

# Liquid nitrogen cryotherapy for common warts – comparing single vs double freeze techniques

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## Abstract

**Background:** Nongenital viral warts caused by the human papilloma virus represent one of the most common diseases of the skin and cytotoxic methods, such as cryotherapy, remain the primary treatment modality. However, knowledge about its efficacy and side effects is lacking.

**Aims:** 1. To compare the efficacy of liquid nitrogen cryotherapy for common warts using single vs double freeze techniques, 2. to find the value of a second freeze-thaw cycle to warts at different anatomical sites and 3. to compare the common adverse effects of cryotherapy between the two regimes.

**Method:** 300 patients were randomly divided into 2 groups and liquid nitrogen was advocated using the spray gun. Both groups received one freeze-thaw cycle and the second group a second cycle at each visit. The treatment was continued every 2 weeks for a maximum of 6 visits. The overall cure rate, the cure rate of warts at different sites and the side effects of treatment modalities were compared. Significance was calculated employing the Z test.

**Results:** A total of 242 (80%) patients (first group – 119, second group – 123) completed the study. Thereof, 68 (57%) patients in the single freeze group as compared to 77 (63%) in the double freeze group showed overall clearance, a difference of 6% ( $p>0.05$ ). The cure rate of periungual warts in the first group was 39% and it was 66% in the second group, a difference of 27% ( $p<0.05$ ). Hypopigmentation was the most common side effect noted in both groups (single – 49%, double – 41%,  $p>0.05$ ) and infection was the least common (single – 2%, double – 3%,  $p>0.05$ ).

**Conclusion:** The use of a second freeze-thaw cycle is ineffective on the overall cure rates, but separate analysis of subjects with periungual warts revealed considerable improvement. There was no significant difference in the rates of side effects between the two groups.

## Introduction

Cutaneous warts are caused by benign epidermal proliferations of human papillomavirus (HPV)<sup>1</sup>. To date, more than 120 different types of HPV are known, of which 80 have been completely characterized.

Prevalence studies on types of HPV present in cutaneous warts have been carried out: 80% of lesions reveal HPV 2/27/57<sup>2</sup>. Any area of skin can be affected although the hands and feet are by far the commonest sites<sup>1</sup>.

Warts are treated by local destruction (acids, cryotherapy, electrodesiccation-curettage), chemotherapy or immunotherapy<sup>3,4</sup>. The choice of treatment varies with the age and wishes of the patient, the potential side effects of the treatment and the location of the lesions. Among the available medical and destructive therapeutic options for cutaneous warts, none is uniformly effective or virucidal.

Liquid nitrogen (LN<sub>2</sub>) is commonly used for cryotherapy because it is easy and relatively cost efficient<sup>1</sup>. Cotton wool bud or spray gun is used to advocate LN<sub>2</sub><sup>5</sup>. Different individuals use different freezing techniques and varying freezing times for the lesions<sup>5,6,7</sup>. Moreover, in most cases the safety and efficacy of these treatment options has not been assessed in randomized controlled trials, so that the reproducibility of the many of the listed treatments is difficult to evaluate and a possible placebo effect cannot be ruled out. This article provides indications for the management of patients with cutaneous warts through an evidence-based approach, randomized, parallel group clinical trial comparing the number of freeze-thaw cycles employing LN<sub>2</sub>.

## Objectives

1. To compare the efficacy of LN<sub>2</sub> cryotherapy for common warts using single vs double freeze techniques.
2. To find the value of a second freeze-thaw cycle to warts at different anatomical sites. eg. periungual, plantar warts, hand warts.
3. To compare the common adverse effects of LN<sub>2</sub> between the two regimes and to find out whether a second freeze carries greater morbidity in terms of side effects.

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## Study design

This was an **experimental study**. A randomized, open, parallel group clinical trial to determine the efficacy between 2 treatment regimes.

## Sample size

The study was designed to have an 80% power to detect a difference in cure rate of 20% between the 2 regimes. For this the required sample size was estimated to be 200 (100 in each arm). As clinical experience shows that there can be number of defaulters, a total of 300 patients were taken for the study.

## Study population

All previously untreated patients attending dermatology outpatient clinics at National Hospital of Sri Lanka and the Lady Ridgeway Hospital for Children for treatment of common warts participated in the study. Patients too young to tolerate LN<sub>2</sub>, patients with facial or genital warts, immunocompromised individuals and those who had contraindications to LN<sub>2</sub> cryotherapy were excluded from the study. Patients with more than 30 warts were also not included due to the difficulty in carrying out the study.

Informed verbal consent was taken from the patients and in cases of children, the consent was given by their parents or guardian. The study was approved by the ethical review committee of the Sri Lanka Medical Association.

