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A prospective, randomised, double-blinded trial to study the efficacy of topical tocotrienol in the prevention of hypertrophic scars

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Laser Doppler imaging

Summary *Background:* Despite widespread beliefs regarding the use of topical tocotrienol in the prevention of hypertrophic scars, there is very little evidence from well controlled and randomised clinical trials to justify its benefits for surgical scars.
Objective: This study was conducted to evaluate the efficacy of topical tocotrienol in preventing the development of hypertrophic scars.
Methods: A prospective, randomised, double-blinded study was performed on 122 patients with recently healed (<2 weeks) surgical scars, who were randomised into either a treatment group with 5% topical tocotrienol or a placebo group. The patients were required to apply the preparation to their scars twice a day for 6 weeks starting at 2 weeks after surgery. Assessments of the scars were performed at weeks 0, 2, 6 and 16 following the onset of topical application using three methods: a clinical assessment using the Patient and Observer Scar Assessment Scale (POSAS), a photographic scar assessment by two independent assessors using a visual analogue scale and laser Doppler imaging (LDI). Data analysis was performed on 85 patients (tocotrienol group: 45 patients; placebo group: 40 patients), who had completed four assessments.
Results: There was no statistically significant difference in scar parameters between the tocotrienol and the placebo groups in the POSAS, photographic scar assessment or mean flux of LDI ($p > 0.05$) categories. The mean LDI flux showed a decreasing trend over time, which was positively correlated with vascularity (correlation coefficient = 0.325, $p = 0.008$) and total scores (correlation coefficient = 0.248, $p = 0.034$) of the observer scar assessment scale on week 0. No significant adverse effect was observed.
Conclusions: Twice-daily application of 5% topical tocotrienol had no significant effect on the appearance and vascularity of scars over 4 months post-surgery. LDI has a promising role as

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a scar assessment tool.
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Hypertrophic scars are pathological cutaneous scars that are characterised by a proliferation of dermal tissue with excessive deposition of fibroblast-derived extracellular matrix.[1] Clinically, the scars are elevated above the skin surface but limited to the borders of the initial injury.[2] This condition is common, occurs in up to 64% of surgical incisions and can cause a wide range of functional and psychological impacts.[3,4]

Over the years, the development of hypertrophic scars has remained an unsolved problem in wound healing and their management has been proven to be challenging. A wide variety of techniques, and systemic or topical therapeutic agents have been employed and newer therapies are under development.[5–7] When used as a monotherapy or in combination, most treatment protocols for scars are prone to recurrence or yield inconsistent or mixed results.[5,8] In addition, most of the previous studies were either not controlled, had lacked objective means for measuring improvement or did not have an adequate follow-up period.

Vitamin E (tocopheryl acetate) is increasingly popular among the public for scar prevention and treatment. A significant number of health professionals believe that topical vitamin E could help in improving the cosmetic appearance of scars despite the lack of scientific evidence.[9] There is little evidence from well-controlled and randomised clinical trials to justify the beneficial use of vitamin E in surgical scars.

Tocotrienols are subfamilies of vitamin E , similar to tocopherols, but differ structurally from tocopherols by the presence of three unsaturated double bonds in their hydrocarbon tails. Tocotrienols are known to have powerful neuroprotective, anti-cancer, cholesterol-lowering and potent antioxidant properties that are different from the properties of tocopherols.[10–13] Despite these promising qualities, it has been reported that tocotrienol research accounted for less than 1% of all vitamin E research published in PubMed.[10]

Previous studies have suggested the involvement of free radicals in the formation of hypertrophic scars following thermal injuries.[14] This condition may be attenuated by the antioxidant properties of tocotrienol that cause scavenging of the free radicals. Vitamin E can inhibit the inflammatory response and collagen synthesis, as reflected by decreased tensile strength and a lower accumulation of collagen.[15] A recent study has revealed that tocotrienol can inhibit collagen synthesis by human Tenon's fibroblasts *in vitro* with possible anti-scarring potentials.[16] Moreover, studies have identified increased amounts of histamine in keloid and hypertrophic scar tissues, and an increased production of collagen by fibroblasts in response to histamine. Tocotrienol, which blocks histamine release, could perhaps normalise or at least decrease collagen production by hypertrophic scar fibroblasts. All these unique properties of tocotrienol may be valuable in modifying undesirable scar formation.

