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Different vitamin K forms in hemodialysis patients: a simple dietary supplement to battle vascular calcification—randomized controlled trial

Howaida Abdelhameed Elshinnawy[1], Tamer Wahid El-Said[1], Sarah Farid Fahmy[2], Ahmed Shamseldin[1], Sherin Ibrahim[1] and Reem Mohsen Elsharabasy[1*]

Abstract

Background and aim Vascular calcification is a significant risk factor for cardiovascular diseases in patients with end-stage renal disease, particularly those on hemodialysis. Previous research on vitamin K found that it had a positive on calcification markers. However, clinical data is still limited. This study aimed to compare the efficacy and safety of vitamin K2 versus vitamin k1 on a calcification regulator in hemodialysis patients.

Methods A prospective randomized placebo-controlled trial was conducted on 120 patients, who were divided into three groups; group 1: administered 10 mg of vitamin K1 (phytomenadione thrice weekly); group 2: administered 90 µg of vitamin k2 (MK-7); group 3: administered placebo for 3 months. Matrix Gla protein (MGP), calcium, phosphorous, and intact parathyroid hormone levels were measured.

Results MK-7 significantly increased active MGP levels compared to phytomenadione and placebo groups ($p<0.0001$). No correlations were found between calcium, phosphorous, PTH, and MGP levels at baseline or after treatment.

Conclusion Vitamin k supplementation was effective and tolerable in modulating MGP in hemodialysis patients, with MK-7 outperforming phytomenadione.

Keywords Vitamin k1, Vitamin k2, MGP, Hemodialysis; Vascular calcification, Vitamin K supplements

Introduction

Adults with end-stage renal disease (ESRD) are at high risk for cardiovascular complications caused by vascular calcification. Due to cardiovascular diseases, ESRD patients have a 20-fold higher mortality rate than the general population [1].

Vascular calcification is a complex process that occurs in both intimal and medial blood vessels; however, medial calcification is considered the most common in ESRD patients [2].

Medial calcification is characterized by a diffuse distribution among the digital, internal mammary, and radial arteries leading to arterial stiffness and loss of vascular elasticity, which increases systolic blood pressure and cardiac work, ultimately leading to left ventricular hypertrophy with increased risk of heart failure and atrial

*Correspondence:
Reem Mohsen Elsharabasy
reemmohsen@med.asu.edu.eg
[1] Department of Nephrology, Faculty of Medicine, Ain Shams University, Cairo, Egypt
[2] Department of Clinical Pharmacy, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt

fibrillation, both of which are associated with elevated cardiovascular mortality [3].

It is evident that vascular calcification was induced by the passive deposition of minerals due to their high levels in ESRD patients. Vascular calcification has recently been proven to be a pathologic cell-mediated process that primarily affects the trans-differentiation of vascular smooth muscle cells (VSMCs) to their phenotype osteoblast-like cells [2–4].

Moreover, ESRD patients suffer from a deficiency in the regulatory calcification inhibitors that puts them at increased risk for vascular calcification [5].

Matrix Gla protein (MGP) is a vitamin k dependent protein and one of the most potent inhibitors of vascular calcification in the vessel wall. It is a calcium-binding protein that is involved in the organization of the vascular calcification process. It contains glutamate residues that require vitamin K to become actively carboxylated and fully functional as a calcification inhibitor molecule [6].

Under vitamin k insufficiency, the circulating levels of uncarboxylated Gla-proteins, as dephosphorylated-uncarboxylated MGP levels increase, accompanied by poor vascular health [6].

Several studies have demonstrated that the restricted diet of hemodialysis (HD) patients and their divergent appetite and limited intake of nutrients due to nausea and anorexia can lead to vitamin K deficiency in ESRD patients, increasing their risk of poor overall vitamin k status [7].

Vitamin K naturally exists in two forms: vitamin K1 (phytomenadione) and vitamin K2 (menaquinones). Vitamin k1 is abundant in green and leafy vegetables, whereas k2 is preferentially found in meats, eggs, curd, cheese, and fermented soybeans [8].

Vitamin K2 is mainly accumulated in arteries and is responsible for the carboxylation of vitamin K-dependent proteins in bone and blood vessels, while vitamin K1 is primarily involved in the carboxylation of liver coagulation factors [9].

