

TITLE: Cryotherapy Systems for Wart Removal: A Review of the Clinical Effectiveness, Cost-effectiveness, and Guidelines

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CONTEXT AND POLICY ISSUES

Cutaneous viral warts, a common skin condition, are caused by the human papilloma virus (HPV), which infects epithelial cells.¹ With over 100 types of HPV, the appearance of cutaneous viral warts varies depending on both the anatomical site and HPV type.² The warty papules on the skin are a result of viral replication and proliferation in fully-differentiated epithelium.² Infection with HPV is caused by skin-to skin contact. In some cases, the virus can remain dormant and may not produce a visible wart. The diagnosis of cutaneous warts is based upon clinical appearance.³

High quality epidemiological data on viral warts is limited, as the majority of studies focus on specific population subsets.⁴ In Canada, it is estimated that 10% to 30% of adults are infected with HPV, with the majority of these individuals being under the age of 25.⁵ Risk factors for the development of viral warts include exposure of bare feet in public areas such as changing rooms and swimming pools,⁶ and individuals with immunosuppression (e.g. organ transplant recipients, AIDS patients).² Certain meat handling occupations, for example butchers and fishmongers, are at increased risk of developing cutaneous warts on the hands.⁷

Cryotherapy is a treatment method that induces cold damage to cutaneous warts.² Cryotherapy using liquid nitrogen is an effective and established treatment, though the optimum method for delivery remains uncertain.⁸ Cryotherapy using liquid nitrogen can be applied as a spray, by using a cotton bud, or melamine foam sponge.² The freezing with liquid nitrogen destroys tissue, interrupting the vascular supply and stimulates the immune system, eventually leading to the resolution of the cutaneous warts.⁹ In view of the different liquid nitrogen cryotherapy systems, this report aims to review the clinical effectiveness, safety, cost-effectiveness, and guidelines of these treatments for cutaneous warts.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of cryotherapy systems for wart removal?

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2. What is the cost-effectiveness of cryotherapy systems for wart removal?
3. What are the evidence-based guidelines for the use of cryotherapy systems to remove warts?

KEY FINDINGS

Limited evidence suggested that cryotherapy with liquid nitrogen using a melamine foam sponge (MFS) applicator was superior to cotton wool bud (CWB) applicators for reducing wart size after one treatment, with a lower mean number of treatments at complete remission and fewer adverse events, though the generalizability of these findings to a Canadian context is unclear. There was no evidence identified for the cost-effectiveness comparing different cryotherapy systems. Guidelines suggest first line treatment using cryotherapy with liquid nitrogen every two to three weeks, up to three months for the removal of cutaneous warts.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (May 2014), University of York Centre for Reviews and Dissemination (CRD), OVID's Medline and Joanna Briggs databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 01, 2009 and May 11, 2014.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed for relevance. Full texts of any relevant titles or abstracts were retrieved, and assessed for inclusion. The final article selection was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with warts
Intervention	Cryotherapy systems for wart removal
Comparator	Cryotherapy systems compared to each other
Outcomes	Clinical effectiveness, safety, cost-effectiveness
Study Designs	Health technology assessments (HTA), systematic reviews (SRs), and meta-analyses (MAs), randomized controlled trials (RCTs), non-RCTs, economic evaluations, evidence-based guidelines.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 2009, if they were duplicate publications of the same study, or if they were referenced in a selected systematic review.

Critical Appraisal of Individual Studies

The quality of the included trial was assessed using the Downs and Black checklist.¹⁰ Clinical practice guidelines were appraised using the AGREE II instrument.¹¹ Numeric scores were not calculated. Instead, the strengths and limitations of the study are summarized and presented.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 117 citations. After screening of abstracts from the literature search and from other sources, 8 potentially relevant studies were selected for full-text review. One clinical trial¹² comparing cryotherapy applicator systems and one set of clinical practice guidelines for the treatment of non-genital cutaneous warts¹³ were included in the review. The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Study Characteristics

A detailed summary of the included study and guidelines is provided in Appendix 2.