Based on these postulations, a randomised double-blinded clinical trial was performed in our study to evaluate the efficacy of 5% topical tocotrienol in the prevention of hypertrophic scar formation following surgical incisions when compared with the placebo using clinical and photographic methods. In addition, we sought to determine possible adverse reactions resulting from the application of topical tocotrienol as well as to evaluate the correlation of clinical scar assessment with laser Doppler imaging (LDI) as a scar assessment tool.

Materials and methods

Materials

The treatment cream consisted of 5% tocotrienols, 71.7% deionised water and other minor ingredients. The formulation for the placebo cream was similar to that of the tocotrienol cream but with the tocotrienols replaced by Quinoline Yellow Lake (0.7%) and Sunset Yellow Lake (0.07%) as colouring agents to make it indistinguishable from the treatment cream in appearance. The significant lack of dose–response studies defining the optimal dosage of topical vitamin E is highlighted in a review article.[17] The 5% topical tocotrienols in this study was chosen based on a previous study, which showed that tocotrienols in 5% solution can penetrate rapidly through the skin within 30 min with the largest fraction found in the subcutaneous and dermal layers.[18]

Selection of study subjects and randomisation

The study was approved by the Medical Ethics Committee of our institution. The patients, who had recently (less than 2-week-old) healed wounds, caused by general surgery or gynaecological operations, were screened for participation. The selection of the participants was based on strict inclusion and exclusion criteria. The wounds must have been graded as either clean or clean–contaminated wounds, which were closed using standard two-layer closure methods and must have healed within 2 weeks. The wounds were at least 2 cm in length and not situated in areas with a propensity for hypertrophic scarring. Written informed consent was obtained from all patients prior to enrolment.

A total of 122 patients were recruited for the study. They were randomised according to computer-generated simple randomisation into either the treatment group with tocotrienol cream or the placebo cream group (Figure 1).

Treatment protocol

Both the patients and the investigators were blinded to the topical application. The treatment commenced at 2 weeks after surgery. The patients were required to apply the preparation generously to their scars twice a day for 6 weeks. If the patients developed allergic reactions or wound

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infection, the treatment was discontinued. Patients should not have received other concomitant scar treatments during the study. Defaulters or non-compliant patients, who did not strictly follow treatment instructions as required, were excluded from the study.

Clinical assessment with Patient and Observer Scar Assessment Scales (POSAS)

The assessment of the scars was performed at the beginning of the treatment (week 0) as a baseline, and then again at weeks 2, 6 and 16. During each visit, the scars were clinically assessed using the POSAS.[19] The patient scored the characteristics of scar colour, pliability, thickness, relief, itching and pain whereas the observer scored scar vascularisation, pigmentation, pliability, thickness and relief. All items of the two scales were scored numerically on a scale of 1–10 with a score of 10 corresponding to the worst possible scar characteristic.

Photographic scar assessment by independent assessors

Digital photographs of the scars were also obtained during each visit using identical frontal views under standard lighting conditions with the same digital camera by the same group of investigators. The printed images were subsequently assessed by an image assessment panel consisting of two independent plastic surgeons. Each assessor was required to assess a series of photographs of scars from each visit using a visual analogue scale, which included vascularisation, pigmentation and thickness on a scale of

