Systematic review of treatments for anogenital warts

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ABSTRACT

Anogenital warts (also referred to as genital warts, GW) are a frequent sexually transmitted infection occurring in men and women worldwide. They are benign proliferative lesions caused by human papillomavirus (HPV) types 6 & 11. They very frequently cause a degree of psychological morbidity, and much more rarely are associated with significant pathology. They have increased in incidence and prevalence over the last 40 years, and are responsible for significant healthcare costs. Genital warts are mucosal viral infections arising in ano-genital squamous epithelia, and there are various topical therapeutic approaches. Although to date there have systematic reviews of individual therapies for GW, there has been no overarching systematic review of treatments. As part of the development of treatment guidelines we decided to conduct such a systematic review.

Introduction

Anogenital warts (also referred to as genital warts or condylomata acuminata) are one of the most commonly reported sexually transmitted diseases. A recent study of 70,000 women in 4 Northern European countries, for example, found that ~10% of women reported at least one episode of anogenital warts before the age of 45, and that prevalence increased in younger birth cohorts[1]. In the UK, where all cases of genital warts diagnosed through sexual health clinics are centrally reported, there has been a gradual increase in diagnoses since recording began in 1971, and in 2009 there were over 91,000 diagnoses of first episode genital warts[2;3].

There are several treatments available for genital warts, including both provider-administered therapies and home treatments which can be applied by the patient. Treatment patterns differ enormously[4], and all available therapies suffer from high failure and recurrence rates[5]. We carried out a systematic review of treatments for anogenital warts as part of the process of updating the IUSTI/WHO guideline on the diagnosis, management and treatment of anogenital warts[6]. The methods and results of this review are presented here in full.

Methods

A scoping search of existing systematic reviews of genital warts treatments was carried out by searching the Cochrane Database of Systematic Reviews, MEDLINE and EMBASE.

Searches were carried out in MEDLINE, EMBASE and the Cochrane library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews and Effects and Cochrane Central Register of Controlled Trials) according to a pre-defined search strategy (see Appendix 1). Randomised controlled trials (RCTs) of provider-administered or prescribed therapies for anogenital warts were eligible for inclusion where participants were 16 years old or over; the warts had been clinically diagnosed and clearance or recurrence rates were reported as an outcome measure. The search was restricted to English-language publications and all databases were searched up to May 2011.

Study selection was a two stage process; abstracts and titles were reviewed and full papers were obtained for any papers which potentially met the eligibility criteria, at which point the eligibility criteria were applied to the full manuscript. The reference lists of the included papers were hand searched to identify other potentially eligible papers. Due to resource constraints, while the initial electronic search and identification of papers was carried out by two reviewers, the final decision about eligibility was carried out by a single reviewer.

Data extraction was carried out using a piloted data extraction template. Data extraction was carried out by one reviewer, with a sample of ~10% of papers being double checked for accuracy by another reviewer. No major errors or discrepancies were found on this check.

Study quality was determined by applying the Cochrane Collaboration's tool for assessing risk of bias (available from: http://www.cochrane-handbook.org).

Results

Systematic reviews were identified which reported on the efficacy of imiquimod[7-9]. Results from the imiquimod reviews are incorporated into this review, although a full search for papers reporting these treatments was carried out to identify papers published since those reviews had been carried out or which had originally not been included. One systematic review on interferon treatments covering both systemic and local use, and a further review on topical 5-Fluourouracil were published during the period of conducting review[10;11]. These results were deemed to be sufficiently up to date not to warrant a further search as part of this review.

Ranges of clearance rates and recurrence rates for different treatments as reported in the included papers are presented in Table 1.

Heterogeneity of study design

While only RCTs were included, the study methodologies and patient populations were substantially heterogeneous in relation to several factors including age, sex, anatomical site, number and severity of warts, time at which clearance was measured and follow up rates for measuring recurrences. Due to this heterogeneity, statistical meta-analysis was not considered appropriate.

Treatment-specific results

Podophyllotoxin

Seventeen papers reporting clearance rates for podophyllotoxin were included. These included a variety of formulations (cream, solution, gel), although with similar treatment cycles (twice daily for 3 consecutive days followed by 4 days treatment break, with treatment period ranging from 2 to 6 weeks). The trials only assessed efficacy in relation to external genital and perianal warts, although some studies also assessed warts in the introitus. One paper assessed the use of podophyllotoxin and cryotherapy in comparison with cryotherapy alone[12]. One paper[13] reported data from two separate trials (parallel studies in males and females), and therefore the results were extracted separately. One paper reported an RCT of podophyllotoxin versus imiquimod[71].

