Sir,

Recurrent herpes labialis (RHL) or cold sores affect 20–40% of the population, some of whom develop frequent attacks.¹ Systemic therapy with aciclovir, valaciclovir or famciclovir can suppress or shorten the duration of attacks,² although the cost of these agents restricts their availability. Topical therapy with aciclovir is popular, although studies assessing the effects of treatment have yielded inconsistent results.³ The essential oil of *Melaleuca alternifolia*, or tea tree oil (TTO), has broad-spectrum antimicrobial activity *in vitro*,⁴ including activity against herpes simplex virus (HSV),⁵ the aetiological agent of RHL.

We undertook a pilot study to evaluate the efficacy of topically applied TTO in the treatment of RHL. A randomized, placebo-controlled, investigator-blinded protocol was used. Double-blinding was not attempted because of the distinctive odour of TTO. Patients aged 18–70 years with a self-reported history of recurrent RHL were recruited. Exclusion criteria included antiviral therapy in the previous month, long-term steroid therapy, immunocompromised status, pregnancy, lactation or known allergy to TTO. The protocol was approved by the local institutional review board and informed written consent was obtained from...
each patient. Participants presented as soon as possible after onset of an attack and were randomized to receive either 6% TTO in an aqueous gel base or placebo gel (Australian Bodycare Pty. Ltd, Mudgeeraba, QLD, Australia). Patients applied the gel five times daily, recorded treatment applications and adverse events in a daily diary, and were assessed daily (except Sunday) in the clinic, where swabs were collected for HSV detection by PCR and culture. Visits continued until re-epithelialization occurred and PCR was negative for HSV DNA on two consecutive days. Patients did not apply the gel 3 h before their visit to minimize carry-over onto swabs for HSV detection and to maintain blinding of the investigators. The parameters measured were time to re-epithelialization, time to crust formation, duration of virus detection by PCR and culture, and virus titre. The duration of each parameter was measured from the time the patient first noticed their lesion and results compared using the Mann–Whitney test.

Swabs were placed in viral transport medium. One aliquot was stored at 4°C and processed by PCR within 48 h of collection and the other stored at –75°C for later cell culture. In–house primers directed at the glycoprotein B gene of HSV–1 and HSV–2 were selected (GenBank accession numbers S65444 and U12175, respectively) and used in a nested PCR using 45 cycles per round with an annealing temperature of 60°C. Perkin–Elmer TaqGold enzyme was used to provide a ‘hot–start’. PCR products were detected in agar gel electrophoresis with ethidium bromide staining. Viral culture was performed by standard methods using HF–32 cells. Titrations were done in quadruplicate using serial 10-fold dilutions of the original virus transport medium.

One patient of 10 in the TTO group did not develop clinical RHL, was PCR negative and was withdrawn due to an adverse event. One patient of 10 in the placebo group was lost to follow–up. All remaining patients (n = 18) were PCR positive for HSV–1 and developed clinical RHL. Three TTO patients and one placebo patient were never HSV culture–positive but their median times to presentation were 2 and 1 days, respectively, and later presentation may have contributed to the failure to detect HSV by
PCR or culture. The median time to re-epithelialization after treatment with TTO was 9 days, compared with 12.5 days after placebo. Similarly, TTO treatment effected a modest reduction in the median duration of culture positivity (3 compared to 4 days). However, after both treatments, the median duration of PCR positivity was 6 days and the median time to crust formation was 4 days. HSV was detectable by PCR for 3–4 days longer than by culture in both groups. Viral titres appeared lower in the TTO group than in the placebo group at days 3 ($5.1 \times 10^4$ to $5.8 \times 10^6$ pfu/mL, respectively) and 4 ($10$ to $2.1 \times 10^3$ pfu/mL, respectively) after onset, but these differences did not reach statistical significance.

Our data indicate some benefit from TTO treatment; however, none of the differences between groups reached statistical significance, probably owing to the small sample size and the influence of including patients with lesions beyond the papule stage. Eight of the nine patients in the TTO group commenced treatment at the vesicle stage or beyond, compared with six in the placebo group, and earlier therapy may prove more effective. Despite these limitations, the reduction in time to re-epithelialization seen in the TTO group was similar to reductions reported previously for other topical therapies. TTO may be a potentially useful cheaper alternative, acceptable to patients, and which poses little threat of inducing resistance to systemic antiviral agents. A larger study has begun to further evaluate TTO as a topical treatment for RHL.

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