


Nettle-induced Urticaria Treatment Study (NUTS): demonstrating the joy of research through a randomised, blinded, placebo-controlled trial

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ABSTRACT

The use of dock leaves to ease the discomfort of nettle stings is a well-known folk remedy in the British Isles, yet has never been tested in a clinical trial. A group of Emergency Department doctors designed and conducted the Nettle-induced Urticaria Treatment Study (NUTS) as a research training and team-building exercise to address this gap in the Emergency Medicine evidence base.

INTRODUCTION

The common nettle *Urtica dioica* is an abundant native plant in the British Isles.¹ Nettle stems and leaves are covered in trichomes, specialised stinging hairs with a brittle tip that snaps off when touched, exposing a sharp point through which a combination of bioactive substances (histamine, acetylcholine and serotonin) is injected into the skin.^{2,3} Many thousands of people are probably stung by nettles every year in the UK, and while TOXBASE records no cases of severe or fatal poisoning, most people regard nettle stings as unpleasant and look for a remedy.

The use of broad-leaved dock *Rumex obtusifolius* to rub on nettle stings is a well-known folk remedy in the British Isles⁴. This practice is referenced by Chaucer (*Troilus and Criseyde*: 'Netle in, dokke out...') so is at least 600 years old, and probably much older. No convincing biochemical mechanism has been suggested to explain why dock leaves help with nettle stings. It is possible that rubbing the area and/or the cooling effect of sap evaporating from a crushed leaf may be soothing; if so any large, fresh and non-toxic leaf would do the job, and dock may have become the leaf of choice simply because it grows in similar habitats to nettle (online supplemental figure 1).²

To our knowledge the effect of dock on nettle stings has never been tested in a clinical trial. We conducted a research training and team-building exercise by designing the Nettle-induced Urticaria Treatment Study (NUTS), a randomised, double-blind, active placebo-controlled trial which follows in a long tradition of medical self-experimentation.⁵

METHODS

Population

The participants were the authors of this paper, a group of healthy Emergency Department doctors.

Each participant acted as their own control by having treatment applied to one of their arms and active placebo to the other.

Procedures

Nettle stems of 30 cm with leaves attached were freshly harvested on the day of the study from one small area and confirmed to sting prior to the study. Stems were handled by the tip and base only, to avoid discharging trichomes prematurely.

Choice of placebo was considered at length. An appropriate active placebo (to mimic the physiological but not the therapeutic effect of the experimental intervention)⁶ required a leaf of similar size, shape and texture to dock leaves, that was neither anti-inflammatory (eg, comfrey *Simphytum* spp) nor toxic (eg, foxglove *Digitalis purpurea*). Thus, a domesticated plant of no known toxicity (*Lactuca sativa* var. *Longifolia* – the sweet gem lettuce) was chosen.

Experiment

Nettle stems were brushed ten times over demarcated areas of the flexor aspect of the participant's right and left forearms simultaneously, two stems to each arm. The participant then applied a blindfold. After 60 seconds (to simulate the time it might take to find a dock leaf under field conditions) the participant rolled a die. If an odd number was rolled, dock leaf was applied to their right arm and active placebo to their left. For even numbers the arms were reversed.

Two dock leaves were rubbed on the designated intervention arm for 60 seconds, and two lettuce leaves rubbed on the placebo arm simultaneously. All leaves were then disposed of in an opaque bag, before the participant removed their blindfold. For consistency, one individual (not blindfolded) applied treatment and placebo to all study participants; the leaves were passed to this person in two identical bags, and she was unaware of which bag contained which leaf for each run of the experiment.

To assess blinding, after the 60 second treatment participants were asked which arm they thought was treated with dock and which with lettuce. Participants rated the discomfort felt in each arm at minutes 1–5, 10, 15 and 20 after stinging. The vague term 'discomfort' was used to integrate the varied sensations provoked by nettle stings, sometimes



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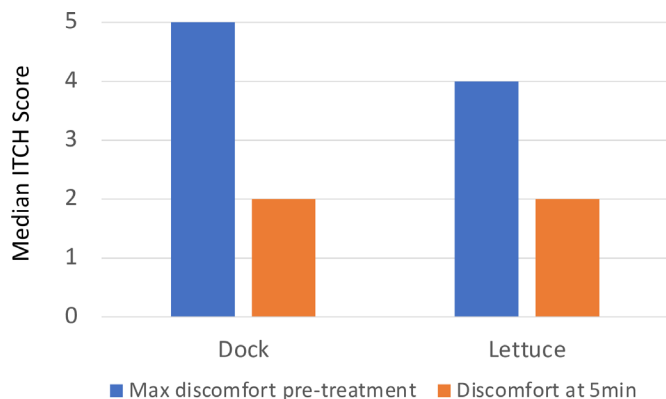


Figure 1 Median ITCH scores at minute 1 or 2 (whichever was greater, representing maximum pre-treatment discomfort) and at minute 5 in dock and lettuce treated arms. Possible ITCH scores range from 0 ('no discomfort at all') to 5 ('the most discomfort you could imagine from a nettle sting').

described as burning, itching, tingling or just 'stinging'. Based on a single previous study of the sting of the nettle tree *Dendrocnide moroides*,⁷ we asked participants to rate discomfort on a scale from 0 ('no discomfort at all') to 5 ('the most discomfort you could imagine from a nettle sting'). This score was tracked until resolution of symptoms, and so was named the Insult to Complete Healing (ITCH) score.

