Randomised controlled trial and economic evaluation of podophyllotoxin solution, podophyllotoxin cream, and podophyllin in the treatment of genital warts


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of podophyllotoxin 0.5% solution and podophyllotoxin 0.15% cream in the treatment of genital warts. Both were self-applied twice daily for 3 consecutive days, with 4 days off therapy. The comparator was clinic-applied 25% podophyllin, applied twice weekly.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised immunocompetent men and women with genital warts. The inclusion criteria were age 18 to 65 years, and current anogenital warts with a history of 3 months or less and no therapy in that time. The exclusion criteria included known human immunodeficiency virus infection or immunosuppression, homosexual men with perianal warts, total lesional area of greater than 400 mm2, any individual lesion with an area of greater than 100 mm2 intrameatal or vaginal warts. Other criteria for exclusion were ulcerative or inflammatory sexually transmitted diseases (STDs) of the anogenital region, and pregnancy.

Setting
The setting was secondary care (STD clinics). The economic analysis was conducted in UK.

Dates to which data relate
The dates to which the effectiveness and cost data related were not reported. The price year was 1998.

Source of effectiveness data
The effectiveness data were derived from a single prospective study.

Link between effectiveness and cost data
The costing was undertaken prospectively on the same group as that used in the effectiveness study.

Study sample
The sample size was selected on the basis of power calculations (power=80% and alpha=5%). Assuming that the highest efficacy was 80% and the minimum difference considered clinically important to detect was 20%, a total of 249 patients (89 in each group) was required for analysis. Since the authors further assumed that 20% of the
participants would not provide valid data, the target sample size was increased to 300 patients. However, due to the high rate of non-analysable data, the target sample was expanded to 350 patients and 25 patients were recruited from each of the 11 centres involved in the study. A total of 354 patients were randomised to either podophyllotoxin solution (n=120; 52% men), podophyllotoxin cream (n=118; 51% men), or podophyllin (n=116; 52% men).

Study design
The study was an open, randomised controlled multi-centre trial, which was carried out in 11 STD clinics in the UK. Randomisation was stratified according to gender and the number of warts (at least 10 or less than 10) using treatment assignment envelopes for each stratum. The duration of follow-up was 12 weeks after trial entry. Only 276 patients (78%) completed the trial, 96 (podophyllotoxin solution), 82 (podophyllotoxin cream) and 98 (podophyllin) in each group, respectively. Many patients withdrew during the course of the study because of adverse events, the lack of effect, or for other reasons.

Analysis of effectiveness
The basis of the principal analysis was treatment completers only. Further analyses assumed that patients who defaulted were either not cured (worst-case scenario) or were cured (best case-scenario). The primary health outcome was the complete remission of all or original anogenital warts present at study entry. The effect of treatment on the clearance of all or original warts was further analysed using a logistic regression model after adjusting for gender, smoking status and the number of warts at entry. Therefore, the results were presented as the odds ratio (OR), with 95% confidence intervals (CIs), of having complete remission with podophyllotoxin treatment relative to podophyllin. The local side effects and the relapse rate in each group were also analysed. The characteristics of the patients in the three groups were similar at entry, except for circumcision. There were slightly more circumcised men in the podophyllotoxin solution group, (p=0.02). There was one significant difference between the principal analysis population and defaulters, smokers were over-represented in the defaulters group (70% versus 52% in the principal analysis population), (p=0.004).

Effectiveness results
In the principal analysis, both podophyllotoxin solution and podophyllotoxin cream were associated with significantly increased odds of remission of all warts or original warts in comparison with podophyllin. For remission of all warts, the OR was 2.93 (95% CI: 1.56 - 5.50) for podophyllotoxin solution and 1.97 (95% CI: 1.04 - 3.70) for podophyllotoxin cream. For remission of original warts, the OR was 2.88 (95% CI: 1.52 - 5.45) for podophyllotoxin solution and 1.67 (95% CI: 0.89 - 3.15) for podophyllotoxin cream.

When patients defaulting from follow-up were assumed to have been cured, increased odds were observed for both podophyllotoxin solution and podophyllotoxin cream. For podophyllotoxin solution, the OR was 3.04 (95% CI: 1.68 - 5.49) for all warts and 2.91 (95% CI: 1.59 - 5.34) for original warts. For podophyllotoxin cream, the OR was 2.46 (95% CI: 1.38 - 4.40) for all warts and 2.14 (95% CI: 1.19 - 3.82) for original warts.

When patients defaulting from follow-up were assumed not to have been cured, the odds of remission of all warts were significantly increased for podophyllotoxin solution (OR 1.92, 95% CI: 1.13 - 3.27), but not for podophyllotoxin cream (OR 1.17, 95% CI: 0.69 - 2.00).

Local side effects were seen in 33% of the podophyllotoxin solution group, 24% of the podophyllotoxin cream group, and 17% of the podophyllin group.

Ulceration occurred in 18% of the podophyllotoxin solution group, 12% of the podophyllotoxin cream group, and 10% of the podophyllin group.

