ORIGINAL ARTICLE

A Randomized Prospective Placebo-Controlled Study of the Effectiveness of Aromatherapy on Preoperative Anxiety in Intravitreal Injection Patients

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Objective: To assess the effect of lavender aromatherapy on preprocedural anxiety, pain, and vital signs in patients undergoing intravitreal anti-VEGF injections.

Materials and Methods: This randomized, prospective, placebo-controlled trial enrolled 114 patients undergoing their first intravitreal injection at Thammasat University Hospital between May 2024 and March 2025. The intervention group received lavender essential oil via inhalation, while the control group received normal saline. Anxiety levels were assessed using the State-Trait Anxiety Inventory (STAI) scale, along with vital signs and pain scores, both before and after the injection.

Results: Fifty-eight patients received aromatherapy, and fifty-six patients received a placebo. Baseline characteristics were comparable. Both groups demonstrated a significant reduction in STAI scores following treatment (treatment group: –2.69±5.17, p<0.001, and control group: –1.39±7.54, p=0.016). Although the reduction was greater in the treatment group, the between-group difference was not statistically significant (p=0.233). Systolic and diastolic blood pressure increased slightly in both groups , with no significant differences between groups. Mean pain scores were lower in the treatment group (2.77±2.07) compared to the control group (2.93±2.09), but without statistical significance.

Conclusion: Lavender aromatherapy was associated with lower anxiety and pain scores in patients undergoing intravitreal injection compared with placebo, but differences were not statistically significant.

Keywords: Aromatherapy; Lavender; Intravitreal injection; Anxiety; Anti-VEGF; STAI; Placebo-controlled trial

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Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents represents the mainstay treatment for various retinal diseases, including age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusion (RVO)[1]. Despite its well-established safety and efficacy, the intravitreal injection procedure is often associated with considerable patient anxiety and emotional distress[2]. This is particularly pronounced among patients undergoing the procedure for the first time, due to fear of pain, potential complications such as infection, and concerns about treatment outcomes[3].

Aromatherapy, the therapeutic use of natural essential oils, has been increasingly studied within complementary and integrative medicine, particularly for its effects on stress, anxiety, and procedural pain[4]. Among various essential oils, lavender has demonstrated notable anxiolytic effects, especially in surgical and medical settings[5]. Previous studies have shown that lavender aromatherapy can alleviate anxiety in individuals undergoing labor[6], cataract surgery[7], and other minor procedures[8,9].

Accordingly, the present study aims to evaluate the impact of lavender aromatherapy on preprocedural anxiety levels in patients receiving intravitreal anti-VEGF injections. The findings may underscore the value of a holistic approach to patient care and contribute to improved service delivery in ophthalmic settings.

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Materials and Methods

The present study was a randomized, prospective, placebo-controlled trial. Participants aged 21 to 75 years who attended the Ophthalmology Outpatient Department at Thammasat University Hospital and required their first intravitreal anti-VEGF injection in a single eye were enrolled. Indications for treatment included DME, neovascular glaucoma (NVG), central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), neovascular age-related macular degeneration (wet AMD), and proliferative diabetic retinopathy (PDR). Data collection was conducted between May 2024 and March 2025. One hundred and fourteen participants were recruited and randomly assigned to two groups using computerized randomization, and the results were sealed in envelopes provided by the authors. This study was registered with the Thai Clinical Trials Registry (TCTR20260407001).

The intervention group received lavender aromatherapy by inhalation: three to five drops of lavender essential oil were applied to a cotton pad and provided to the participants for inhalation. The essential oil used in this study was formulated specifically for therapeutic purposes via inhalation or dilution for massage. It was manufactured and distributed by Bangkok Chemical Company, certified with GMP manufacturing standards and USDA Organic approval, with an expiration date of November 2025. The control group received placebo inhalation using three to five drops of normal saline on a cotton pad for the same duration of 20 minutes prior to the injection.