Clinical Trial

Na et al. 2012¹²

A non-randomized, open-label, paired comparison (within-subject) study design was conducted. A total of 27 patients (15 males) diagnosed with viral warts at Chosun University Hospital between January and October 2009 were included. The patients' age varied ranging from 3 to 42 years. Patients must have had at least two warts of the same clinical type in order to minimize differences in patient characteristics by allowing within-patient comparisons. Patients were excluded if they had received any previous treatment for warts. The investigators recorded the number, diameter and clinical type (palmo-plantar [PPW], periungual [PUW], and common wart [CW]). Paired comparisons were performed on comparable lesions. In total, there were 51 PPW, 34 PUW, and 19 CW. CWB and MFS, cut to fit the wart size, were compared as applicators in the treatment of warts with liquid nitrogen. Both applicators, using a double freeze thaw cycle, were soaked with liquid nitrogen and applied until a 2 to 3 mm halo was visible around each wart. The procedure was performed by one operator for all warts who measured the size of the wart during the study. Patients were treated at 2 to 3 week intervals. The mean treatment duration was 16.5 months (range 3 to 32 months). Outcome measures included mean number of treatments at complete remission, defined as the complete elimination of the wart 4 weeks after the last treatment (evaluated by a dermatologist), mean size reduction rate after first treatment, and pain severity measured using a 100mm visual analogue scale (VAS) with 0 mm representing no pain and 100 mm the worst possible pain. Outcomes were compared using paired t-tests.

Guidelines

Mulhem et al. 2011¹³

The evidence-based clinical practice guidelines were published in 2011 from the American Academy of Family Physicians (AAFP). The guidelines provide recommendations for treatments including cryotherapy for non-genital cutaneous warts.

Summary of Critical Appraisal

Details of the strengths and limitations of the included study and guidelines are summarized in Appendix 3.

Clinical trial

The aim of the study by Na et al. 2012¹² was clearly described. The main outcomes, interventions, patient characteristics and main findings were clearly described. Though the investigators did not randomize patients, the within-subject study design likely minimized confounding bias. The investigators attempted to minimize differences according to individual characteristics by only including patients with at least two warts of the same clinical type. The analyses were stratified by wart type to determine if the effect of cryotherapy applicators differed between anatomical locations. It was unclear whether both patients and assessors (operator and dermatologist) were blinded, potentially leading to non-differential misclassification of outcomes, specifically the subjective pain outcome among patients. Complete remission was based on the opinion of one dermatologist and results for both treatments may have been subject to detection bias. The included sample size was relatively small, thus it remains uncertain whether study was adequately powered to detect meaningful differences between the two treatments. The study population also consisted of patients of varying ages (3 to 42 years), who received various treatment durations (3 to 32 months), therefore the interpretation of findings is challenging. Generalizability of the findings is further questioned as the publication stated that patients were excluded from the study if they had any previous treatment for warts. It is not clear whether the authors were referring to any warts or just those at current presentation.

Guidelines

The AAFP¹³ guidelines clearly described the scope, purpose, applicability and editorial independence. The guidelines were clearly presented, but lacked detail regarding the rigour of development and stakeholder involvement. Specifically, the guidelines did not mention the consideration of views and preferences of patients with non-genital cutaneous warts. Though the strength of evidence and grade of recommendations were provided using The Strength of Recommendation Taxonomy (SORT), the methods used to search the evidence and the criteria for selecting the evidence were not clearly stated. In addition the AAFP guidelines did not provide the procedure for updating their guidelines.

Summary of Findings

Main findings of the included study is summarized in detail in Appendix 4.