Relapse rates were 45% (15 out of 33) in the podophyllotoxin solution group, 55% (12 out of 22) in the podophyllotoxin cream group, and 26% (5 out of 19) in the podophyllin group. These differences were not statistically significant.
Clinical conclusions
Podophyllotoxin solution and cream showed greater efficacy for the treatment of anogenital warts than clinic-based treatment with podophyllin.

Measure of benefits used in the economic analysis
The authors did not develop a summary measure of benefits. The primary health outcome, that is, complete remission of all warts, was expressed as benefits.

Direct costs
A societal perspective was adopted. The direct costs were for outpatient visits at clinics (with differing costs for an initial or a follow-up visit), drug treatment and travel. The costs for the treatment of adverse events and relapse were included. The quantities and costs were estimated from actual data. The costs of outpatient visits at clinics were obtained from six of the units participating in the study, and an average value was calculated. A nurse, together with the patient, collected data about the use of resources at each visit. The costs and the quantities were not reported separately. Discounting was unnecessary since all the costs were incurred in less than one year. The price year was 1998.

Statistical analysis of costs
No statistical analysis of the costs was performed.

Indirect Costs
The indirect costs related to production losses were calculated. These were estimated according to the average incomes for men and women employees in the UK in 1998. The costs and the quantities were not reported separately. Discounting was unnecessary since all the costs were incurred in less than one year.

Currency
UK pounds sterling ( ).

Sensitivity analysis
No sensitivity analysis was performed.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The total average direct cost per patient was 189.00 with podophyllotoxin solution, 203.84 with podophyllotoxin cream and 208.75 with podophyllin.

The total average indirect cost per patient was 328.07 with podophyllotoxin solution, 369.38 with podophyllotoxin cream and 326.72 with podophyllin.

The total cost per patient was 517.07 with podophyllotoxin solution, 573.22 with podophyllotoxin cream and 535.47 with podophyllin.

Synthesis of costs and benefits
The authors did not report an incremental analysis in the "Results" section since the podophyllotoxin solution was
more effective and less costly than podophyllotoxin cream and podophyllin. However, in the "Discussion" section, the authors reported the incremental cost-effectiveness of podophyllotoxin cream in comparison with podophyllin. The authors reported the average costs per complete remission.

The total average cost per complete remission was 736.57 (95% CI: 652.87 - 863.23) with podophyllotoxin solution, 921.58 (95% CI: 788.48 - 1,128.39) with podophyllotoxin cream and 1,141.72 (95% CI: 934.50 - 1,455.07) with podophyllin.

The marginal cost-effectiveness ratio of podophyllotoxin cream was 246.73 per complete remission in comparison with podophyllin.

**Authors' conclusions**
Podophyllotoxin solution emerges as the most cost-effective treatment, followed by podophyllotoxin cream, with podophyllin being the least cost-effective treatment.

**CRD COMMENTARY - Selection of comparators**
A justification was given for the comparators used. The authors stated that the three treatments represented widely used interventions for the treatment of genital warts. You should consider whether these are widely used technologies in your own setting.

**Validity of estimate of measure of effectiveness**
The estimate of effectiveness should be internally valid given the use of a randomised controlled trial, and a justification was given for the end points used. The impact on the patients' satisfaction or acceptability would also have been appropriate to assess the effectiveness of podophyllotoxin solution versus podophyllotoxin cream. Appropriate statistical analyses were undertaken to take potential biases and confounding factors into consideration. The study sample was unselected and was representative of the study population. The study groups were well balanced at baseline. Power calculations were performed to ensure that an appropriate number of patients were enrolled. However, the analysis of the clinical study was conducted on the basis of treatment completers only. The authors stated that their ability to draw conclusions about differences in recurrence rates was limited by the rate of patient default observed at the end of the trial.

**Validity of estimate of measure of benefit**
The authors did not derive a specific measure of health benefit. The primary health outcome was expressed as benefits. However, the use of a disease-specific benefit measure, namely remission rate, makes comparisons with the benefits of other health care interventions difficult.

**Validity of estimate of costs**
A societal perspective was adopted, hence direct and indirect costs were introduced in the study. The costs and the quantities were not reported separately and only limited details of the cost items included in the cost analysis were given, although a breakdown of the costs was provided. This fact partially limits the reproducibility of the results to other settings. The price year was reported, thus aiding reflation exercises. A statistical analysis of the costs was not performed, and neither was a sensitivity analysis. The authors reported some assumptions used to attribute costs in the different study groups.

**Other issues**
The generalisability of the results was discussed to a certain extent and the authors made appropriate comparisons of their findings with those from other studies. The study enrolled patients with genital warts and this was reflected in the authors' conclusions. The results appear to have been presented selectively (e.g. there was no reference to the incremental cost-effectiveness analysis in the "Results" section). Using the incremental analysis, podophyllotoxin...
cream and podophyllin were strictly dominated by podophyllotoxin solution (both less effective and more costly). Surprisingly, the authors did not clearly report this conclusion. The authors did not report any further limitations of their study.

**Implications of the study**
Since podophyllotoxin solution and cream showed greater efficacy and cost-effectiveness than podophyllin, and given the well-recognised pharmacological deficiencies of podophyllin, the authors suggested that the guidelines for the treatment of genital warts may need further modifications in due course.

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