All participants received topical anesthesia (one drop every 15 minutes for a total of six applications) per standard clinical protocol. Baseline demographic information, vital signs (blood pressure, respiratory rate, and heart rate), and anxiety levels were assessed using the State-Trait Anxiety Inventory (STAI) scale prior to injection. Subsequently, all injections were performed by the same ophthalmologist on the same day following standard intravitreal injection procedures. No aromatherapy or placebo inhalation was administered during the injection itself. Following the procedure, vital signs and STAI scores were reassessed. Participants also rated their pain using a pain score scale (numeric rating scale, NRS)[10], and any immediate post-operative adverse events were monitored and recorded.

The sample size was calculated based on the study by Stanley et al.[7]. That study reported a mean ± standard deviation (SD) of anxiety scores of 4.5±8.0 in the aromatherapy (treatment) group and 0.8±5.9 in the control group. A two-sample comparison of means with a two-tailed test, a type I error (α) of 5%, power of 80%, and an allocation ratio of 1:1 was used. The minimum required sample size was 114 participants.

Ethics approval

This study was approved by the Thammasat University Hospital Human Ethics Committee (MTU-EC-OP-0-002/67) and performed in accordance with the Declaration of Helsinki.

Statistical analysis

Data were analyzed using IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics included frequencies, percentages, means, standard deviations (SD), medians, and ranges. They were used to summarize participant characteristics.

Inferential statistical analysis was conducted with a significance threshold set at a p-value of less than 0.05. Categorical variables such as sex, underlying diseases, medication use, ocular diagnoses, STAI scores, and pain scores were compared between groups using chi-square tests or Fisher's exact tests, as appropriate. Continuous variables such as age, baseline vital signs, and STAI scores were compared between groups using independent t-tests when data were normally distributed, or Mann-Whitney U-tests when non-normally distributed.

Post-treatment comparisons of vital signs and STAI scores between the two groups were performed using analysis of covariance (ANCOVA), adjusting for baseline (pre-treatment) values as covariates. Within-group comparisons of pre- and post-treatment measures were analyzed using paired t-tests for normally distributed data or Wilcoxon signed-rank tests for non-normally distributed data.

Results

One hundred and fourteen eyes were included in this study, with 58 assigned to the aromatherapy group (treatment group) and 56 to the control group. Baseline characteristics, including sex, age, underlying medical conditions, history of medication use (anti-hypertensive agents), and pre-existing ocular diagnoses, were comparable between the two groups, with no statistically significant differences observed, as shown in Table 1.

As shown in Table 2, a comparison of vital signs before and after intravitreal injection in both the treatment and control groups revealed an increase

Table 1. Demographic and clinical characteristics of participants (n=114)

Characteristics	Total (n=114) n (%)	Treatment (n=58) n (%)	Control (n=56) n (%)	p-value
Sex				0.864
Male	52 (45.6)	26 (44.8)	26 (46.4)	
Female	62 (54.4)	32 (55.2)	30 (53.6)	
Age (years)				0.451
<50	17 (14.9)	8 (13.8)	9 (16.1)	
50-59	35 (30.7)	21 (36.2)	14 (25.0)	
60-69	41 (36.0)	21 (36.2)	20 (35.7)	
≥70	21 (18.4)	8 (13.8)	13 (23.2)	
Mean±SD	59.93±11.30	59.31±11.31	60.57±11.36	0.554
Underlying disease				0.317
Yes	105 (92.1)	55 (94.8)	50 (89.3)	
No	9 (7.9)	3 (5.2)	6 (10.7)	
• Hypertension	56 (49.1)	33 (56.9)	23 (41.1)	0.091
• DLP	35 (30.7)	21 (36.2)	14 (25.0)	0.195
• DM	86 (75.4)	44 (75.9)	42 (75.0)	0.915
• CKD	7 (6.1)	5 (8.6)	2 (3.6)	0.439
Underlying disease (continued)				
• Gout	3 (2.6)	2 (3.4)	1 (1.8)	1.000
• Heart	3 (2.6)	1 (1.7)	2 (3.6)	0.615
• Others	10 (8.8)	4 (6.9)	6 (10.7)	0.524
Medication				0.705
Yes	103 (90.4)	53 (91.4)	50 (89.3)	
No	11 (9.6)	5 (8.6)	6 (10.7)	
• Anti-hypertensive	60 (58.3)	37 (69.8)	23 (46.0)	
• Others	43 (41.7)	16 (30.2)	27 (54.0)	
Ocular Dx				
DME	57 (50.0)	26 (44.8)	31 (55.4)	0.261
NVG	54 (47.4)	31 (53.4)	23 (41.1)	0.186
CRVO	21 (18.4)	13 (22.4)	8 (14.3)	0.263
BRVO	11 (9.6)	6 (10.3)	5 (8.9)	0.798
Wet AMD	3 (2.6)	1 (1.7)	2 (3.6)	0.615
PDR	21 (18.4)	12 (20.7)	9 (16.1)	0.525