1. What is the comparative clinical effectiveness of cryotherapy systems for wart removal?

As seen in Appendix 4, among 27 patients, MFS was statistically significantly more effective in reducing wart size after one treatment and had a lower mean number of treatments at complete remission compared with CWB. Differences in VAS pain scores were not statistically significant. Overall three patients experienced bullae when treated with the CWB applicator, while only 1 patient experienced bullae with MFS applicator. Stratified results demonstrated that treatment with MFS applicator was generally greater for mean reduction size after 1 treatment and fewer mean number of treatments at complete remission among CWs compared with PPWs and PUWs (Appendix 4).

2. What is the cost-effectiveness of cryotherapy systems for wart removal?

There was no evidence found on the cost-effectiveness of cryotherapy systems compared to each other.

3. What are the evidence-based guidelines for the use of cryotherapy systems to remove warts?

The AAFP evidence-based clinical practice guidelines by Mulhem et al.¹³ indicated that first-line treatment for new warts that is readily available at family physician offices or over the counter include watchful waiting with no treatment, salicylic acid, and cryotherapy with liquid nitrogen. Suggested approaches for cryotherapy with liquid nitrogen include paring down dead skin with sharp blade (especially for plantar warts) and applying liquid nitrogen using a cryogun (spray gun) or cotton swab until the wart has a 2-mm white halo for about 10 seconds. Based on limited quality evidence, the guidelines state that aggressive cryotherapy (10 to 30 seconds) was more effective than less aggressive cryotherapy, though this significantly increases pain and blistering. For plantar warts, a “freeze-thaw-freeze” technique which consists of repeating the application of liquid nitrogen after the white halo completely disappears was recommended. The guideline further recommended that treatment should be repeated every two to three weeks, up to three months (or four treatments). In order to avoid spreading the virus, the cryoguns were recommended to be disinfected and cotton swabs and liquid nitrogen should be discarded. It was stated that additional treatment with salicylic acid between treatments can be considered. The guidelines suggested that cryotherapy used by primary care physicians may be more effective in freezing warts as liquid nitrogen typically freezes the tissue to -196°C while other over the counter products freeze the tissue to -94°C .

Limitations

With one limited-quality study¹² meeting the inclusion criteria, the comparative clinical effectiveness of different cryotherapy systems for wart removal remains uncertain. Based on the limitations of the methods employed, results should be interpreted with caution. In addition, the results may not be generalizable to the Canadian population given the small sample size taken from a specific hospital in South Korea. No Canadian clinical practice guidelines were retrieved in the search and the majority of recommendations found in the AAFP guidelines¹³ were based on lower quality clinical evidence.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Limited evidence suggested that cryotherapy with liquid nitrogen using a MFS applicator was superior to CWB applicators for reducing wart size after one treatment, with a lower mean

number of treatments at complete remission and fewer adverse events. No conclusions can be made on the cost-effectiveness of different cryotherapy systems for wart removal due to the absence of economic studies. One set of clinical practice guidelines for non-genital cutaneous warts identified both salicylic acid and cryotherapy with liquid nitrogen every two to three weeks, up to three months as first-line treatment.

A recent clinical review¹⁴ indicated that cryotherapy treatment with liquid nitrogen is typically employed in secondary care or specialist community clinics, given the challenges of obtaining and storing liquid nitrogen in primary care settings.¹⁴ Furthermore, the authors specified that the preferred method for application is by cryogun for adults, and cotton buds for children, for the reason as noted above that over the counter products containing dimethyl ether and propane are not as effective as reaching freezing temperatures as the cryogun.

Thus, there remains an unmet need for high quality trials, and further research addressing different cryotherapy systems may help to reduce uncertainty, providing insight for the optimal cryotherapy treatment for wart removal.

