

Silver Nitrate may be far Superior to Podophyllin in Clearing HPV External Anogenital Warts

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ABSTRACT

Longitudinal data from a case series indicated that clearance rates (95% CIs) of anogenital warts (AGW) by silver nitrate (n = 14) and podophyllin (n = 34) were 93% (79.35, 100) and 14.7% (3, 27) respectively; and RR, 6.31 (95% CI 2.77, 14.37, p = 0.052), relative benefit increase, 532% (410, 654), and NNT, 1 (1, 2). The total effort needed US\$28(BB\$56) vs US\$598 in 1–3 vs 1–37 visits to achieve one successfully treated patient respectively. While subject to the errors of an open, non-randomized case series, silver nitrate was highly efficacious and cost-effective and should replace podophyllin at the Winston Scot Polyclinic.

El Nitrato de Plata Puede ser muy Superior a la Podofilina para la Eliminación de Verrugas Anogenitales Externas Causadas por HPV

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RESUMEN

Datos longitudinales de una serie de casos indicaron que las tasas de eliminación (95% CI) de verrugas anogenitales (VAG) mediante nitrato de plata (n = 14) y podofilina (n = 34) fueron 93% (79.35, 100); y 14.7% (3, 27) respectivamente; y RR, 6.31 (95% CI 2.77, 14.37, p = 0.052), aumento relativo de beneficios, 532% (410, 654), y NNT, 1 (1, 2). El esfuerzo total necesitó \$28 USD (BB\$56) vs \$598 USD en 1–3 vs 1–37 visitas para lograr un paciente tratado con éxito respectivamente. Aunque sujeto a los errores de una serie de casos abierta no aleatorizada, el nitrato de plata fue altamente eficaz y costo-efectivo y debe reemplazar la podofilina en Winston Scot Polyclinic.

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INTRODUCTION

The 50%–70% clearance rates of anogenital warts (AGW) and their recurrence rates are unsatisfactory (1). Calls were made to abandon the inexpensive 4-week podophyllin (PO) therapy (£3) for imiquimod £57 (2). In the United Kingdom (UK) cryotherapy and podophyllotoxin are the first line of treatment of warts irrespective of site unlike the United States of America (USA) where silver nitrate (SN) is over the counter and widely used.

Despite historical use of SN and PO, both lack reliable clinical evidence (3). At the Ministry of Health polyclinic in Barbados prior to 2003, antimetabolic PO (25% solution) was either solely used and/or in association with surgery or cryotherapy. Chemical cautery utilizing SN pencil (silver and potassium 95% and 5% w/w) already on the clinic formulary became the alternative. Patients' records to evaluate sexually transmitted infection (STI) revealed a wide difference in the SN vs PO outcomes.

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SUBJECTS AND METHODS

Data were collected from a cohort of patients with anogenital warts treated with PO or SN. All had received STI counselling and screening. The choice of treatment depended mainly on the doctor in attendance.

Costs, in US\$ (=2BB\$), were modelled at current rates and derived as follows: cost per patient's visit: (1a + [2a or 2b] + 2c + 3b + 3c + 3d) where (1a, nursing time, \$3.95 per 20 minutes; 2a or 2b, cost of medicine \$3.99 if PO or \$5.82 if SN; 2c, cost of other material, \$0.25; 3a, absenteeism, \$0.00; 3b, travel time, \$2.50 ph; 3c, waiting time, 1.5 h x \$2.50 ph; 3d, bus fare, \$1.50 pd). Cost for total effort to achieve one successfully treated patient with a specific medicine = (specific average cost per visit) x (specific average number of visits) x (1/specific clearance rate).

RESULTS: Table 1, the 45 patients with anogenital warts, were all immunocompetent and made a total of 13%

DISCUSSION

One to three SN applications was superior to any ever reported for clearing external AGW (4–6). Others have reported lower clearance with other treatments. Podophyllotoxin treatment was associated with high recurrences internationally (7). Recurrences with imiquimod was 37% in 8–16 weeks vs 4% on placebo with NNT 3 (8). The study is limited by retrospective data collection from a case series, non-randomization, performance and measurement bias and the small number of patients that inflate random variation with imprecision especially of rare events *eg* a case of an adverse incidence in SN. However, despite an unplanned case series, neither confounders nor bias apparently favoured

Table 1: Characteristics and outcomes of patients with HPV external AGW at WSPC, Barbados, 2003–6.

Part A	Range	Median	Mean	95% CI
Age, all, (n = 45)	15–58	24	27	23.74 – 30.26
Age, Females, n = 20	15–30	20	21.5	19.30 – 23.70
Age, Males, n = 25	19–58	28	31.95	30.58 – 33.32
Visits for ¹ Podophyllin, (n = 34)	1–37	3.5	6.7	5.52 – 7.78
Visits for silver nitrate, (n = 14)	1–3	2	1.6	1.26 – 1.94
Part B				
² Estimated wart size	Not recorded	Small, 1–2 groups or < 2 cm ²	Medium, 3 – 5 gps or 2–4 cm ²	Large, > 5gps or ≥ 5 cm ²
– Podophyllin	19	9	5	1
– Silver nitrate	1	3	4	6
Part C				
³ Lost to follow up	Total Application	After 1 Application	After 3–4 Application	After 5–37 Application
– Podophyllin,	25/34 (74%)	7/34 (20.5%)	4/34 (11.7%)	8/34 (23.4%)
Part D; Outcomes: “as treated” analysis				
– Podophyllin	Clearance during follow up at clinic	Relative Risk	ARR	⁴ NNT
– Podophyllin	5/34 (14.7%, 95% CI 3, 27)	1		
– Silver nitrate	13/14 (92.85%, (95% CI, 79.35, 100)	6.31 (95% CI 2.77, 14.37, Yates <i>p</i> = 0.0 ⁵ 2)	78.2%	1 (95% CI, 1, 2)