Podophyllotoxin cream (0.25%, 0.5%), solution (0.3%, 0.5%) and gel (0.5%) were all associated with significantly higher proportions of patients experiencing clearance compared to placebo[14-20]. There was no significant difference in clearance rates between podophyllotoxin cream and solution [13;21;22], although two studies found a trend towards higher clearance rates with solution formulations [21;22]. Podophyllotoxin has been shown to be superior to podophyllin in five different trials[22-26]. One study found no significant difference between these two treatments[27], although a subgroup analysis of penile lesions demonstrated improved clearance rates at week one compared to podophyllin[27]. No significant difference was found in the study reporting combined podophyllotoxin and cryotherapy with cryotherapy alone[12]. No significant difference was found in clearance rates in the study reporting podophyllotoxin solution compared to imiquimod[71].

Recurrence was commonly reported after treatment with podophyllotoxin, but rates vary between trials from 6% to 55% with cream and 13% to 100% with solution[13;14;20;22;23]. These rates must be interpreted with caution, however, as loss to follow up was common and rates are reported at different times post treatment. The study that compared podophyllotoxin to imiquimod did not compare recurrence rates[71].

Side effects at the application site are commonly reported and include erythema, erosion, itching, burning, pain and tenderness. One study found a significant correlation between side effects and clearance ($p<0.001$)[27], suggesting that application site reactions are a normal part of the mechanism of clearance.

Imiquimod

Eleven papers reported results from RCTs using imiquimod in various formulation (5%, 2% and 1% imiquimod in cream)[28-38]. Table one presents clearance rates for HIV negative populations using the recommended preparation and frequency (5% cream, 3 times per week). One trial assessed imiquimod in HIV positive men[38]. Two trials compared different treatment regimens of imiquimod. One compared imiquimod given three times per week, once daily, twice daily and three times per day. Patients who applied imiquimod more than three times per week experienced an increase in the severity and frequency of adverse events, but there was no significant difference in clearance rates observed between the groups[33]. This supports a recommendation for treatment three times a week, a recommendation which has been confirmed in a previous meta-analysis of RCTs[9]. The second trial compared duration of treatment, using imiquimod three times per week for four, eight, twelve and sixteen weeks. There was no significant difference between groups in clearance at sixteen weeks and the majority of those who cleared did so within eight weeks[34]. These results are suggestive that a shorter period of application with appropriate follow up might be a feasible and more cost effective treatment strategy, but further work would be required to repeat these findings before treatment recommendations are changed.

In HIV negative patients, imiquimod has been demonstrated to lead to higher clearance rates than placebo[28-30;37]. One trial compared imiquimod to physical ablation therapies. Although physical ablative methods were found to have higher clearance rates after treatment, imiquimod-treated patients had a lower rate of recurrences and therefore a higher rate of sustained clearance at three months[35]. No significant difference was found in clearance rates in the study reporting podophyllotoxin solution compared to imiquimod[71].

Recurrence rates for 5% imiquimod have been reported in four trials. Two reported rates of 19% and 13% at ten and twelve weeks after the end of treatment respectively[29;30] and a further two reported rates of 6% and 26% at six months after the end of treatment[35;37]. As with podophyllotoxin results, however, the small numbers in this analysis and loss to follow up in some trials makes recurrence rates difficult to estimate precisely.

Local side effects are commonly reported by patients using imiquimod. These include erythema, erosion, oedema, ulceration, burning, irritation and pain/tenderness[28;29;33-35;37-39]. Patients with erythema are more likely to clear their warts, although this is not a necessary reaction for clearance to occur[29;37].

Polyphenon E

A new pharmaceutical treatment, Polyphenon E, is available in the US, but not yet available in Europe.

Three trials report clearance rates for two different preparations (15% and 10%)[40-42]. The licensed product is a 15% formulation, although both preparations have demonstrated significantly improved clearance rates compared to placebo[40-42].

Local skin reactions were commonly reported for both the 15% and 10% preparations[41].

