EVerT: cryotherapy versus salicylic acid for the treatment of verrucae – a randomised controlled trial

S Cockayne,[1]* M Curran,[2] G Denby,[2] F Hashmi,[3] C Hewitt,[1] K Hicks,[1] S Jayakody,[1] A Kang'ombe,[1] C McIntosh,[4] N McLarnon,[5] E Stamuli,[1] K Thomas,[6] G Turner,[1] D Torgerson[1] and I Watt[1,7] on behalf of the EVerT team

[1]Department of Health Sciences, York Trials Unit, University of York, York, UK
[2]School of Health, University of Northampton, Northampton, UK
[3]University of Brighton, School of Health Professions, Division of Podiatry, Eastbourne, UK
[4]The National University of Ireland Galway, School of Podiatry, Galway, Ireland
[5]Glasgow Caledonian University, School of Health and Social Care, Glasgow, UK
[6]Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK
[7]Hull York Medical School, University of York, York, UK

*Corresponding author

Executive summary

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Executive summary

Objective

To compare the clinical effectiveness and cost-effectiveness of cryotherapy using liquid nitrogen versus 50% salicylic acid for the treatment of verrucae (plantar warts).

Methods

Design

A multicentre, pragmatic, open, two-armed randomised controlled trial was undertaken with an economic evaluation. Participants were randomised using simple randomisation, with the allocation sequence generated by a computer in a 1 : 1 ratio. The sample size calculation was based on the difference in cure rates at 12 weeks between the two groups. In order to give 80% power to show a difference in cure rates of 70% versus 85% required 120 patients in each group or 133 patients after allowing for 10% attrition, i.e. a total of 266.

Setting

Participants were recruited from 14 sites in England, Scotland and Ireland: two podiatry clinics, one of which was in Scotland, four university podiatry schools, one of which was in Ireland and eight general practitioner (GP) practices in five different regions of England.

Participants

Potential participants were identified by a health-care professional from the study site from GP referrals or self-referrals received by the podiatry or GP practice for the treatment of verrucae. Patients were eligible to participate in the trial if they presented with a verruca that, in the opinion of the health-care professional, was suitable for treatment with both salicylic acid and cryotherapy, and were aged 12 years and over.

Interventions

Participants randomised to cryotherapy using liquid nitrogen received a maximum of four treatments, 14–21 days apart, delivered by a health-care professional. The first treatment was a gentle freeze lasting approximately 10 seconds, with subsequent treatments undertaken according to the site's usual practice. Debridement, masking and padding of the site were also undertaken according to the site's usual practice. Participants randomised to patient self-treatment with 50% salicylic acid (Verrugon, William Ransom & Son Plc, Hitchin, UK) were instructed on how to use the acid by a health-care professional and instructed to apply it once daily for a maximum of 8 weeks.

Main outcome measures

The primary outcome was complete clearance of all verrucae at 12 weeks. Secondary outcomes were complete clearance of all verrucae at 12 weeks, controlling for age, whether or not the verrucae had been previously treated and type of verrucae, with a second model to explore the effect of patient preferences, time to clearance of verrucae, clearance of verrucae at 6 months, number of verrucae at 12 weeks and patient satisfaction with the treatment.

Results

A total of 240 participants (90% of the sample size) were recruited to the trial, with 117 patients allocated to the cryotherapy group and 123 to the salicylic acid group. There was no evidence of a difference between the proportions of participants with complete clearance of all verrucae at 12 weeks between the salicylic acid and cryotherapy groups {14.3% vs 13.6%, chi-squared test statistic 0.02 [1 degrees of freedom (df)]; $p = 0.89$}. Cryotherapy was also associated with higher mean costs per additional healed patient [£101.17, 95% bias-corrected and accelerated confidence interval (CI) £85.09 to £117.26]. The probability of cryotherapy being cost-effective is 40% for a range of willingness-to-pay thresholds of £15,000–30,000 per patient healed. The results of the study did not change when the analysis was repeated but controlled for age, whether or not the verrucae had been previously treated and type of verrucae or patients' preferences at baseline.

There was no evidence of a difference in the clearance of verrucae at 6 months between the salicylic acid and the cryotherapy groups [30.5% vs 33.7%, chi-squared test statistic 0.22 (1 df); $p = 0.64$] nor in time to clearance between the two groups [hazard ratio (HR) 0.80, 95% CI 0.51 to 1.25; $p = 0.33$]. There was no evidence of a difference in the number of verrucae at 12 weeks between the two groups (incidence rate ratio 1.10, 95% CI 0.84 to 1.45; $p = 0.47$).

Conclusions

There was no evidence of a difference in clearance rates of verrucae between the 50% salicylic acid and the cryotherapy using liquid nitrogen groups. However, the results of this study are applicable only to verrucae or plantar warts and not to warts at other sites, such as the hands, which may respond differently to cryotherapy.

The findings of this study would not be generalisable to other freezing agents, such as nitrous oxide or over-the-counter (OTC) freezing treatments, as they freeze at a higher temperature than liquid nitrogen. Nor could the results be extrapolated to other concentrations of salicylic acid available as OTC preparations, which are usually of a lower concentration, or to the treatment being applied by a health-care professional.

Cryotherapy is associated with higher mean costs per patient healed compared to salicylic acid. Both higher mean costs and lack of evidence of a difference in effectiveness result in cryotherapy having a low probability of being cost-effective, even at high (> £15,000 per patient healed) cost-effectiveness threshold values.

Implications for future research

There are other treatments available for cutaneous warts, but with very little good-quality evidence assessing their effectiveness. The effectiveness of these treatments is worthy of further study.

Trial registration

This trial is registered as ISRCTN18994246.

Funding

This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 15, No. 32. See the HTA programme website for further project information.

Publication

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 05/513/02. The contractual start date was in October 2006. The draft report began editorial review in July 2010 and was accepted for publication in January 2011. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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