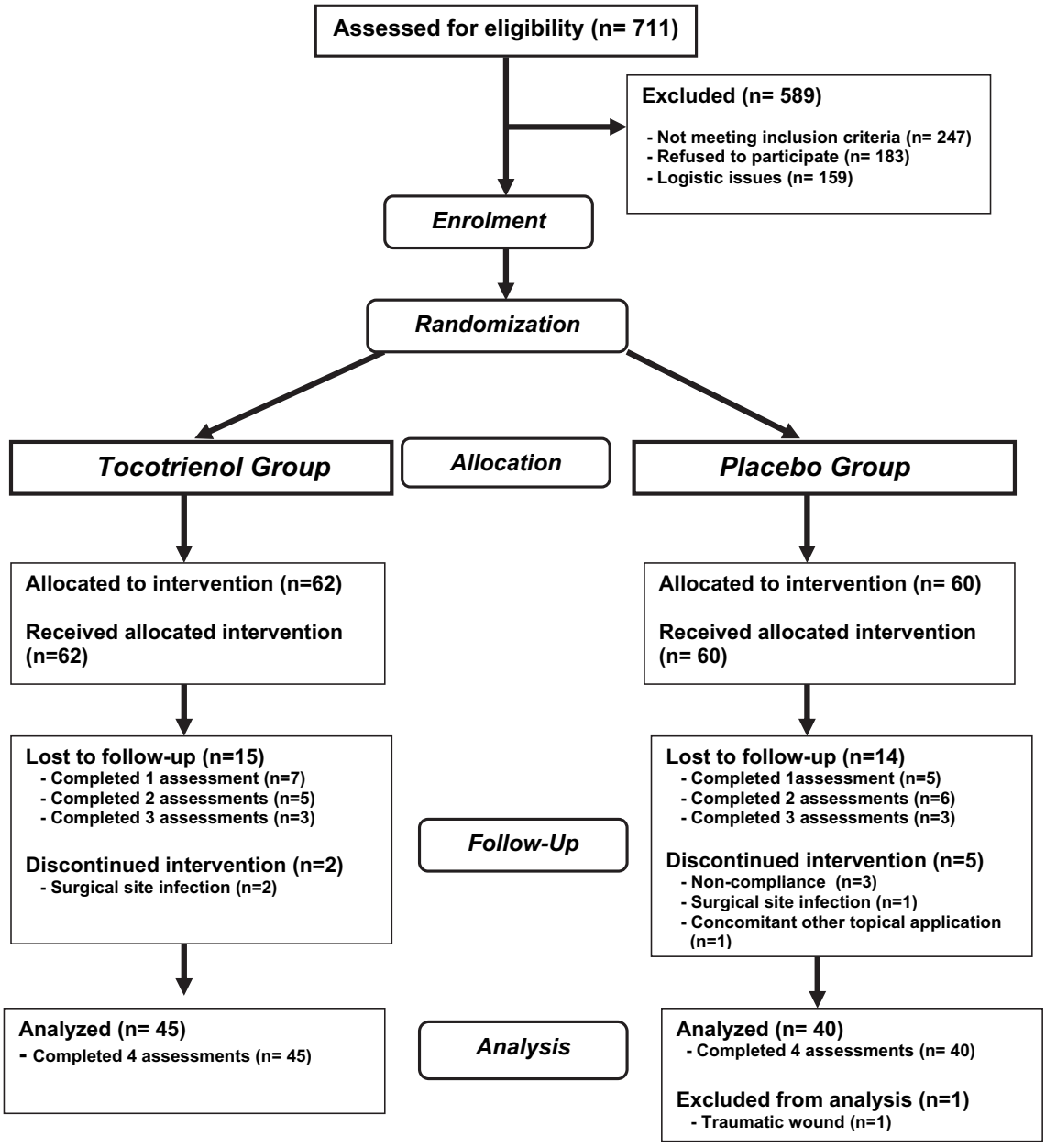

Figure 1 The CONSORT Flow chart.

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1–10 (excellent to poor), and whether the scar was hypertrophic or not.

Scar assessment with laser Doppler images

LDI is a technique that can accurately assess cutaneous blood perfusion. A laser beam scans a predetermined area, and discrete measurements of the perfusion in that area are acquired. The colour-coded perfusion images obtained represent a scale of blood-flow perfusion in units of 'flux'. The arbitrary unit of 'flux' is defined as the product of the concentration of the moving red blood cells and their mean velocity. In contrast to laser Doppler flowmetry, which gives information about tissue perfusion only within a focal point (about 2 mm^2), LDI creates an image of tissue perfusion in a wide area (about 120 mm^2) without the necessity for surface contact.[20]

The colour-coded images of LDI were obtained during each visit using the laser Doppler imager (moorLDI2™, Moor Instrument Ltd., Devon, UK). The recording was performed only in a special room by specially trained personnel. The room lighting, temperature (24–28 °C), scan resolution (256×256), scan speed (4 ms $pixel^{-1}$), bandwidth (250–15 KHz) and distance of the LDI aperture from the scars (40–60 cm) were standardised according to the protocol set up for the study. Using the provided computer software, the mean flux of the LDI of the scars was calculated using region of interest methods, reflecting the average vascularity of the scars (Figure 2).

Statistical analysis

The statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 12.0 for Windows. Statistical significance of the difference was determined when $p < 0.05$ on the basis of 95% confidence level. The demographic data of both groups was analysed with non-parametric tests, such as the Mann–Whitney test for age and length of scars or Pearson's chi-square test for other demographic data due to violation of normality. Repeated measures analysis of variance were applied to calculate the differences between the tocotrienol and placebo groups for POSAS, the visual analogue scales used by the two independent assessors as well as the mean flux of the laser Doppler images from week 0 to week 16. Whenever there was violation of sphericity, the Greenhouse–Geisser test was employed. Correlation between the mean LDI flux and the mean scores of POSAS was determined with Spearman's correlation test.