Podophyllin

Fifteen trials reported clearance rates with provider-applied podophyllin 20% or 25% solution on a once or twice weekly basis[22-27;43-50]. Clearance rates were measured at four weeks to three months, and are reported in Table 1.

Podophyllin has been demonstrated to have lower clearance rates compared to podophyllotoxin and ablative therapies.

Podophyllin application has been associated with pain/tenderness, erythema, ulceration and burning[22-25]. There is also a risk of systemic absorption, and although a full regulatory review of podophyllin has not been conducted, there is evidence from animal studies of potential carcinogenicity and teratogenicity[51]. In addition, the formulation of podophyllin is not properly quality controlled due to the extraction process and it is unstable during clinic storage[51].

Ablative therapies: cryotherapy, electrosurgery, curettage, laser, photodynamic therapy

Fewer trials have evaluated the physical ablative techniques. Six report on the use of cryotherapy alone[43;44;52-55]; four on electrosurgery techniques[44;56-58] two on surgical excision[48;49] and four on laser treatment[53;59-61]. Cryotherapy, electrosurgery and surgical excision are all associated with significantly higher clearance rates than podophyllin[43;44;48-50;53]. Commonly report side effects include pain (cryotherapy, electrosurgery, excision, laser), scabbing (cryotherapy), swelling (electrosurgery), erosion (laser) and bleeding (excision, laser)[44;48-50;52;53;58;59].

Three trials have reported on the use of photodynamic therapy after application of aminolevulinic acid (ALA-PDT), either alone[61;62] or as an adjuvant to laser treatment[60]. Two trials have reported significantly lower recurrence rates following ALA-PDT compared to laser treatment alone [61;62]. No significant difference was

found in recurrence rates between ALA-PDT following laser combined to laser ablation alone. ALA-PDT was well tolerated in all three trials[60-62].

Isotretinoin/Retinoids

Two trials were reviewed which assessed oral isotretinoin in patients who had all been unsuccessfully treated with another therapy and had persistent warts for more than three months[63;64]. One study found isotretinoin to be associated with significantly increased rates of clearance than placebo[63], although none of the ten patients treated with isotretinoin in the other study experienced clearance[64].

The most commonly reported side effects were cheilitis and skin and mucosal dryness, which were reported in 90 – 100% of patients[63;64].

TCA

Three studies reported clearance rates for TCA application[43;52;53]. Side effects reported differed in the different studies with ulceration/scabbing and discharge being very commonly reported[52;53].

Other

One study reported the use of a 'natural product', a tablet incorporating Echinacea, Uncria, Tabebuja, papaya, grapefruit and Andrographis[65]. Significantly lower rates of recurrence following surgical excision were found in the group who took a course of the tablets compared to those who did not, however no placebo tablets were provided to the control group. It was unclear at the time of preparing this report whether this product is licensed for use.

Clinical considerations

Perianal warts

Several studies included patients with either perianal or genital warts, but clearance rates were not reported separately according to site of the wart. Three RCTs reported clearance rates for podophyllin compared to surgical excision in patients with only perianal warts[48-50]. Recurrence rates were found to be lower in the surgical excision group in all cases[48-50]. All of these studies were carried out before podophyllotoxin was available. One further study reported clearance rates for anal warts after use of a natural product[65].

Warts among patients with HIV

HIV status affects the clinical course of anogenital warts. One trial of imiquimod among HIV positive patients found no significant difference in the number of patients who totally cleared their original warts, although more patients in the imiquimod group experienced a reduction in baseline wart area[38] It should be noted that this

study was done before the highly active antiretroviral therapy became widespread in the UK, so the applicability of these findings to the current context is unclear. In a trial of Argon plasma coagulation (APC) versus APC and imiquimod HIV positive patients cleared their warts later and experienced more recurrences than HIV negative patients ($p<0.0001$ and $p=0.0039$ respectively). This finding is supported by a cohort study of 241 HIV positive and 1,095 HIV negative patients with genital warts, where HIV positive patients were found to have a significantly higher rate of recurrences within one year[66].

Warts in pregnancy

None of the RCTs included pregnant women. BASHH guidelines state that podophyllotoxin, podophyllin and 5-Fluourouracil should be avoided during pregnancy due to possible teratogenic effects. Imiquimod is not approved for use in pregnancy.