Previous preliminary studies revealed that both forms have a beneficial effect in HD adult patients, with some vitamin k2 studies reporting reduced calcification markers in a linear and dose-dependent manner [9].

However, no previous studies compared the efficacy and safety of vitamin k1 and vitamin k2 in HD patients. Consequently, our study aimed to compare the effect of vitamin K2 (MK-7) and vitamin k1 (phytomenadione) supplementation on circulating levels of MGP and assess their safety in patients on regular HD.

Methods

Study design

The current study is a prospective, controlled, and permuted block randomized trial conducted on HD patients.

Patients

All patients were assessed for inclusion and exclusion criteria. Inclusion criteria: Adult patients over the age of 18 who started HD in the last 3 months or longer and HD frequency three times or more weekly. Exclusion criteria: Patients with intestinal malabsorption, hypercoagulable state, hypersensitivity to vitamin k, or were on warfarin therapy were excluded.

One hundred and twenty eligible patients were randomly recruited and divided into three groups:

Group 1 (vitamin K1): 40 patients received 10 mg phyto k (phytomenadione 10 mg) manufactured by MultiCare pharma, Egypt, thrice weekly orally, in addition to their standard therapy

Group 2 (vitamin K2): 40 patients received 90 µg per day orally (two 45 µg tablets) menaquinone (MK-7) tablets manufactured by Devartlab Pharmaceuticals in addition to their standard therapy.

Group 3 (the control group): 40 patients were given placebo (starch tablets) supplied by MultiCare pharma, Egypt, in addition to their standard therapy.

Standard treatment includes calcium supplementation, vitamin D supplementation, phosphate binder (calcium carbonate, sevelamer), together with their antihypertensive medications, all of which are tailored according to individual patients' needs.

In the 3 days of the HD, patients were given the vitamins K1 and K2 directly at the end of the hemodialysis session under nurse supervision; the patients were given the study medications for the rest of the week, and the patient's adherence was followed up via telephone calls during these days. All patients received nutritional counseling regarding the phosphorous and fat diet limitation; the clinical pharmacist evaluated the side effects.

Clinical evaluation and laboratory measurements

A complete history was obtained from the participating patients in the form of an interview (age, gender, weight, geight, occupation, and both past and current medical and medication history) by a nephrologist and clinical pharmacist who are unaware of the patient group.

Blood samples were withdrawn from patients at the beginning and after 3 months before the dialysis session. Specimen collection was done by clotting serum for

10–20 min at room temperature, centrifuged at 2000–3000 RPM for 20 min, and stored at −80 °C till analysis. The laboratory staff was blind to the study setup. MGP was analyzed by ELISA kit (Shanghai Korain Biotech, Co, Catalog No.E1248Hu). All measurements were carried out according to the manufacturer's instructions. Serum calcium, phosphorous, and intact parathyroid hormone were measured using standard laboratory techniques.

Outcomes

The primary outcome was to assess the efficacy of vitamin K1 and vitamin k2 on vascular calcification by measuring the level of carboxylated MGP. The secondary outcome was to assess the effect of vitamins on calcium, phosphorous, and PTH and to assess the side effects experienced by study subjects in both groups.

Ethical considerations

All patients signed written informed consent to be enrolled in the study and have their results published. The study was approved by the local Research Ethical Committee and was following the Helsinki Declaration as revised in 2000. It also applied CONSORT guidelines and ICMJE recommendations.

Statistical methods

Analysis of data was done using SPSS program version 23. The sample size was calculated using application clinical [10], with MGP as the key marker using the mean of MGP (-404± 167) pmol/l [11, 12] and an estimated decrease in MGP with 90 μg will be 550 pmol/l using Power 85%, alpha 0.05. Taking a 15% dropout rate into account, we obtained a sample size of 40 patients.

Statistical analyses were done using the SPSS software (Statistical Package for the Social Sciences) (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Quantitative data were presented as mean and standard deviation. Qualitative data were presented as count and percentage. Student's *t*-test was used to compare quantitative data between two groups, and one-way ANOVA was used when more than two groups were compared. Mann-Whitney *U* test was used to compare non-parametric quantitative data between two groups. *P*-value < 0.05 is considered significant.

