ORIGINAL ARTICLE

Cryotherapy to treat anogenital warts in nonimmunocompromised adults: Systematic review and meta-analysis

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Background: Cryotherapy is one of the most commonly used therapeutic modalities to treat anogenital warts (AGWs), but this treatment was not clearly established in the recent international recommendations.

Objective: To compare the efficacy and safety of cryotherapy versus other AGW treatments.

Methods: Through a systematic search of 12 electronic databases, we identified 11 randomized controlled trials, screened from database inception through October 2016, that met the inclusion criteria (including immunocompetent adults with AGWs receiving cryotherapy in 1 of the comparison groups). Primary endpoint was complete clearance of AGW. Risk-for-bias assessment was based on Cochrane Handbook recommendations. Meta-analyses used Review Manager v5.3 software.

Results: Cryotherapy efficacy did not appear to differ from that of trichloroacetic acid, podophyllin, or imiquimod. Electrosurgery was weakly associated with better AGW clearance than cryotherapy (risk ratio [RR] 0.80, 95% confidence interval [CI] 0.65-0.99). Cryotherapy was associated with more immediate low-level adverse events (erythema, stinging, or irritation; RR 3.02, 95% CI 1.38-6.61) and immediate pain requiring oral analgesics (RR 2.11, 95% CI 1.07-4.17) but fewer erosions (RR 0.57, 95% CI 0.36-0.90).

Limitations: All but 1 randomized-controlled trial had a high risk for bias.

Conclusion: With low-level quality of the evidence, cryotherapy is an acceptable first-line therapy to treat AGWs. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2017.04.012.)

Key words: anogenital warts; condyloma; cryotherapy; genital; HPV; infection; meta-analysis; penile; sexually transmitted disease; STD; systematic review; vulvar.

Anogenital warts (AGWs) are one of the most frequent reasons for consultation in sexually transmitted disease clinics[1]; they come in second, after the potential for infection with nononcogenic human papillomaviruses (HPVs; eg, HPV types 6 and 11) and oncogenic HPVs.[2] Annual AGW incidence is around 1%-2%, depending on the world region considered.[1] The AGW burden remains relatively high, affecting quality of life[3,4] and health care costs,[4] despite HPV vaccination campaigns.[5] AGWs may be monitored with many different therapeutic options, which can be divided into

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Conflicts of interest: None declared.

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provider-administered (ie, bi- or trichloroacetic acid [TCA] application, podophyllin resin, CO_2 laser surgery, cryotherapy, surgical excision, and electrosurgery) and patient-administered treatments (ie, podophyllotoxin, imiquimod, sinecatechins, and 5-fluorouracil cream). The efficacies of these agents vary, and notable adverse events (AEs) of patient-administered therapies might affect treatment adherence and follow-up in clinics.

Cryotherapy, an inexpensive and simple provider-administered procedure using liquid nitrogen in a spray or cryoprobe, is frequently used in many countries.[6-9] It destroys warts by cold-induced cytolysis. In the most recent versions of European and American guidelines,[10,11] first-line treatments for AGWs in immunocompetent adults are listed without priority as follows: provider-administered cryotherapy, TCA or surgery (scissor, electrosurgery, curettage, or laser) and patient-applied products (imiquimod, podophyllotoxin, or sinecatechins). Expert consensuses concluded that the decision should take into account the patient's preference, physician's experience, cost, anatomic site, and AGW size and number. Use of locally developed and monitored treatment algorithms was encouraged because no conclusive evidence suggests that any recommended treatment is superior to another.[11]

A recent systematic review of randomized controlled trials (RCTs) on local treatments for immunocompetent and HIV-infected patients (inclusion ended September 2014) globally concluded that ablative techniques are immediately clinically more effective at completely clearing AGWs posttreatment.[12] The results of several new RCTs examining cryotherapy for AGWs have become available since that review. Moreover, no specific systematic review of cryotherapy efficacy with meta-analysis has been published. The objectives of this systematic review and meta-analysis were to assess cryotherapy efficacy and safety compared with either placebo or other interventions to treat AGWs.

CAPSULE SUMMARY

- International recommendations do not prioritize first-line anogenital wart treatments.
- Low-level quality of the evidence indicated that cryotherapy was neither superior nor inferior to trichloroacetic acid or imiquimod; cryotherapy was slightly less efficacious than electrosurgery.
- Cryotherapy is an acceptable first-line therapy for anogenital warts.

METHODS

Protocol

This review was registered on PROSPERO (no. CRD42015025827). PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement recommendations were followed.[13]

Data sources and search strategy

Two independent reviewers (Drs Bertolotti and Derancourt) systematically and individually searched 12 databases, which were screened from inception of each database to October 1, 2016. We used a search strategy adapted to specific descriptor-based logic (English language) linked to the Boolean operators (AND and OR). Search terms included 3 synonym groups (AGW, cryotherapy, or RCT) with adjustments made for each database. Attempts were made to locate unpublished and ongoing trials through correspondence with authors, pharmaceutical laboratories, and trial registers. Reference lists in review articles[14-16] were searched to identify any additional studies. No language restriction was imposed.

Selection

The same 2 reviewers independently selected studies initially on the basis of title and abstract. Study inclusion selection criteria were 1) being an RCT; 2) having original data providing risk ratio (RR) estimates with confidence intervals (CIs) or enough data to calculate them; 3) including immunocompetent men and nonpregnant women >16 years old who were clinically diagnosed with AGWs; 4) cryotherapy reported in at least 1 comparison treatment group; and 5) 1 provider-administered therapy (TCA, electrosurgery, CO_2 laser surgery, surgical excision, podophyllin, or bleomycin) or patient-administered treatment (imiquimod or KOH) in the other group. Studies not satisfying these criteria were excluded at this stage. Selected studies were further screened for suitability by reading the full text.

Data extraction, outcomes, and risk for within-trial bias

An extraction grid was developed after collegial discussion. After consulting public hospital and private-practice dermatologists at regional and national meetings Drs Milpied, Bertolotti, and Derancourt initially retained primary (clearance at 3 months, recurrence 3 months later) and secondary outcomes (AEs, time to complete clearance, percentage