.; Rivens, I.; Giussani, D.A.; Lees, C.C. Noninvasive high-intensity focused ultrasound treatment of twin-twin transfusion syndrome: A preliminary in vivo study. *Sci. Transl. Med.* **2016**, *8*, 347ra95. [CrossRef]
21. Aksoy, A.N.; Laloglu, E.; Ozkaya, A.L.; Yilmaz, E.P.T. Serum heme oxygenase-1 levels in patients with primary dysmenorrhea. *Arch. Gynecol. Obstet.* **2017**, *295*, 929–934. [CrossRef] [PubMed]
22. Wong, J.; Chiang, Y.-F.; Shih, Y.-H.; Chiu, C.-H.; Chen, H.-Y.; Shieh, T.-M.; Wang, K.-L.; Huang, T.-C.; Hong, Y.-H.; Hsia, S.-M. *Salvia sclarea* L. Essential Oil Extract and Its Antioxidative Phytochemical Sclareol Inhibit Oxytocin-Induced Uterine Hypercontraction Dysmenorrhea Model by Inhibiting the Ca^{2+}-MLCK-MLC20 Signaling Cascade: An Ex Vivo and In Vivo Study. *Antioxidants* **2020**, *9*, 991. [CrossRef] [PubMed]
23. Ke, Y.; Ou, M.; Ho, C.; Lin, Y.; Liu, H.; Chang, W. Effects of somatothermal far-infrared ray on primary dysmenorrhea: A pilot study. *Evid.-Based Complement. Altern. Med.* **2012**, *2012*, 240314. [CrossRef] [PubMed]
24. Li, M.; Bi, J.; Lv, B.; Zheng, W.; Wang, Z.; Xiao, W.; Sun, Y.; Li, E. An experimental study of the anti-dysmenorrhea effect of Chinese herbal medicines used in Jin Gui Yao Lue. *J. Ethnopharmacol.* **2019**, *245*, 112181. [CrossRef] [PubMed]
25. Oladosu, F.A.; Tu, F.F.; Hellman, K.M. Nonsteroidal antiinflammatory drug resistance in dysmenorrhea: Epidemiology, causes, and treatment. *Am. J. Obstet. Gynecol.* **2018**, *218*, 390–400. [CrossRef] [PubMed]

26. Correyero-León, M.; Llamas-Ramos, R.; Calvo-Rodrigo, J.; Alvarado-Omenat, J.J.; Llamas-Ramos, I. Transcutaneous Tibial Nerve Stimulation for Primary Dysmenorrhea: A Protocol for a Randomized Controlled Trial. *Healthcare* **2023**, *11*, 1633. [CrossRef] [PubMed]
27. Gøtzsche, P.C. Niels Finsen's treatment for lupus vulgaris. *J. R. Soc. Med.* **2011**, *104*, 41–42. [CrossRef]
28. Avci, P.; Gupta, A.; Sadasivam, M.; Vecchio, D.; Pam, Z.; Pam, N.; Hamblin, M.R. Low-level laser (light) therapy (LLLT) in skin: Stimulating, healing, restoring. *Semin. Cutan. Med. Surg.* **2013**, *32*, 41–52.
29. Busanello-Costa, M.; Renno, A.C.M.; de Goes Santos, C.P.; Quintana, H.T.; Martignago, C.C.S.; Tim, C.R.; Assis, L. Red LED light therapy associated with epidermal growth factor on wound repair process in rats. *Lasers Med. Sci.* **2023**, *38*, 36. [CrossRef]
30. Barolet, A.C.; Litvinov, I.V.; Barolet, D. Light-induced nitric oxide release in the skin beyond UVA and blue light: Red & near-infrared wavelengths. *Nitric Oxide* **2021**, *117*, 16–25. [CrossRef]
31. Chen, A.C.-H.; Huang, Y.-Y.; Sharma, S.K.; Hamblin, M.R. Effects of 810-nm laser on murine bone-marrow-derived dendritic cells. *Photomed. Laser Surg.* **2011**, *29*, 383–389. [CrossRef]
32. Zdagkas, A.; McDonnell, C.; Deng, J.; Shen, Y.; Li, G.; Ellenbogen, T.; Papasimakis, N.; Zheludev, N.I. Observation of toroidal pulses of light. *Nat. Photon.* **2022**, *16*, 523–528. [CrossRef]
33. Piccolo, D.; Crisman, G.; Kostaki, D.; Cannarozzo, G.; Sannino, M.; Chimenti, S. Rhodamine intense pulsed light versus conventional intense pulsed light for facial telangiectasias. *J. Cosmet. Laser Ther.* **2016**, *18*, 80–85. [CrossRef] [PubMed]
34. Tang, L.; Jiang, H.; Sun, M.; Liu, M. Pulsed transcranial photobiomodulation generates distinct beneficial neurocognitive effects compared with continuous wave transcranial light. *Lasers Med. Sci.* **2023**, *38*, 203. [CrossRef] [PubMed]
