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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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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.

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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 a scar assessment tool.

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