Results

We had 120 patients in the present trial, and there was no loss or dropouts during the study. Patients' compliance was estimated at each hemodialysis session, where the enrolled patients reported their daily schedule and returned the drug package when it was empty, after which a new one was provided. The consort flow diagram is depicted in Fig. 1

At baseline, there were no significant differences in demographics, comorbidities, and standard lab values between the study groups (Tables 1 and 2). Standard laboratory parameters for studied groups of patients at the beginning and after 3 months are presented in Table 3.

End of study serum carboxylated MGP levels

MGP levels significantly increased in the vitamin k2 group more than that shown in vitamin k1 or placebo groups after 3 months. The vitamin K2 group demonstrated the most significant increase compared to the other groups. In the vitamin k2, k1, and placebo groups, the percentage of change was 700%, 78%, and 40%, respectively. Table 4 depicts the differences in mean MGP values between patient groups at baseline and during follow-up.

End of study serum calcium, phosphorus, and PTH

Mean serum levels of calcium, phosphorus, and PTH did not significantly differ between groups or after 3 months of the study, where we observed that the placebo group showed a significant decrease in serum phosphorous levels compared to their baseline results and in comparison to the other groups, which did not show any change compared to the baseline values. In addition, no correlations were detected between patients' demographics and MGP levels either at baseline or after 3 months. Also, serum calcium, phosphorous, and PTH showed no correlations with MGP levels in the three groups.

Side effects

Four patients in group 1 and two patients in group 2 complained of mild gastrointestinal side effects (abdominal discomfort). The medications were well tolerated with no other complaints, and no patients were withdrawn from the study.

Discussion

Vascular calcification (VC) is a common complication of ESRD patients, a fundamental cause of CVD, and an independent predictor of all-cause death [13]. Numerous previous studies have demonstrated that vitamin K deficiency has a significant impact on vascular calcification in hemodialysis patients. The present is the first study to compare the efficacy and safety of vitamin k1 and vitamin k2 supplementation on MGP a VC inhibition marker hemodialysis patients [9].

In the current study, there was a significant increase in levels of carboxylated MGP compared to baseline in