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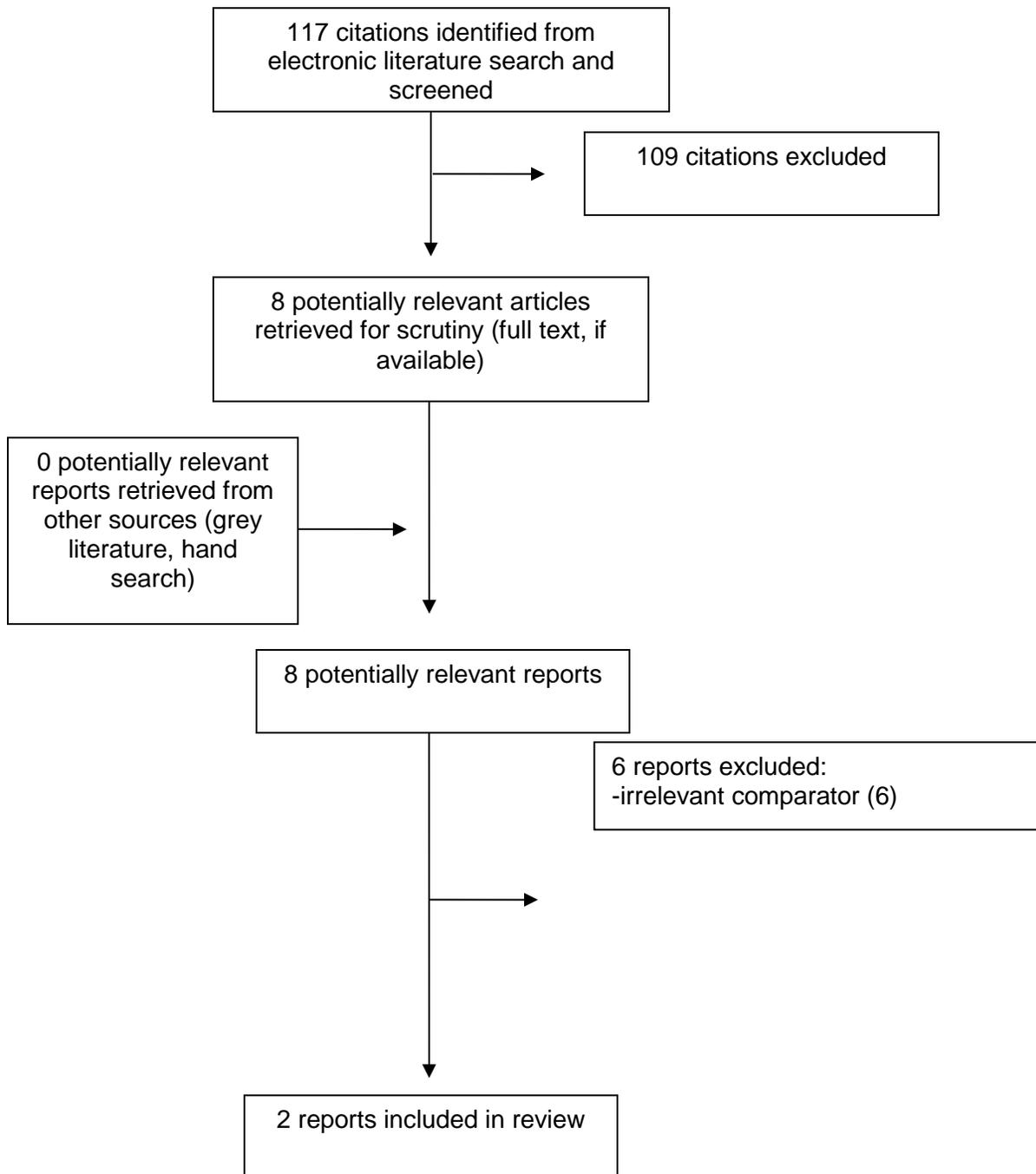
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APPENDIX 1: Selection of Included Studies



Appendix 2: Summary of Included Study Characteristics

Table 1: Characteristics of Included studies

Included Study				
First Author, Year, Country	Design, Sample Size, Length of Follow-up	Intervention	Comparator(s)	Main Study Outcomes
Na, 2012, ¹² South Korea	Open-label , non-RCT, n=27, 4 weeks-post final treatment	Melamine foam sponge	Conventional cotton wool bud	<ul style="list-style-type: none"> • number of treatments at complete remission • mean size reduction rate • pain severity