The primary outcome was absolute reduction in ITCH score between minute 1 or 2 (whichever was greater) and minute 5 (3 minutes post-treatment). Secondary outcomes included absolute reduction in ITCH score at 10 and 20 minutes. We also recorded the Observable Urticaria / Count of Hives (OUCH) score as the total number of discrete wheals visible within the demarcated area at 5, 10, 15 and 20 minutes. Participants photographed their own forearms at these time points, and OUCH scores were counted at a later date by an observer blinded to treatment arm to determine peak OUCH and time to peak OUCH.

RESULTS

Nine individuals took part in the study, and all completed data collection.

Three participants correctly stated which arm had been treated with dock, three were incorrect, and three were completely unable to say, suggesting that participants were adequately blinded.

The median absolute reduction in ITCH score at 5 minutes was 3 points for dock vs 2 points for lettuce, which was not statistically significant (figure 1; 2-tailed Paired Sign Test, $p=1$).

For secondary outcomes (figure 2) while there was a statistically significant decrease in ITCH score with time across both study arms, there was no significant difference between dock and lettuce arms.

The median peak OUCH score was 27 in the dock arm and 20 in the lettuce arm, while the median time to peak OUCH was 5 minutes in both arms, neither of which were statistically significant (online supplemental figures 2 and 3).

DISCUSSION

In this randomised trial on eighteen nettled forearms belonging to nine individuals, reduction in discomfort at 5 minutes was 1 point greater with dock than with lettuce.

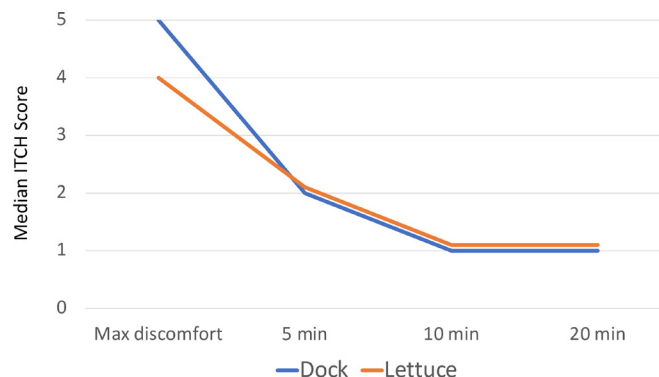


Figure 2 Median ITCH scores at minute 1 or 2 (whichever was greater, representing maximum pre-treatment discomfort) and minutes 5, 10 and 20 in dock and lettuce treated arms. Two Way ANOVA, $p=0.0056$ for time, $p=0.391$ for treatment arm.

Though representing a 16.7% difference in favour of dock, this was not statistically significant, and mirrored the difference of 1 point in the initial ITCH score.

We observed that the discomfort of nettle stings eased rapidly over 15–20 minutes in both the dock and the lettuce arms, but that the effect was not significantly different between the two interventions. It is possible that the same relief would have occurred with no treatment at all, and our study design does not permit us to conclude that either dock or lettuce is better than simply doing nothing. This was quite deliberate. Patient/Public Involvement work from other studies suggests that children in particular do not consider *doing nothing* to be an acceptable option when they are in pain,⁸ and we feel this may well be applicable to nettle stings.

Limitations of our study include our small sample size, which was dictated by volunteer number and precluded any power calculation. Nonetheless, we believe this to be the first clinical trial of this ancient treatment, and a signal towards benefit in the primary outcome suggests that an appropriately powered superiority trial should follow. Alternatively, if a few other Emergency Department research teams were to replicate our design, a participant-level meta-analysis of multiple small studies could reach a statistically valid conclusion.

Ultimately, the goal of this study was to get our team talking about research in Emergency Medicine, providing a practical opportunity to explore concepts such as blinding, placebo choice and measurement while investigating a benign condition. We conclude that dock leaf *may* work for nettle stings, lettuce *may* be just as good, relief comes quickly either way, and research training in Emergency Medicine can be made extremely entertaining.

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Patient consent for publication Not applicable.

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REFERENCES

- 1 Stace C. *New Flora of the British Isles*. 4th edn. Cambridge University Press, 2019.
- 2 Wheeler KGR. *A Natural History of Nettles*. Trafford Publishing, 2007.
- 3 Ensikat H-J, Wessely H, Engeser M, *et al*. Distribution, Ecology, chemistry and toxicology of plant stinging hairs. *Toxins (Basel)* 2021;13:141.
- 4 Mabey R. *Flora Britannica*. Chatto & Windus / Sinclair Stevenson, 1996.
- 5 Tagg A, Roland D, Leo GS, *et al*. Everything is awesome: don't forget the Lego. *J Paediatr Child Health* 2019;55:921–3.
- 6 Jensen JS, Bielefeldt AØ, Hróbjartsson A. Active placebo control groups of pharmacological interventions were rarely used but merited serious consideration: a methodological overview. *J Clin Epidemiol* 2017;87:35–46.
- 7 Christina Leung T-W, Williams DH, C J Barna J, *et al*. Structural studies on the peptide Moroidin from Laportea Moroides. *Tetrahedron* 1986;42:3333–48.
- 8 Perry DC, Achten J, Knight R, *et al*. Immobilisation of Torus fractures of the wrist in children (FORCE): a randomised controlled equivalence trial in the UK. *Lancet* 2022;400:39–47.