SD=standard deviation; DLP=dyslipidemia; DM=diabetes mellitus; CKD=chronic kidney disease; DME=diabetic macular edema; NVG=neovascular glaucoma; CRVO=central retinal vein occlusion; BRVO=branch retinal vein occlusion; Wet AMD=neovascular age-related macular degeneration; PDR=proliferative diabetic retinopathy

Table 2. Comparison of the mean vital signs and mean STAI scores between the treatment and control groups

	Treatment (n=58) Mean±SD	Control (n=56) Mean±SD	Difference Mean (95% CI)	p-value
SBP				
Pre	138.07±18.16	135.50±17.40	2.569 (–4.036 to 9.174)	0.443@
Post	148.31±23.72	148.25±26.50	0.060 (–9.266 to 9.386)	0.399#
Changed	10.24±24.44	12.75±22.64	–2.509 (–11.260 to 6.243)	0.468†
DBP				
Pre	79.07±11.45	75.45±14.85	3.623 (–1.288 to 8.533)	0.147@
Post	80.78±15.25	80.64±15.73	0.133 (–5.616 to 5.882)	0.115#
Changed	1.71±14.83	5.20±16.05	–3.490 (–9.221 to 2.241)	0.243†
PR				
Pre	84.12±13.63	84.77±15.58	–0.647 (–6.075 to 4.781)	0.814@
Post	81.38±14.00	80.98±14.83	0.397 (–4.952 to 5.746)	0.661#
Changed	–2.74±12.04	–3.79±12.02	1.044 (–3.421 to 5.509)	0.687†
RR				
Pre	19.67±1.57	19.77±1.64	–0.095 (–0.691 to 0.501)	0.617@
Post	19.90±1.53	20.38±1.53	–0.478 (–1.047 to 0.090)	0.563#
Changed	0.22±1.63	0.61±1.51	–0.383 (–0.967 to 0.201)	0.100†
STAI				
Pre	44.66±7.93	44.77±8.83	–0.113 (–3.224 to 2.998)	0.697@
Post	41.97±9.45	43.38±7.58	–1.409 (–4.596 to 1.777)	0.437#
Changed	–2.69±5.17	–1.39±7.54	–1.297 (–3.689 to 1.095)	0.233†
Pain score	2.77±2.07	2.93±2.09	–0.163 (–0.610 to 0.936)	0.427†

SBP=systolic blood pressure; DBP=diastolic blood pressure; PR=pulse rate; RR=respiratory rate; STAI=State-Trait Anxiety Inventory
@ p-value for post treatment were calculated with the use of ANCOVA (pre-treatment as a covariate), # Independent t-test, † Man-Whitney U test

in systolic blood pressure post-injection in both groups, although the difference between groups was not statistically significant. A similar pattern was observed for diastolic blood pressure. Pulse