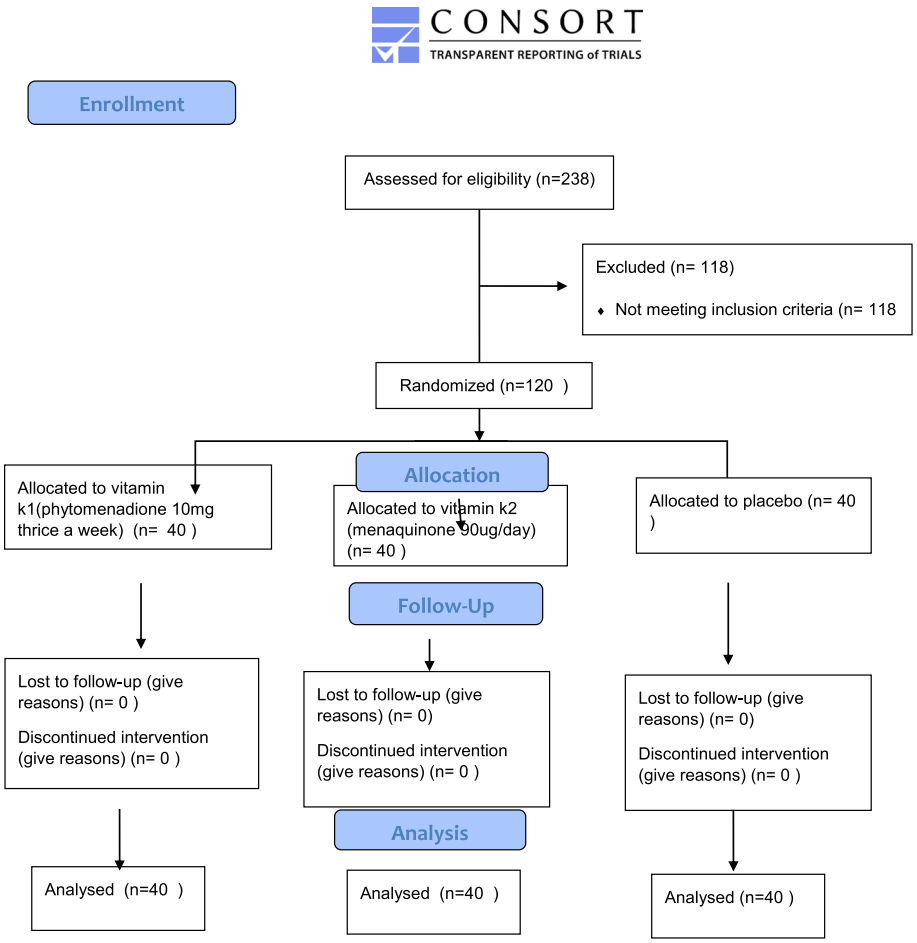

Fig. 1 Flow diagram of patients

Table 1 Baseline demographics, duration of dialysis, and access in three studied groups

		Groups				
		Vitamin K1	**Vitamin K2**	**Placebo**		
Age (years)	**Range**	21–67	20–70	18–66	***F*:** 0.53	***P*-value:** 0.59
	Mean ±SD	47.35±14.42	46.2 ±14.73	49.5±14.51		
Gender	**Male,*N*(%)**	18 (45%)	20 (50%)	16 (40%)	***X*^{2}:** 0.808	***P*-value:** 0.668
	Female,*N*(%)	22 (55%)	20 (50%)	24 (60%)		
Duration of dialysis (years)	**Range**	1.5–16	1–20	0.5–15	***F*:** 1.858	***P*-value:** 0.161
	Mean ±SD	5.263±3.158	6.738±4.496	5.281–4.008		
Access	**AV fistula N(%)**	38 (95%)	37 (92.5%)	37 (92.5%)	***X*^{2}:** 0.268	***P*-value:** 0.875
	Permicath,*N*(%)	2 (5%)	3 (7.5%)	3 (7.5%)		

the study groups (78.05% and 714. 52% for vit K1 and vit K2, respectively) than the placebo group (40.60%).

The present study revealed that vitamin K2 and vitamin K1 supplementation had beneficial effects on vascular calcification through increasing the active form of MGP (from 328±161.04 ng/l to 584±437.913 ng/l in vitamin k1 and from 332.25±117.528 pmol/ml to 2706.25±1513 pmol/ml in the vitamin k2 group) with the most significant increase was found in group 2 that administered vitamin K2.

Table 2 Comorbidities in the studied groups

		Group			Chi-square	
		Vitamin K1	Vitamin K2	Placebo		
		N (%)	*N* (%)	*N* (%)	X^2	*P*-value
HTN	**No**	11 (27.5)	11 (27.5)	12 (30)	0.1	1
	Yes	29 (72.5)	29 (72.5)	28 (70)		
DM	**No**	31 (77.5)	31 (77.5)	26 (65)	2.1	0.3
	Yes	9 (22.5)	9 (22.5)	14 (35)		
HCV	**No**	32 (80)	33 (82.5)	35 (87.5)	0.8	0.7
	Yes	8 (20)	7 (17.5)	5 (12.5)		
Smoking	**No**	31 (77.5)	33 (82.5)	32 (80)	0.3	0.9
	Yes	9 (22.5)	7 (17.5)	8 (20)		
Heart failure	**No**	34 (85)	31 (77.5)	33 (82.5)	0.8	0.7
	Yes	6 (15)	9 (22.5)	7 (17.5)		
ISHD	**No**	37 (92.5)	35 (87.5)	36 (90)	0.6	0.8

Table 3 Laboratory parameters in the studied groups at the baseline and after 3 months