Data analysis was performed on patients according to the treatment groups they were initially assigned to, according to the principles of intention-to-treat analysis. Statistical analysis included patients, who were compliant with the treatment and completed all four assessment visits ($n = 85$) (Figure 1). Incomplete assessments due to loss to follow-up visits, non-compliance to treatment protocol, concomitant other topical cream application and surgical site infection ($n = 36$) were considered missing values and were not included in the analysis. One patient with post-traumatic scars, who was initially recruited, was not included in the analyses to reduce the confounding factors of traumatic wound healing on scar formation.

Results

Patient demographic and clinical data

The statistical analysis showed that there was no statistically significant difference between the tocotrienol group and the placebo group in terms of distributions of age, gender, race, type of surgery or site of the scar, except for the scar length (Table 1).

Clinical assessment with POSAS

There was no significant difference with respect to the mean scores of all parameters of POSAS between the tocotrienol and the placebo groups from week 0 to week 16

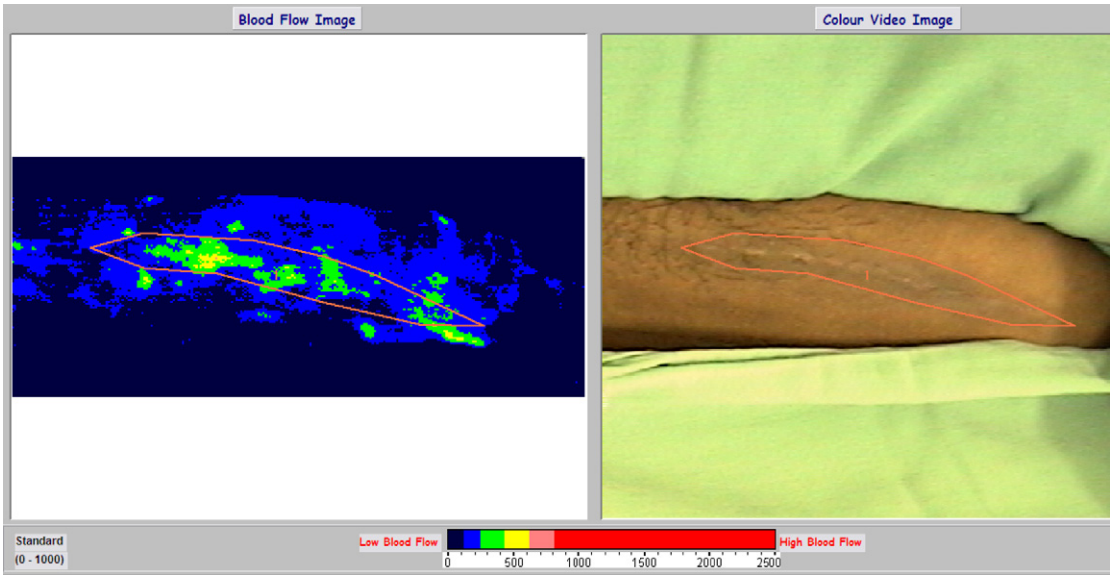

Figure 2 The mapping of colour-coded laser Doppler imaging of scar using region of interest methods to measure the mean flux.

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($p > 0.05$) (Tables 2 and 3). No overall treatment effect was detected for the total score of the Patient Scar Assessment Scale ($p = 0.382$) and the total score of the Observer Scar Assessment Scale ($p = 0.863$). An overall time effect was observed in all parameters, suggesting an improvement of scars over time from week 0 to week 16 for both groups as scored by both the patients and the observer ($p < 0.001$).

Photographic scar assessment by independent assessors

Repeated measures analysis of variance showed no significant difference among the two independent assessors in scoring the parameters of scars on the series of photographic images from week 0 to 16 using the visual analogue scale ($p = 0.711$), suggesting that there was no significant variability of scoring between the assessors.

Scar assessment by both of the independent assessors studying the digital photographic images of the scars revealed no significant differences in the overall scores or in the individual components between the tocotrienol and placebo groups over time from week 0 to week 16 with $p > 0.05$ (Table 4). The observations made by the assessors 1 and 2 in categorising whether a scar was hypertrophic or not at week 16 showed no significant difference between the two groups ($p = 0.646$, $p = 0.405$, respectively).