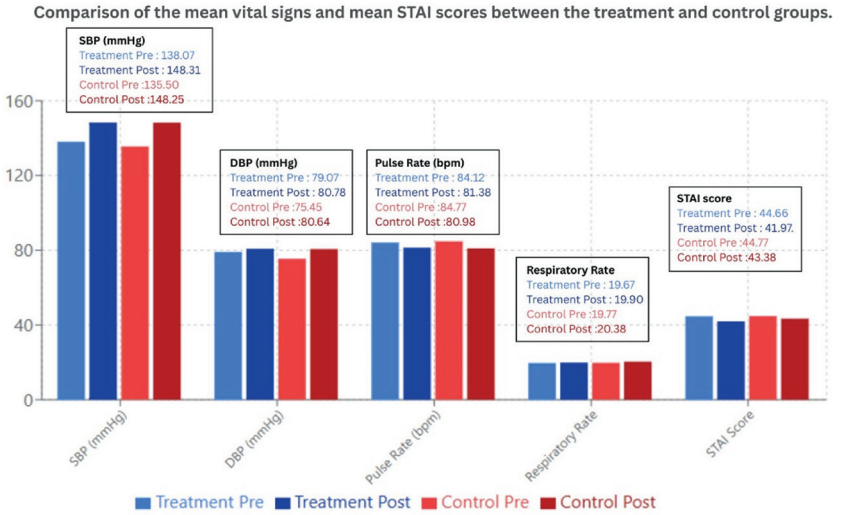

Figure 1. Comparison of the mean vital signs and mean STAI scores between the treatment and control groups.

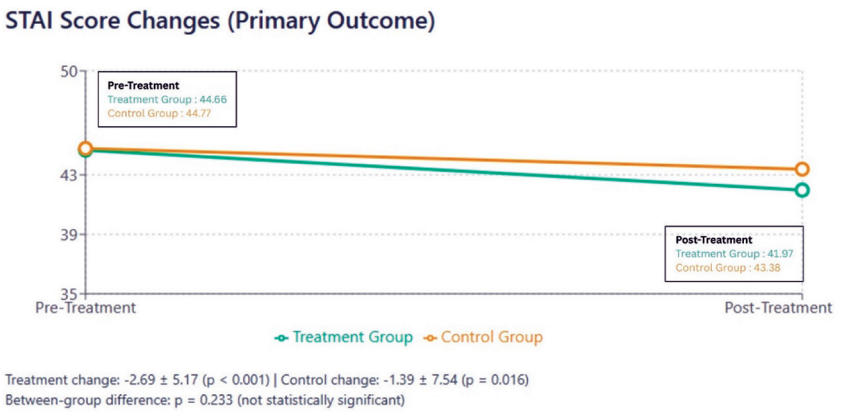

Figure 2. Comparison of the mean STAI scores between the treatment and control groups.

rate slightly decreased in both groups without a statistically significant difference. Respiratory rate remained stable before and after the injection, with no significant intra-group or inter-group differences. These trends are visually represented in Figure 1, which illustrates the mean pre- and post-injection values of systolic and diastolic blood pressure, pulse rate, respiratory rate, and STAI score in both study groups. The graphical comparison highlights the similarity in hemodynamic responses between the treatment and control groups.

Regarding anxiety levels, as measured by the STAI scale, the treatment group demonstrated a reduction in mean STAI scores following intravitreal injection (–2.69±5.17), indicating decreased anxiety after lavender aromatherapy. The control group also exhibited a reduction in STAI scores (–1.39±7.54). Although the treatment group showed a greater reduction, the between-group difference was not statistically significant (p=0.233). These findings are illustrated in Figure 2, which compares the magnitude of STAI score reduction between the treatment and control groups.

In Figure 3, the treatment group reported a lower mean pain score (2.77±2.07) compared to the control group (2.93±2.09) following intravitreal injection. Nevertheless, the difference between groups was not statistically significantly different in pain scores (p=0.427), and no adverse events were reported in either group.

When comparing pre- and post-injection outcomes within each group, both the treatment and control groups demonstrated a statistically significant reduction in STAI scores following intravitreal injection. The treatment group exhibited a greater mean reduction in STAI scores (–2.69, p<0.001)

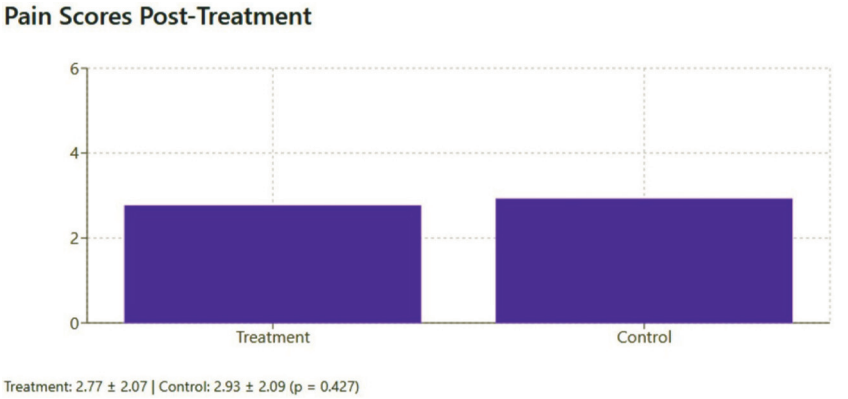

Figure 3. Comparison of post-injection pain scores between treatment and control groups.