¹After failing on podophyllin, 3 crossed over to SN, thus the “as-treated” was 48 instead of 45. ²podophyllin (predominantly smaller) vs silver nitrate (predominantly larger), excluding those where sizes were not registered: Chi-square (df = 2) = 6.57, *p* = 0.037. ³Did not come back for more treatment or review. None lost in silver nitrate group. ⁴NNT, number needed to treat.

(232/1790) visits out of all visits to the STI clinic while on either treatment. If all had been on silver nitrate, the visits would be fewer, 4%.

Silver Nitrate had superior clearance of AGW of 93% vs PO of 17.7%, RR, 6.31, (95% CI, 2.77, 14.37, *p* = 0.000005).

Some PO patients complained of disabling pain and burning sensation. One, against advice, caused SN burns to self and changed to PO. Another, with large wart area developed secondary local infection, 1/14 (7%, 95% CI, -6, 21), due to neglected self-care but it healed quickly on hygienic measures and a few days of oral antibiotic.

Average cost for patient's visit on PO was US\$14.32 with \$598 (95% CI 537.55, 757.62) per patient healed. Similarly, average for patient on SN \$16.15 per visit and \$28.47 (95% CI 21.86, 33.68) per patient healed.

SN performance or abstracted outcome measurements. On the contrary, selection bias was significant as SN treated more complicated warts, including the delayed referrals. Despite that, SN registered no loss to follow-up, no recurrence and more satisfaction. SN caused less irritation. Seemingly, SN-stick can be directed more precisely, thus reducing toxic effects. In all SN treated patients, warts, including recalcitrant ones, disappeared. Only one silver nitrate patient with urethral warts was referred to hospital but all his external lesions had healed. Four patients given local anaesthesia, lidocaine HCL 2% on the first application of SN, chose to do without it subsequently. Efficacy of wart treatment is known to be affected by age, immuno-competence, nature of the warts, location and duration of the warts, compliance, method of application, skills of healthcare provider and of the patient (9). Spontaneous clearance rates

of common non-AGW can occur in 23%, 30% and 67–78% within 2, 3 and 24 months, respectively (10). Thus, spontaneous regression may confound prolonged treatment as with PO.

Silver nitrate was better at fulfilling the criteria for efficacious AGW treatment than PO (11). In order to save on time and money, and reduce defaulting and morbidity, the cost-effective SN should replace PO for AGW at primary care at the Winston Scot Polyclinic.

REFERENCES

1. Gibson RJC, Mindel A. STI Recent Advances. *BMJ* 2001; **322**: 1160–4.
2. Maw R, von Krogh G. The management of anal warts. *BMJ* 2000; **321**: 910–11.
3. Lipke MM. An armamentarium of wart treatments. *Clin Med Res* 2006; **4**: 273–93.
4. Stone KM, Becker TM, Hadgu A, Kraus SJ. Treatment of external genital warts, a randomised clinical trial comparing podophyllin, cryotherapy, electrodesiccation. *Genitourin Med* 1990; **66**: 16–19.
5. A comparison of interferon alpha-2a and podophyllin in the treatment of primary condylomata accuminata. The condylomata International Collaborative Study Group. *Genitourin Med* 1991; **67**: 394–99.
6. Kirby P, Dunne A, King DH, Corey L. Double-blind randomised controlled clinical trial of self-administered podofilox solution vs vehicle in the treatment of genital warts. *Am J Med* 1990; **88**: 465–9.
7. Harewood J, Hicks D, Moore RA, Edwards JE, Imiquimod for treatment of genital warts: quantitative systematic review. *BMC Infectious Diseases*, 2001; **1**: 3 (biocentral.com/147-2334/1/3, accessed Jan 2007)
8. Sterling JC, Handfield-Jones S, Hudson PM. British Association of Dermatologists Guideline for management of cutaneous warts. *Br J Dermatol* 2001; **144**: 4–11.
9. Kuykendall-Ivy TD, Johnson SM. Evidence-based review of management of anogenital cutaneous warts. *Cutis* 2003; **71**: 213–22.
10. Yazar S, Basaran E. Efficacy of silver nitrate pencils in the treatment of common warts. *J Dermatol* 1994; **21**: 329–33.
11. Helberg D, Sverrer T, Nillsson S, Valentin J. Self-treatment of female external warts with 0.5% podophyllotoxin cream (Condylline) vs weekly application of 20% podophyllin solution. *Int J STD AIDS* 1995; **6**: 257–61.