	Vitamin k1		Vitamin K2		Placebo		ANOVA	
	Mean ±SD	Range	Mean ±SD	Range	Mean ±SD	Range	*F*	*P*-value
Baseline PTH (pg/ml)	618±598.07	15–3380	690.88±535.81	20–2024	570 ±457.742	49–2357	0.52	0.596
Baseline Ca+ (mg/dl)	8.845±1.09	6.3–11.3	8.525±0.793	6.6–10.4	8.685±0.689	7.5–10.4	1.341	0.266
3 months Ca+ (mg/dl)	8.82±1.227	5.3–11.3	8.555±0.981	4.9–10.3	8.768±1.048	4.8–11.3	0.663	0.517
Differences	0.025±0.801		(− 0.03±0.633)		(− 0.083±0.834)			
***P*-value**	0.845		0.766		0.535			
BaselinePO4 (mg/dl)	4.3±1.759	0.8–10	4.543±1.791	2.2–10.3	4.865±1.649	1.8–8.6	1.069	0.347
3 monthsPO4 (mg/dl)	4.25±1.974	1.2–9.6	4.263±1.572	2.2–8.5	4.13±1.399	1.5–7.7	0.077	0.926
Differences	0.05±1.334		0.28±1.21		0.735±1.355			
***P*-value**	0.814		0.151		0.001*			
BaselineCa2+ and PO4 product	37.639±15.859	9.04–88	39.106±17.858	17.82–107.12	42.101±14.386	16.56–76.54	0.799	0.452
3 months Ca2+ and PO4 product	37.35±19.267	11.76–99.84	36.817±15.621	16.94–73.47	36.182±13.359	16.95–74.69	0.052	0.95
Differences	0.289±11.438		2.289±10.97		5.92±11.105			
***p*-value**	0.874		0.195		0.002*			

Table 4 Matrix Gla protein levels in the studied groups at baseline and after 3 months

	Vitamin k1	Vitamin K2		Placebo		ANOVA		
	Mean ±SD	Range	Mean ±SD	Range	Mean ±SD	Range	*F*	*P*-value
MGP (ng/l)	328±161.04	40–640	332.25±117.528	80–580	125–40.573	20–200	40.673	<0.001*
3 months MGP (ng/l)	584±437.913	200–2800	2706.25±1513.57	300–6400	175.75±69.831	80–350	89.035	<0.001*
Difference	(− 256±491.193)		(− 2374±1477.808)		(− 50.75±76.507)			
***P*-value**	0.002*		<0.001*		<0.001*			
% of change	78.05		714.52		40.6			

Our results are inconsistent with those of Saad et al., who found a statistically significant increase in MGP level in group 1 patients who received vitamin k1 for 3 consecutive months ($P < 0.037$) compared to patients in the control group (no treatment). In addition, their study examined the effect of oral vitamin k1 on MGP level

and vascular calcification in 57 long-term hemodialysis patients [14].

Moreover, the importance of vitamin K in preventing vascular calcifications was highlighted in the study held by Delanaye and colleagues on 160 hemodialysis patients; 23 of them received VKA (vitamin k antagonists). Vitamin k antagonists increase the concentration of dp-uc MGP (P<0.0001) that significantly correlated with calcification score in hemodialysis patients ($P = 0.049$), demonstrating the impact of vitamin k1 in improving vascular calcification score and decreasing uc-MGP levels [15].

Similarly, Westenfeld et al. reported that vitamin K2 supplementation induced a dose- and time-dependent decrease in circulating dephosphorylated-uncarboxylated MGP in a study of 53 long-term stable hemodialysis patients divided into three parallel groups who received menaquinone-7 (vitamin K(2)) treatment at 45, 135, or 360 g/day for 6 weeks, assessing plasma levels of dephosphorylated-uncarboxylated MGP [11].

Consistent with our results, Kurnatowska et al. as well mentioned that after 9 months of vitamin K2 supplementation at a dose of 90 μg in 42 CKD stage 3–5 patients, a significant decrease of uc-MGP was observed (p<0.06) [16].

Moreover, despite the difference in the assessed form of the MGP, results by Aoun and colleagues are consistent with our findings. In their perspective, a pre-post intervention clinical trial involving 50 hemodialysis patients who received daily 360 μg of menaquinone-7 for 4 weeks demonstrated a significant decline in dp-ucMGP at 4 weeks of treatment [17].

In another study, Caluwé and colleagues recruited 200 HD patients to receive different doses of MK-7 thrice weekly for 8 weeks; vitamin K2 dose-dependently reduced uc-MGP level after 8 weeks of treatment compared to baseline [18].

With regard to the bone profile assessed in our patients, neither baseline levels of Ca, PO4, and their product nor the values assessed after 3 months of vit K1/K2 administration differed between the vit K1/K2 groups. However, after 3 months of follow-up, a small yet statistically significant decrease in PO4 level was observed in the placebo group compared to baseline and consequently in the Ca/Po4 product (P=0.002) in the same group. This finding might be explained by the different medications/dosing of vitamin D, calcium, and phosphate binders between the studied groups.