Appendix 3: Summary of Critical Appraisal of Included Study and Guidelines

Table 2: Summary of Critical Appraisal of Included Study and Guidelines		
First Author, Publication Year	Strengths	Limitations
Critical appraisal of included trial (Downs and Black¹⁰)		
Na, 2012 ¹²	<ul style="list-style-type: none"> • study aim clearly described • main outcomes, interventions, patient characteristics, and main findings clearly described • for main outcomes, analysis was stratified by type of wart to provide • adverse events were reported • statistical test (t-tests) were used to compared both treatments 	<ul style="list-style-type: none"> • assessors not blinded to intervention • patients not randomized • patients not blinded to intervention • estimates of random variability and actual probability values not provided • unknown if study had sufficient power to detect a clinically important effect • unknown if patient population was representative of entire population from which they were recruited
Critical appraisal of guidelines (AGREE II)¹¹)		
American Academy of Family Physicians, Mulhem, 2011, ¹³ United States	<ul style="list-style-type: none"> • Scope and purpose properly described • Very clear presentation • Applicability well described • Strength of evidence and grade of recommendation are provided. 	<ul style="list-style-type: none"> • Uncertainty regarding stakeholder involvement • The procedure for updating the guideline is not transparent • Rigour of development lacks detail

Appendix 4: Main Study Findings and Summary of Recommendations from Clinical Practice Guidelines

Table 3: Main Study Findings and Authors' Conclusions		
First Author, Publication Year	Main Study Findings	Authors' Conclusions
Research question 1 (clinical effectiveness and safety of cryotherapy systems compared to each other)		
Na, 2012 ¹²	<p>Mean reduction size after 1 treatment (CWB vs MFS) Palmo-plantar: 27.1% vs 52.0 (p=0.047) Periungual: 36% vs. 59.8% (p=0.02) Common:44.1% vs. 75.9% (p= 0.01)</p> <p>Mean number of treatments at complete remission (CWB vs MFS) Palmo-plantar: 3.4 vs. 2.4 (p=0.04) Periungual: 2.8 vs. 2.2 (p=0.04) Common:2.9 vs. 1.6 (p= 0.005)</p> <p>Mean VAS pain score (mm) (CWB vs MFS) 61.7 vs. 74.7 (p>0.05)</p> <p>Adverse effects (bullae) (CWB vs MFS) 3 cases vs 1 case</p>	<p><i>“Cryotherapy with an MFS applicator could be more effective than cryotherapy with a CWB applicator in treating various types of warts, although its effectiveness should be further evaluated in large controlled studies comparing the therapeutic effects of MFS using cryotherapy and other conventional cryotherapies” (p 559)</i></p>
Research question 2 (cost-effectiveness of cryotherapy systems compared to each other)		
No evidence found		
Research question 3 (guidelines associated with cryotherapy for wart removal)		
First Author, Publication Year	Recommendation	Rating of Evidence
American Academy of Family Physicians, Mulhem, 2011, ¹³ United States	<ul style="list-style-type: none"> Salicylic acid and cryotherapy with liquid nitrogen are first-line treatments for cutaneous warts Aggressive cryotherapy (10 to 30 seconds) is more effective than less aggressive cryotherapy Best results of cryotherapy can be achieved when the patient is treated every two or three weeks. There is no therapeutic benefit beyond three months When using cryotherapy for plantar warts, paring the wart before treatment can increase the clearance rate 	<ul style="list-style-type: none"> Based on high quality SR/MA or RCTs with consistent findings Based on lower quality clinical trial, cohort, or case-control studies Based on lower quality clinical trial, cohort, or case-control studies Based on lower quality clinical trial, cohort, or case-control studies
CWB=cotton wool bud; MFS=melamine foam sponge; VAS=visual analogue scale		