Quality assessment of papers

Only four articles included in the review[33;41;42;48] fulfilled five of the six quality criteria as set out in the Cochrane Collaboration's tool for assessing risk of bias. The method of generating the allocation sequence was not stated in 49 papers; in 54 papers it was unclear whether the allocation sequence had been adequately concealed (either as nothing was stated or the description was inadequate); and 41 studies either did not maintain patient and clinician blinding or it was unclear whether the assessor was blinded to treatment allocation. Two papers were excluded pm the basis of quality concerns: one which reported a very low clearance immediately following electrosurgery, suggesting the procedure was not carried out correctly[57]; a second was excluded as there was insufficient recording of information at baseline to allow proper assessment of clearance rates[67].

Discussion

We carried out a systematic review of randomised controlled trials of genital warts treatments as part of the process of updating the IUSTI/WHO guideline on the diagnosis, management and treatment of anogenital warts.

Several RCTs were identified as part of the review, with the more modern pharmaceuticals such as podophyllotoxin and imiquimod having been most widely investigated in this manner. Podophyllin and other provider administered therapies have been most commonly reported in the context of being comparator groups in these trials, but reported clearance rates for all of the commonly available therapies have been collated here.

As shown by the reported clearance rates in RCTs, all available treatments have significant failure and recurrence rates. In clinical practice therefore, it will often be necessary to switch therapies after initial failure or recurrence, but there is insufficient evidence relating to the choice of treatment regimen in terms of first line and subsequent treatments. Treatment algorithms have been demonstrated to be effective in reducing persistence and recurrence[68]. In the absence of evidence of any

single therapy being dominant, it is recommended that the choice of first line therapy be based on patient preference and morphology and distribution of lesions, and that a clinic treatment algorithm is implemented where possible to enable monitoring of the success of treatment and switching therapy in the case of failure.

Clearance rates reported are ranges and differ enormously, possibly reflecting the different study populations and study designs. This and previous reviews provide evidence that for the home treatments, while podophyllotoxin appears to have higher rates of initial clearance, recurrence rates may be lower with imiquimod[5;69]. Polyphenon E may offer a new treatment option with comparable efficacy in the future, although it is not currently available in Europe. We did not include studies which looked solely at 5-FU or interferon due to the recently published systematic reviews on these treatments. The Cochrane review of topical 5-FU for genital warts in non-immunocompromised individuals, found that while this treatment had a therapeutic effect, the available evidence was weak and heterogeneity in study design made it difficult to carry out meta-analysis[11]. Interferon was found to be a well-tolerated therapy, with topical interferon demonstrating superiority to both placebo and systemic treatment[10]. Both reviews highlighted the need for further, high quality randomised controlled trials to strengthen the evidence for use of these products.

We did not examine the cost of treatment in this review, which can vary considerably dependent on choice of treatment and duration of episode. Provider administered treatments do not involve costly pharmaceuticals but they often include costs of repeated clinic visits, which must be taken into account when considering economics of treatment choice.

We applied a quality assessment tool to the selected papers. While all of the papers were RCTs, most of the papers did not report key features of the randomisation allocation and in several studies appeared to have been conducted without assessor blinding, which would be a substantial source of bias. Many of the included studies were published before the CONSORT statement (a minimum set of recommendations for reporting RCTs, see http://www.consort-statement.org) came into existence, but over half were published after this date. Future studies of genital warts treatments would benefit from improved reporting.

This review has highlighted a number of areas which would warrant further investigation. Firstly, due to substantial heterogeneity in the study design and populations, we were unable to carry out a meta-analysis to pool data to compare the efficacy of different treatments. Further high quality RCTs comparing the main available therapies would therefore be required to increase the evidence base for recommendations. There has been no head to head trial of podophyllotoxin versus imiquimod. Given the higher per treatment cost of imiquimod, but suggestion of lower recurrence rates, a direct comparison of patient-applied treatments incorporating an economic evaluation would be valuable. Secondly, while treatment algorithms are recommended, there is little evidence on the choice of first or second line strategies for treatments for genital warts. Finally, accurately assessing recurrence rates remains a problem. Trials often experienced high loss to follow up and few studies assessed long term recurrence rates (over 6 months post clearance). Future studies should consider the feasibility of extended follow up time and approaches to

minimise loss to follow up in order to assess the long term effectiveness of treatments more completely. A standard approach to defining recurrence would also be valuable, as some trials reported recurrence as development of any anogenital wart after initial clearance, whereas other trials only counted warts in the original treatment area as recurrences.