Similarly, in their study of 52 HD patients assigned to receive oral 200 g of vitamin K2 daily for 1 year or no treatment to assess UC-MGP concentrations, Oikonomaki et al. concluded that Vit K2 did not induce a significant change in serum Ca levels. In contrast to our findings, they stated that Vit K2 supplementation caused a statistically significant increase in serum PO4 level and, consequently, the Ca/PO4 product [19].

Also, Saad and colleagues, in their previously mentioned study, using vitamin K1 versus no treatment, revealed similar outcomes as regard Ca level, but in contrast to our results, they showed no change in serum PO4 level or Ca/PO4 product after 3 months of follow-up in either group [14].

Caluwé and colleagues' study also revealed that MK-7 did not affect Ca, PO4, or Ca/PO4 product levels at baseline and 8 weeks after Vit K2 supplementation in any tested doses [18].

Vitamin k supplements, whether k1 or k2, were well tolerable. One potential limitation of the present study is its short duration and lack of imaging to show the carotid intimal thickness; thus, long-duration studies are required.

In our study, there was no significant difference between both groups regarding their risk factors, including smoking, HTN, and hypertension as the most prevalent comorbid condition among patients of all groups (72.5%, 72.5% and 70%, respectively). Similarly, in their previously mentioned study, Delanaye et al. found no significant difference between the two study groups in relation to the associated comorbid conditions [15].

In the current study, no significant correlation could be detected between the baseline MGP level nor its level 3 months after vitamin K1/K2 administration and either of patients' age, duration on dialysis, or the bone profile assessed. These data are consistent with Saad et al., who stated that neither PTH, serum calcium, nor serum phosphorus levels did not affect MGP levels before and after vitamin K1/ placebo administration [14].

Moreover, these results were further supported by Mizuiri et al. and Cranenburg et al., who illustrated that neither the age of participants nor their duration of hemodialysis affected serum MGP levels pre- and post-therapy in both groups [20, 21]. Differences in the outcomes and results between our study and the mentioned studies above might be attributed to the different dosing/form of vitamin K1/K2 administered, whether participating patients were ESKD patients on hemodialysis or CKD population, and finally, which form of the MGP was assessed.

In conclusion, the present study results showed that vitamin k2 at a dose of 90 ug/ day over the course of 3 months had beneficial effects over calcification regulator MGP. It is recommended that vitamin k supplements, especially MK-7, be given as part of the treatment regimen given to hemodialysis patients due to their safety, tolerability, and significant impact on MGP levels and thus vascular calcification among hemodialysis patients.

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Practical application
Our study provides important data to nephrologists, nutritionists, pharmacists, and cardiologists, a multidisciplinary team managing patients on hemodialysis, with a simple, yet proven effective, dietary modification to help improve vascular calcification, one of the significant morbidities confronting this group of patients.

Study limitations
No cardiovascular outcomes were assessed during the study period due to difficulty in performing scans during the COVID pandemic.

Authors' contributions
TE and SF contributed to the study conception and design. Material preparation and data collection were performed by SI and AS. All authors performed the analysis and data interpretation. The first draft was written by SF and RM. HE, TE, RM, and SF supervised the project. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
All data analyzed during this study are included in this published article, and row data are available from the corresponding author on reasonable request 6–12 months after publication.

Declarations

Ethics approval and consent to participate
The institutional review board of the ethics committee of the Faculty of Pharmacy, Ain Shams University, revised and approved the study protocol (ENREC-ASU 2020-4). The trial was registered in clinical trial.gov (NCT04145492), and it was performed in accordance with the Declaration of Helsinki, and it also applied CONSORT guidelines and ICMJE recommendations. All caregivers of eligible children were informed about the study protocol and signed written informed consent prior to participation.
All patients signed written informed consent to be enrolled in the study and have their results published. The study was approved by the Research Ethical Committee of the Faculty of Medicine, Ain Shams University (ethical committee number: Sid 343) and was following the Helsinki Declaration as revised in 2000. It also applied CONSORT guidelines and ICMJE recommendations. The trial was registered in clinical trials.gov Identifier: NCT04477811.

Competing interests
The authors declare that they have no competing interests.

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