Scar assessment with laser Doppler images and correlation with clinical assessment

The mean LDI flux of scars was not significantly different between the tocotrienol and placebo groups from week 0 to week 16 ($p = 0.889$) (Figure 3). An overall time effect was detected with a trend of reduction of the mean LDI flux over time from week 0 to week 16 ($p < 0.001$). Spearman's correlation tests revealed a positive correlation between the mean LDI flux and the vascularity (correlation coefficient = 0.325, $p = 0.008$) and total scores (correlation coefficient = 0.248, $p = 0.034$) of the observer scar assessment scale on week 0.

Adverse effects

There was no report of any severe adverse effect from topical tocotrienol and placebo application among the participants. The adverse effects that were monitored were contact dermatitis, skin excoriation, ulceration and any local allergic manifestations. Three patients reported symptoms of mild itchiness following the application of the tocotrienol cream, but there were no significant skin rashes to suggest contact dermatitis upon clinical assessment.

Discussion

This study was a prospective, randomised, placebo-controlled clinical trial to investigate the efficacy of topical tocotrienol in the prevention of hypertrophic scar development in recently healed, clean or clean–contaminated surgical wounds. Both the investigators and the patients were blinded to the treatment modality received, and adequate follow-up assessment was provided up to 4 months after topical cream application. This study is among the few available that provides evidence on topical tocotrienol based on a randomised controlled trial (RCT) design.

Our study has revealed no statistically significant difference in any of the measured properties of scars treated with 5% topical tocotrienol when compared with

Table 1 Patient demographic and clinical data ($n = 85$)

	Tocotrienol Group		Placebo Group		Total		p value
	Median	Range	Median	Range	Median	Range	
Age (years)	38.5	17.0 – 59.0	34.0	16.0–51.0	34.0	16.0–59.0	0.127[a]
Length of scar (cm)	8.25	2.0–23.0	6.0	2.0–14.0	7.0	2.0–23.0	0.050[a]
	N	%	N	%	N	%	
Number of patients	45	52.9%	40	47.1%	85	100%	
Gender							
Male	40	88.9%	35	87.5%	75	88.4%	0.125[b]
Female	5	11.1%	5	12.5%	10	11.6%	
Race							
Malay	56	90.3%	51	86.4%	107	88.4%	0.843[b]
Others	6	9.7%	8	13.6%	14	11.6%	
Types of surgery							
Breast lumpectomy	9	20.0%	13	32.5%	22	25.9%	0.403[b]
Thyroidectomy	12	26.7%	10	25.0%	22	25.9%	
Abdominal surgery and others	24	53.3%	17	42.5%	41	48.2%	
Site of scar							
Breast	9	20.0%	13	32.5%	22	25.9%	0.418[b]
Neck	14	31.1%	10	25.0%	24	28.2%	
Abdomen and others	22	48.9%	17	42.5%	39	45.9%	

[a] Mann–Whitney Test was applied due to violation of normality.
[b] Pearson chi-Square test (2-sided).

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Table 2 Comparison of scoring of Patient Scar Assessment Scale among treatment groups based on time

Patient Scar Assessment Scale	Treatment Group	Week 0		Week 2		Week 6		Week 16		*p* value
		Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	
Total Score	Tocotrienol	18.47	16.67, 20.27	14.82	13.53, 16.12	12.80	11.48, 14.12	11.64	10.36, 12.93	0.842[a]
	Placebo	17.90	15.99, 19.81	13.75	12.38, 15.12	11.95	10.55, 13.35	11.43	10.06, 12.79	
Pain	Tocotrienol	2.22	1.76, 2.69	1.67	1.35, 1.98	1.27	1.06, 1.47	1.24	1.03, 1.46	0.484[a]
	Placebo	2.50	2.01, 2.99	1.50	1.17, 1.84	1.18	0.96, 1.40	1.25	1.03, 1.47	
Itchiness	Tocotrienol	2.24	1.83, 2.66	1.73	1.46, 2.01	1.29	1.12, 1.46	1.31	1.13, 1.50	0.741[a]
	Placebo	2.05	1.61, 2.49	1.40	1.11, 1.69	1.15	0.97, 1.33	1.23	1.03, 1.42	
Colour	Tocotrienol	3.69	3.23, 4.15	2.98	2.61, 3.35	2.93	2.50, 3.37	2.40	2.00, 2.80	0.694[a]
	Placebo	3.68	3.19, 4.16	2.83	2.43, 3.22	2.60	2.14, 3.06	2.48	2.05, 2.90	
Stiffness	Tocotrienol	4.00	3.51, 4.49	3.20	2.82, 3.58	2.71	2.36, 3.06	2.40	2.05, 2.75	0.924[a]
	Placebo	3.78	3.25, 4.30	2.90	2.49, 3.31	2.40	2.03, 2.77	2.25	1.88, 2.63	
Thickness	Tocotrienol	3.09	2.66, 3.52	2.56	2.23, 2.89	2.33	1.96, 2.70	2.18	1.88, 2.48	0.977[a]
	Placebo	3.05	2.59, 3.51	2.58	2.23, 2.93	2.28	1.88, 2.67	2.13	1.81, 2.44	
Irregularity	Tocotrienol	3.24	2.79, 3.70	2.76	2.40, 3.11	2.31	1.97, 2.65	2.11	1.81, 2.41	0.850[a]
	Placebo	3.10	2.61, 3.60	2.62	2.23, 3.00	2.36	1.99, 2.73	2.15	1.83, 2.48	