35. Poem, E.; Hiemstra, T.; Eckstein, A.; Jin, X.-M.; Walmsley, I.A. Free-space spectro-temporal and spatio-temporal conversion for pulsed light. *Opt. Lett.* **2016**, *41*, 4328–4331. [CrossRef] [PubMed]
36. Tsai, S.-R.; Hamblin, M.R. Biological effects and medical applications of infrared radiation. *J. Photochem. Photobiol. B* **2017**, *170*, 197–207. [CrossRef] [PubMed]
37. Rosenberg, N.; Gendelman, R.; Noofi, N. Photobiomodulation of human osteoblast-like cells in vitro by low-intensity-pulsed LED light. *FEBS Open Bio* **2020**, *10*, 1276–1287. [CrossRef] [PubMed]
38. Chaudary, S.; Karner, L.; Weidinger, A.; Meixner, B.; Rieger, S.; Metzger, M.; Zipperle, J.; Dungel, P. In vitro effects of 635 nm photobiomodulation under hypoxia/reoxygenation culture conditions. *J. Photochem. Photobiol. B* **2020**, *209*, 111935. [CrossRef]
39. Yu, S.; Xu, J.; Shen, Z.; Wang, Y.; Wei, W.; Guo, X.; Tian, J.; Liu, L.; Yang, Y.; Zeng, F.; et al. Frequency-Specific Alterations in Brain Function in Patients with Primary Dysmenorrhea. *Pain Med.* **2022**, *23*, 902–911. [CrossRef]
40. Assaf, L.; Eid, A.A.; Nassif, J. Role of AMPK/mTOR, mitochondria, and ROS in the pathogenesis of endometriosis. *Life Sci.* **2022**, *306*, 120805. [CrossRef]
41. Li, J.-M.; Liao, C.-C.; Huang, H.-C.; Lin, C.-L.; Lo, H.-Y.; Hsiang, C.-Y.; Ho, T.-Y. Regulation effect and mechanism of Sheng-Hua-Tang on female reproductive system: From experimental transcriptomic analysis to clinical applications. *J. Ethnopharmacol.* **2020**, *249*, 112431. [CrossRef]
42. Li, N.; Cui, X.; Ma, C.; Yu, Y.; Li, Z.; Zhao, L.; Xiong, H. Uncovering the effects and mechanism of Danggui Shaoyao San intervention on primary dysmenorrhea by serum metabolomics approach. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* **2022**, *1209*, 123434. [CrossRef] [PubMed]
43. Li, J.; Liu, X.; Jiang, M.; Xu, Y.; Wang, C.; Hu, Y.; Yang, S.; Gao, J.; Wang, W.; Wang, T. Wenjing Zhitong recipe exhibits potential anti-primary dysmenorrhea properties by inhibiting COX2 and PKC signaling pathway in rats induced by estradiol benzoate and oxytocin. *J. Tradit. Chin. Med. Sci.* **2023**, *10*, 296–309. [CrossRef]
44. Huang, Y.-J.; Chen, Y.-C.; Chen, H.-Y.; Chiang, Y.-F.; Ali, M.; Chiang, W.; Chung, C.-P.; Hsia, S.-M. Ethanolic Extracts of Adlay Testa and Hull and Their Active Biomolecules Exert Relaxing Effect on Uterine Muscle Contraction through Blocking Extracellular Calcium Influx in Ex Vivo and In Vivo Studies. *Biomolecules* **2021**, *11*, 887. [CrossRef] [PubMed]
45. Wang, H.; Zhu, S.; Ding, X.; Deng, Y.; Ma, X.; Gan, J.; Wang, Y.; Sun, A. Metabolomic study combined with the low-level light therapy of Chinese acupuncture points and combined oral contraceptives in treatment of primary dysmenorrhea: A prospective, multicenter, randomized controlled study. *Heliyon* **2023**, *9*, e13821. [CrossRef]
46. Kho, K.A.; Shields, J.K. Diagnosis and Management of Primary Dysmenorrhea. *JAMA* **2020**, *323*, 268–269. [CrossRef]
47. Kaplan, Ö.; Nazıroğlu, M.; Güney, M.; Aykur, M. Non-steroidal anti-inflammatory drug modulates oxidative stress and calcium ion levels in the neutrophils of patients with primary dysmenorrhea. *J. Reprod. Immunol.* **2013**, *100*, 87–92. [CrossRef]
48. de Marchi, T.; Schmitt, V.M.; Da Danúbia Silva Fabro, C.; Da Silva, L.L.; Sene, J.; Tairova, O.; Salvador, M. Phototherapy for Improvement of Performance and Exercise Recovery: Comparison of 3 Commercially Available Devices. *J. Athl. Train.* **2017**, *52*, 429–438. [CrossRef]