Clinic treatments and home treatments continue to be used in parallel in clinical practice, and the available data on treatments for genital warts do not provide evidence for any single treatment approach being dominant over other therapies.

Table 1: Treatment of anogenital warts among HIV negative patients

Note that clearance rates and recurrence rates are not directly comparable as clearance was measured at different times from the start of treatment and high loss to follow up was often experienced in the trials.

Treatment/intervention	Treatment schedule	Clearance rates (range)* [ITT]	Clearance rates (range)** [amongst followed up]	Clearance rates reported at:	Recurrence rates (range)***	Recurrence rates reported at:
Podophyllotoxin Cream 0.15%[13;21;22]	Twice a day for three consecutive days followed by four days break. Maximum four weeks treatment.	43% - 70%	43% - 70%	4 weeks	6% - 55%[13;22]	8 to12 weeks from end of treatment
Podophyllotoxin solution 0.5%[13;14;19;20;22-24;26;71]	Twice a day for three consecutive days followed by four days break. Two to six weeks treatment.	45% - 100%	58% - 100%	3 to 6 weeks	13% -100% [13;14;20;22;23]	12 to 21 weeks from end of treatment
Podophyllin solution 20% - 25%[22-27;43-50;70]	Applied one to three times per week.	18% - 79%	28%-88%	4 weeks to 3 months	14% - 100% [23;25-27;44-50]	3 months post baseline to 12 months post treatment
Imiquimod 5% cream [29;30;33;34;34;35;37;71]	Three times per week.	21% - 68%	42% - 81%	4 to 16 weeks	6% - 26%[29;30;35;37]	10 weeks to 6 months from end of treatment
Cryotherapy [43;44;52-55]	Six to ten weeks of treatment.	44% - 75%	67% - 92%	6 to 10 weeks	21% - 42%[44;52;54;55]	1 to 3 months from end of treatment
Electrosurgery[44;56;58]	One to six treatment sessions.	55% to 100%	93% - 100%	4 to 6 weeks	22% - 74%[44;56]	3 to 6 months from end of treatment
Scissors excision[48-50]	One or two excision sessions.	89% - 100%	89% - 100%	6 weeks	19% - 29%[48-50]	10 to 12 months from baseline
TCA[43;52;53]	One application per week for a maximum of eight to ten weeks.	56% - 67%	81% – 84%	8 weeks to 6 months	36%[52]	(2 months post treatment)
Polyphenon E ointment (10% / 15%) [40-42]	3 times per day for 12 to 16 weeks	47% - 59%	50% - 58%	12 to 16 weeks	7 – 11%[40-42]	12 weeks from clearance

*Clearance rates based on conservative estimates of efficacy, whereby the intent to treat population was included in each case. The number enrolled into each group was taken as the denominator and the number known to have cleared as the numerator. This assumes that for any missing data, participants were assumed not to be cleared.

**Clearance rates based on the non-missing data. The number with evaluable follow up data was taken as the denominator and the number known to have cleared as the numerator.

***Recurrence rates are based on the recurrences observed among those available for follow up who had originally experienced clearance. Several trials experienced high loss to follow up rates, so recurrence rates should be interpreted with caution.

Appendix: Search strategy

<table>
<tr><td rowspan="2">Combine with AND search</td><td>Population
(Combine with OR search)</td><td>Keywords:
genital wart*
anogenital wart*
ano-genital wart*
ano genital wart*
anal wart
condyloma*
venereal wart*

Plus appropriate mapped/MeSH headings</td></tr>
<tr><td>Intervention
(Combine with OR search)</td><td>Keywords:
podophyllotoxin
podofilox
podophyllin
cryotherapy
liquid nitrogen
imiquimod
aldara
TCA
trichloracetic acid
BCA
bichloroacetic acid
curettage
excision
surgical removal
laser
electrosurgery
electrocautery
hyfrecation
ablati*
diathermy
interferon*
5-fluorouracil
polyphenon
photodynamic
tretin (to capture acitretin, tretinoin, isotretinoin)
Retinoids

Plus appropriate mapped/MeSH headings</td></tr>
</table>

In addition, filters described in the Cochrane Handbook of Systematic Reviews (www.cochrane-handbook.org) were applied to limit the searches to RCTs.

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