[a] Greenhouse–Geisser test was applied due to violation of sphericity.

the placebo. The demographic data of our study groups were not statistically different, except for the length of scar. Application of treatment along the whole length of scars homogenously, as instructed to every patient, has eliminated the effect of length of scars as a confounding factor. As multiple independent statistical tests with given levels of significance were undertaken, it could be predicted that at least one statistical test would inadvertently show a significant difference between the two groups, suggesting a type 2 error. This is a limitation in the statistical analysis in this study.

It is well known that the anterior chest, shoulder, scapular area and earlobe are regions in the body with a high predisposition to develop keloids and hypertrophic scars due to frequent mechanical skin stretching by natural daily movement of the body.[2] Patients with scars in these regions were not included in our study to exclude this intrinsic tendency of scar formation. In addition, as the statistical analysis has shown that the site of scars was not statistically different between the groups, site of scar was not considered as a confounding factor in our analysis.

In general, there is no universally accepted scoring system that can reliably define a hypertrophic scar, clinically. As a result, it is difficult to compare the results of studies on hypertrophic scars. Scar assessment scales and measuring devices should include features to ensure validity, reliability, responsiveness and feasibility.[4,19] In this study, we combined the clinical evaluation of scars using the POSAS, which has been proven to be reliable by various researchers in previous studies.[19,21] In contrast to the Vancouver Scar Scale, which only focusses on assessment by healthcare professionals, the POSAS also takes the patient's assessment into consideration.[4] Subjective scar assessment scales performed by observers have important advantages. They are convenient, cheap and can be performed in outpatient clinics because they require little time to complete.[22] These advantages were also noted in our study. The responsiveness of these scales

Table 3 Comparison of scoring of Observer Scar Assessment Scale among treatment groups based on time

Observer Scar Assessment Scale	Treatment Group	Week 0		Week 2		Week 6		Week 16		*p* value
		Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	
Total Score	Tocotrienol	15.44	14.22, 16.67	14.36	12.81, 15.90	13.82	12.12, 15.53	12.00	10.22, 13.78	0.743[a]
	Placebo	15.40	14.10, 16.70	15.18	13.54, 16.81	14.05	12.24, 15.86	11.60	9.71, 13.49	
Vascularity	Tocotrienol	3.24	2.87, 3.62	2.93	2.52, 3.34	2.84	2.35, 3.34	2.09	1.67, 2.51	0.560[a]
	Placebo	3.13	2.73, 3.53	3.13	2.69, 3.57	3.15	2.63, 3.68	2.31	1.86, 2.76	
Pigmentation	Tocotrienol	3.47	3.12, 3.82	3.36	2.88, 3.83	3.22	2.73, 3.71	2.80	2.34, 3.26	0.421
	Placebo	3.35	2.98, 3.72	3.70	3.20, 4.2	3.55	3.03, 4.07	2.78	2.29, 3.26	
Thickness	Tocotrienol	2.62	2.31, 2.93	2.44	2.14, 2.75	2.33	2.00, 2.67	2.40	2.00, 2.80	0.947[a]
	Placebo	2.55	2.22, 2.88	2.43	2.10, 2.75	2.35	2.00, 2.70	2.28	1.85, 2.70	
Relief	Tocotrienol	3.02	2.71, 3.33	2.73	2.39, 3.08	2.67	2.29, 3.05	2.40	2.02, 2.78	0.708[a]
	Placebo	3.08	2.74, 3.41	2.80	2.43, 3.16	2.46	2.05, 2.87	2.26	1.85, 2.66	
Pliability	Tocotrienol	3.16	2.83, 3.48	2.98	2.58, 3.38	2.76	2.32, 3.19	2.31	1.95, 2.67	0.383[a]
	Placebo	3.44	3.09, 3.79	3.08	2.65, 3.51	2.51	2.05, 2.98	2.26	1.87, 2.65	

[a] Greenhouse–Geisser test was applied due to violation of sphericity.