Table 3. Comparison of vital signs and STAI scores before and after treatment within each group

	Pre Mean±SD	Post Mean±SD	Difference Mean (95% CI)	p-value
Treatment (n=58)				
SBP	138.07±18.16	148.31±23.72	10.241 (3.815 to 16.668)	0.002*
DBP	79.07±11.45	80.78±15.25	1.707 (–2.192 to 5.605)	0.384
PR	84.12±13.63	81.38±14.00	–2.741 (–5.906 to 0.424)	0.088
RR	19.67±1.57	19.90±1.53	0.224 (–0.205 to 0.654)	0.310
STAI	44.66±7.93	41.97±9.45	–2.690 (–4.049 to –1.331)	<0.001*
Control (n=56)				
SBP	135.50±17.40	148.25±26.50	12.750 (6.686 to 18.814)	<0.001*
DBP	75.45±14.85	80.64±15.73	5.196 (0.898 to 9.494)	0.019*
PR	84.77±15.58	80.98±14.83	–3.786 (–7.004 to –0.567)	0.022*
RR	19.77±1.64	20.38±1.53	0.607 (0.203 to 1.011)	0.008*
STAI	44.77±8.83	43.38±7.58	–1.393 (–3.412 to –0.627)	0.016*

SBP=systolic blood pressure; DBP=diastolic blood pressure; PR=pulse rate; RR=respiratory rate; STAI=State-Trait Anxiety Inventory
* Significant values, p<0.05

compared to the control group (–1.393, p=0.016), as illustrated in Table 3. Additionally, as shown in Figure 4, the treatment group experienced a slightly greater reduction in pulse rate, whereas the control group demonstrated a more pronounced increase in both systolic and diastolic blood pressure following the injection.

Discussion

The previous studies have demonstrated the efficacy of aromatherapy in alleviating anxiety and pain across various clinical settings. Specifically, lavender aromatherapy has been shown to exert significant anxiolytic and analgesic effects during medical procedures[4,6-9,11]. Its proposed mechanism of action involves olfactory stimulation, which activates neurological pathways within the limbic system, enhancing the release of neurotransmitters such as serotonin and dopamine that are associated with emotional regulation and pain modulation[4,5].

To the authors' knowledge, this is the first study to evaluate the effects of lavender aromatherapy in reducing anxiety and pain among patients undergoing intravitreal anti-VEGF injections. One hundred and fourteen eyes were enrolled, with 58 in the treatment group and 56 in the control group. Post-treatment analysis revealed that the treatment group experienced a greater reduction in anxiety levels, as measured by the STAI, compared to the control group (mean change: –2.69±5.17 versus –1.39±7.54). Although this difference did not reach statistical significance, the trend suggests a potential anxiolytic benefit of aromatherapy in the ophthalmic setting.

Similarly, the mean pain score post-injection was slightly lower in the aromatherapy group (2.77±2.07) than in the control group (2.93±2.09). However,

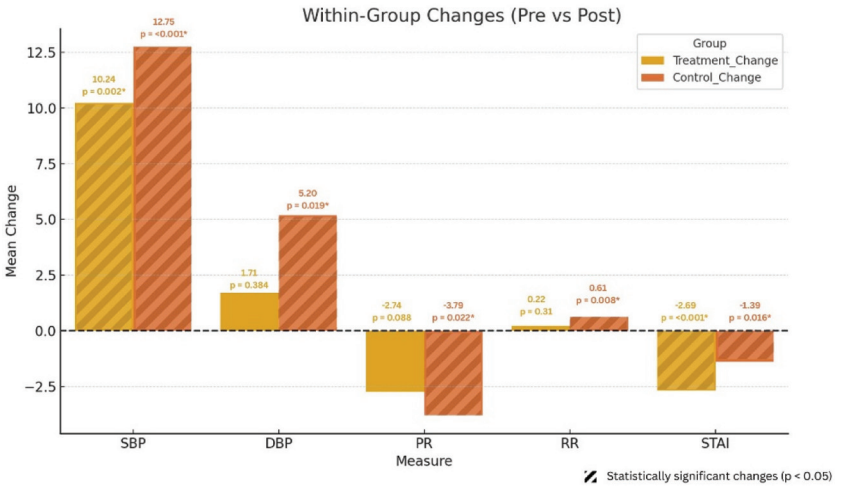

Figure 4. Comparison of the magnitude of change in mean vital signs and STAI scores between the treatment and control groups.

