
DATE: 12 June 2014

CONTEXT AND POLICY ISSUES

Cutaneous viral warts, a common skin condition, are caused by the human papilloma virus (HPV), which infects epithelial cells. With over 100 types of HPV, the appearance of cutaneous viral warts varies depending on both the anatomical site and HPV type. The warty papules on the skin are a result of viral replication and proliferation in fully-differentiated epithelium. 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.

High quality epidemiological data on viral warts is limited, as the majority of studies focus on specific population subsets. 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. Risk factors for the development of viral warts include exposure of bare feet in public areas such as changing rooms and swimming pools, and individuals with immunosuppression (e.g. organ transplant recipients, AIDS patients). Certain meat handling occupations, for example butchers and fishmongers, are at increased risk of developing cutaneous warts on the hands.

Cryotherapy is a treatment method that induces cold damage to cutaneous warts. Cryotherapy using liquid nitrogen is an effective and established treatment, though the optimum method for delivery remains uncertain. Cryotherapy using liquid nitrogen can be applied as a spray, by using a cotton bud, or melamine foam sponge. 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. 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?

Disclaimer: The Rapid Response Service is an information service for those involved in planning and providing health care in Canada. Rapid responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. Rapid responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

Copyright: This report contains CADTH copyright material and may contain material in which a third party owns copyright. This report may be used for the purposes of research or private study only. It may not be copied, posted on a web site, redistributed by email or stored on an electronic system without the prior written permission of CADTH or applicable copyright owner.

Links: This report may contain links to other information available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners’ own terms and conditions.
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>
<thead>
<tr>
<th>Table 1: Selection Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
</tr>
<tr>
<td><strong>Study Designs</strong></td>
</tr>
</tbody>
</table>
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. Clinical practice guidelines were appraised using the AGREE II instrument. 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 trial comparing cryotherapy applicator systems and one set of clinical practice guidelines for the treatment of non-genital cutaneous warts 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. 2012

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. 2011

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. 2012 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 AAFP 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.\textsuperscript{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 study\textsuperscript{12} 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 guidelines\textsuperscript{13} 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 review\textsuperscript{14} 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.\textsuperscript{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 proprane 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.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca
REFERENCES


APPENDIX 1: Selection of Included Studies

117 citations identified from electronic literature search and screened

8 potentially relevant articles retrieved for scrutiny (full text, if available)

0 potentially relevant reports retrieved from other sources (grey literature, hand search)

8 potentially relevant reports

6 reports excluded:
- irrelevant comparator (6)

2 reports included in review
### Appendix 2: Summary of Included Study Characteristics

#### Table 1: Characteristics of Included studies

<table>
<thead>
<tr>
<th>Included Study</th>
<th>Design, Sample Size, Length of Follow-up</th>
<th>Intervention</th>
<th>Comparator(s)</th>
<th>Main Study Outcomes</th>
</tr>
</thead>
</table>
| Na, 2012, South Korea | Open-label, non-RCT, n=27, 4 weeks-post final treatment | Melamine foam sponge | Conventional cotton wool bud | • 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

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical appraisal of included trial (Downs and Black)</td>
<td>• 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</td>
<td>• 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</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Critical appraisal of guidelines (AGREE II)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>American Academy of Family Physicians, Mulhem, 2011, United States</td>
<td>• Scope and purpose properly described • Very clear presentation • Applicability well described • Strength of evidence and grade of recommendation are provided.</td>
<td>• Uncertainty regarding stakeholder involvement • The procedure for updating the guideline is not transparent • Rigour of development lacks detail</td>
</tr>
</tbody>
</table>
Appendix 4: Main Study Findings and Summary of Recommendations from Clinical Practice Guidelines

Table 3: Main Study Findings and Authors’ Conclusions

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Authors’ Conclusions</th>
</tr>
</thead>
</table>
| Na, 2012⁶⁴ | **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) |
| **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) |
| **Mean VAS pain score (mm) (CWB vs MFS)**  
61.7 vs. 74.7 (p>0.05) |
| **Adverse effects (bulla) (CWB vs MFS)**  
3 cases vs 1 case |
| “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) |

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)

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Recommendation</th>
<th>Rating of Evidence</th>
</tr>
</thead>
</table>
| American Academy of Family Physicians, Mulhem, 2011,¹³ United States | • 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 | • 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