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Table 4 Comparison of scoring of Visual Analogue Scale between treatment groups by Independent Assessors based on time

Visual Analogue Scale	Treatment Group	Week 0		Week 2		Week 6		Week 16		*p* value
		Mean	95% CI	Mean	95%CI	Mean	95%CI	Mean	95%CI	
Assessor 1										
Overall Score	Tocotrienol	3.78	3.27, 4.28	3.79	3.28, 4.31	3.85	3.37, 4.32	3.83	3.36, 4.30	0.474[a]
	Placebo	4.31	3.76, 4.85	4.33	3.77, 4.89	4.10	3.59, 4.62	4.08	3.57, 4.59	
Vascularity	Tocotrienol	4.26	3.63, 4.89	4.09	3.47, 4.70	4.02	3.45, 4.59	3.97	3.41, 4.52	0.794[a]
	Placebo	4.55	3.87, 5.24	4.57	3.90, 5.24	4.31	3.69, 4.93	4.37	3.76, 4.97	
Pigmentation	Tocotrienol	5.07	4.52, 5.62	5.09	4.54, 5.63	5.00	4.50, 5.50	4.95	4.44, 5.45	0.842[a]
	Placebo	5.20	4.61, 5.80	5.22	4.63, 5.82	5.20	4.66, 5.75	5.20	4.65, 5.76	
Thickness	Tocotrienol	2.07	1.76, 2.38	2.07	1.76, 2.38	2.07	1.80, 2.34	2.07	1.81, 2.32	0.269[a]
	Placebo	2.27	1.93, 2.60	2.31	1.97, 2.64	2.04	1.75, 2.34	2.02	1.74, 2.30	
Assessor 2										
Overall Score	Tocotrienol	3.67	3.37, 3.98	3.66	3.45, 3.97	3.84	3.52, 4.16	3.82	3.51, 4.13	0.252[a]
	Placebo	3.69	3.35, 4.03	3.71	3.37, 4.06	3.57	3.21, 3.93	3.55	3.20, 3.90	
Vascularity	Tocotrienol	3.46	2.91, 4.01	3.36	2.85, 3.87	3.51	2.97, 4.04	3.48	2.94, 4.01	0.667[a]
	Placebo	3.27	2.66, 3.88	3.00	2.43, 3.57	3.45	2.85, 4.05	3.55	2.96, 4.14	
Pigmentation	Tocotrienol	5.00	4.41, 5.59	5.07	4.49, 5.64	5.54	4.91, 6.17	5.30	4.67, 5.93	0.318[a]
	Placebo	5.18	4.53, 5.84	5.33	4.69, 5.97	4.98	4.27, 5.69	5.43	4.73, 6.13	
Thickness	Tocotrienol	2.48	2.06, 2.90	2.28	1.88, 2.68	2.34	1.96, 2.73	2.61	2.23, 2.98	0.101[a]
	Placebo	2.55	2.08, 3.02	2.47	2.02, 2.92	2.10	1.67, 2.53	2.04	1.62, 2.46	

[a] Greenhouse—Geisser test was applied due to violation of sphericity.

in assessing scar properties is considered reasonable, as similar findings were observed with other methods, such as photographic scar assessment and LDI, in the current study.

A photographic assessment of the scars by an independent expert panel was also included in our study. Beusang et al.[23] had assessors use a visual analogue scale to assign scores for each photograph, similar to the approach used in our study. However, we have adjusted the scoring system to enable us to compare the results with the clinical findings from the POSAS.

In all of the variables assessed using the POSAS, there was no significant difference between the tocotrienol and the placebo groups. The assessment of the photographs by the independent expert panel also failed to reveal any significant differences in the cosmetic appearance of the scars after the topical application of tocotrienol or placebo cream. This suggests that tocotrienol application did not achieve scar reduction as compared with the placebo. These findings were consistent with the findings of two previous controlled studies that showed failure of topical vitamin E to decrease scar formation following Mohs micrographic surgery or post-burn reconstructive surgery, respectively.[24,25]