this difference was not statistically significant. One likely explanation is the routine administration of topical anesthesia, which may have minimized pain perception in both groups and thereby reduced the detectable impact of aromatherapy on pain outcomes.

With regard to physiological responses, both systolic and diastolic blood pressure increased in both groups following intravitreal injection. In contrast, pulse rate decreased, and respiratory rate remained stable. These findings differ from those of Stanley et al., who reported reductions in both systolic and diastolic blood pressure following lavender aromatherapy during cataract surgery[7]. The discrepancy may be explained by factors specific to the current study, including procedural stress and the pharmacological effects of anti-VEGF agents. It is known that anti-VEGF treatments may induce systemic hypertension via suppression of nitric oxide (NO), increased vascular tone, and upregulation of vasoactive substances such as endothelin-1[12].

Limitations should be acknowledged. First, the sample size may have been insufficient to detect statistically significant differences between groups. Second, the use of self-reported anxiety and pain scales is inherently subjective and may be influenced by individual thresholds or expectations. Third, all participants received pre-procedural topical anesthesia, which could have masked any analgesic effects of aromatherapy. Fourth, the odor of lavender aromatherapy can be detected by both patients and assessors; thus, this study cannot be a truly double-blind study. Finally, vital signs were measured immediately before and after the procedure, potentially limiting the detection of any delayed physiological effects of aromatherapy.

Future studies should consider larger, multicenter trials with more rigorous blinding protocols and the inclusion of objective physiological and biochemical markers (e.g., salivary cortisol and heart rate variability) to better evaluate the anxiolytic and analgesic effects of lavender aromatherapy. Additionally, examining the timing, duration, and method of aromatherapy delivery may help optimize its therapeutic potential for use in ophthalmic and other procedural settings.

In conclusion, lavender aromatherapy was associated with a greater reduction in preprocedural anxiety and slightly lower pain scores among patients undergoing intravitreal injections. Although the differences were not statistically significant, the trend suggests potential clinical benefit. Further research into larger sample sizes is needed to confirm these findings.

What is already known about this topic?

According to previous studies, aromatherapy with lavender essential oil has been shown to reduce anxiety and pain in procedures such as undergoing labor, cataract surgery, and other minor procedures. However, the previous evidence was no data, specifically the use of lavender aromatherapy in patients undergoing intravitreal injections.

What does this study add?

This study is the first randomized, placebo-controlled trial to evaluate the effect of lavender aromatherapy on preprocedural anxiety and pain in patients undergoing intravitreal anti-VEGF injections

and showed that lavender aromatherapy could reduce anxiety in STAI evaluation and reduce pain score in patients undergoing intravitreal injection, but the differences were not statistically significant. These findings suggest that lavender aromatherapy may provide a simple, safe, and cost-effective approach to enhance patient relaxation during ophthalmic procedures in the future.

Authors' contributions

NL, Contributed to the conception and design of the study, acquisition of data, data analysis and interpretation, contributed to acquisition of clinical data, drafting of the manuscript, and final approval of the version to be published. PT, Data analysis and interpretation and drafting of the manuscript. CT, Data analysis and interpretation, and drafting of the manuscript. SL, Contributed to acquisition of clinical data and critical revision of the manuscript. PB, Acquisition of data, contributed to acquisition of clinical data, and critical revision of the manuscript. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was approved by the Thammasat University Hospital Human Ethics Committee (MTU-EC-OP-0-002/67) and performed in accordance with the Declaration of Helsinki.

Clinical trial registry

This study was registered with the Thai Clinical Trials Registry (TCTR20260407001).

Use of artificial intelligence

No artificial intelligence (AI) tools were used in this paper.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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