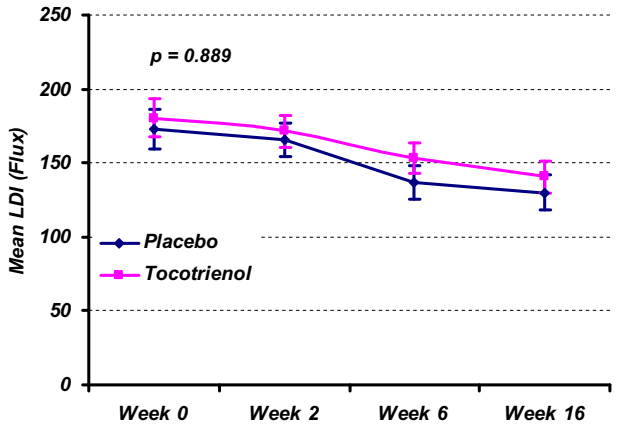

Figure 3 Comparison of mean flux of Laser Doppler imaging (LDI) between treatment groups over time.

Combination of vitamin E with other therapies may yield positive results. Vitamin E used in combination with silicone gel sheets improved the quality of pre-existing hypertrophic scars and keloids as compared with silicone gel sheets alone after 2 months as was noted in a simple-blinded study.[26] This was attributed by the authors to the synergistic effect of the two topical treatments, rather than vitamin E alone. In another study involving 15 patients with keloids and hypertrophic scars in high predisposition areas of the body, the combination of 0.5% hydrocortisone, silicone and vitamin E lotion was noted to be superior to onion extract and placebo.[27]

The positive effect of topical vitamin E (tocopheryl acetate) on surgical scars was recently shown in a prospective single-blinded study of 428 children.[1] The topical vitamin E was applied at least 15 days before and 30 days after elective inguinal surgery. It was based on the Vancouver Scar Scale as scored by the parents instead of the patients themselves at the end of treatment and after 6 months. The authors attributed the improvement in cosmetic results to the preoperative application, which was presumed to cause skin rehydration, improve elasticity and resistance and quicker physiologic healing.

Perhaps the most interesting finding in this study was the absence of adverse effects except for minor itchiness in the study subjects for both the tocotrienol and placebo groups. This finding is in contrast to previous studies, in which there were several reports of adverse effects related to the use of topical vitamin E.[28–31] Almost 20% of patients reported

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local reactions to vitamin E cream in a study by Jenkins et al.[24] Goldman and Rapaport described a patient, who presented with an extensive erythematous, eczematous eruption following topical treatment of a skin condition with vitamin E oil.[32] Baumann and Spencer reported a 33% incidence of contact dermatitis when topical vitamin E was directly applied to surgical wounds immediately after an operation; this was because the creams were applied directly on fresh wounds rather than on scars.[25]

All the adverse effects reported in the literature were related to the use of topical tocopherols, whether in their pure or diluted form. It was noted that less than 1% of all vitamin E studies have examined tocotrienols.[10] So far, no study has been conducted using other forms of vitamin E such as tocotrienols to evaluate their effects on scars. This is perhaps the first study to use the less-popular form of vitamin E with the intent of examining its effect on the cosmetic appearance of scars. With this finding, further research is warranted to investigate other interesting new properties of the lesser-known forms of vitamin E with the hope of finding an appropriate solution to the problem of abnormal scarring.

Hypertrophic scars have been shown to have a higher number of vessels and more dilated vessels than those found in normal skin.[33,34] Because LDI detects cutaneous vascularity, it has the potential to be used as a scar assessment tool. However, only limited studies have reported the use of LDI for the assessment of scars. Nakamura et al. employed LDI to assess the blood flow of median sternotomy scars post-cardiac surgery in 75 paediatric patients and found that the patients with hypertrophic scars exhibited significantly higher skin blood flow.[35] Bray et al. evaluated 20 patients with hypertrophic burn scars and noted a strong and significant correlation of perfusion measurements of the scars using two laser Doppler imagers with a modified Vancouver Burn Scar Scale.[36] Our results have shown that the mean LDI of the scars decreased over time from week 0 to week 16 for tocotrienol and placebo groups. This trend was similar to the vascularity and total scores of the POSAS. These findings correspond with the natural history of scars that show reduction in vascularity and improvement in properties of hypertrophic scar over time as the scars mature. However, future studies with increased patient number and power of study are needed to quantify these observations further.

Twice-daily application of 5% topical tocotrienol had no significant effect on the appearance and vascularity of scars over 4 months post surgery. No significant adverse effect was noted following topical tocotrienol application in the study population. The LDI technique has a promising role as a scar assessment tool.

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Conflict of interest statement

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