## Method

All subjects were randomly divided into 2 groups. The patients' data including age, sex, sites, number of warts and duration prior to treatment were recorded in a questionnaire initially. Spray gun was used for both groups because it is quicker and easier than cotton bud & also does not have the risk of cross infection. The same investigator applied LN<sub>2</sub> to both groups. It was advocated keeping the gun perpendicularly to the wart at a distance of 1 – 2cm until a halo of ice of about 2mm forms around each wart. The second group received a second freeze-thaw cycle when all signs of freezing resolved after the first cycle. In both groups treatment was continued every 2 weeks for a maximum of 6 sessions. These patients were not allowed to use any other forms of anti-wart treatment during the study period. Number of warts, symptoms and signs of side effects were noted at each visit prior to treatment.

The patients who missed two consecutive appointments were considered as defaulters and withdrawn from the study. These defaulters were contacted by post or by telephone if possible to determine whether their warts have resolved.

At the end of 6 sessions subjects with no visible evidence of warts and those who informed that their warts have cleared were taken as cases of cure. Each site was independently assessed as cured or not cured. Subjects whose warts were cured at all sites were taken as cases of overall cure.

## Statistics

Data was calculated with SPSS for Windows (version-11). The median and 25/75 percentiles were chosen as the standard for the descriptive statistics. The total cure rate, cure rate at different sites and the frequency of adverse effects of each group were analyzed separately and were taken as percentages. It was assumed that all defaulters were not cured and the cure rates were expressed as a proportion of all subjects completing the study. Differences between the two groups were tested for their statistical significance employing standard normal deviation (SND) or Z test. The chosen level of significance was  $p < 0.05$ .

## Results

### Baseline comparability of the two groups

The baseline comparability of the 2 groups was assessed. Table 1 shows the number of patients completing treatment in each group with their involved sites and Table 2 compares the demographic details. Although the 2 groups showed slight baseline variations, the differences fell short of statistical significance. Table 3 gives the number of patients who showed overall clearance and clearance at different sites in each group. Warts on the scalp, arms (excluding hands), trunk and lower legs including dorsa of feet were taken as other sites. Table 3 also shows all the observed or complained adverse effects. Pain was defined as the pain that persisted 1 – 2hrs after the procedure.

**Table 1. No of patients in each group with involved sites**

|                     | <i>Single cycle<br/>Group 1</i> | <i>Double cycle<br/>Group 2</i> |
|---------------------|---------------------------------|---------------------------------|
| Total No.           | 150                             | 150                             |
| Defaulters          | 31                              | 27                              |
| Treatment completed | 119                             | 123                             |
| Hands               | 75                              | 74                              |
| Periungual          | 41                              | 44                              |
| Plantar             | 15                              | 14                              |
| Other               | 60                              | 67                              |

**Table 2. Comparison of demographic details**

|                                     | <i>Group 1</i> | <i>Group 2</i> | <i>P value</i>               |
|-------------------------------------|----------------|----------------|------------------------------|
| Age (years)<br>Mean $\pm$ SEM       | 17.5 $\pm$ 1.3 | 18.9 $\pm$ 1.2 | 0.44 (>0.05)                 |
| Male / Female                       | 77/45          | 66/57          | M – 0.14 (>0.05)<br>F – 0.16 |
| Duration (months)<br>Mean $\pm$ SEM | 10.8 $\pm$ 1.1 | 11.9 $\pm$ 1.5 | 0.56 (>0.05)                 |
| No. of Warts<br>Mean $\pm$ SEM      | 6.8 $\pm$ 0.7  | 6.7 $\pm$ 0.7  | 0.89 (>0.05)                 |

SEM – Standard Error of Mean

**Table 3. No of patients with clearance of warts and their side effects**

|                     | <i>Group 1</i> |              | <i>Group 2</i> |              |
|---------------------|----------------|--------------|----------------|--------------|
| <i>Sites</i>        | <i>Total</i>   | <i>Cured</i> | <i>Total</i>   | <i>Cured</i> |
| Overall             | 119            | 68           | 123            | 77           |
| Hands               | 75             | 39           | 74             | 49           |
| Periungual          | 41             | 16           | 44             | 29           |
| Plantar             | 15             | 07           | 14             | 07           |
| Other               | 60             | 39           | 67             | 45           |
| <i>Side effects</i> |                |              |                |              |
| Hypopigmentation    | 119            | 58           | 123            | 50           |
| Blisters            | 119            | 40           | 123            | 41           |
| Pain                | 119            | 13           | 123            | 14           |
| Hyperpigmentation   | 119            | 04           | 123            | 09           |
| Infection           | 119            | 02           | 123            | 04           |

**Analysis of result**

57% of patients in the single cycle group showed total clearance of their warts as compared to 63% in the double cycle group, a difference of 6% and  $p>0.05$  ( $P=0.33$ ) which means that the difference in cure rates is not statistically significant (Figure 1). This is also true for warts on the hands, plantar and other areas. But as subjects with plantar warts were small in both groups (gr.1 – 15, gr.2 – 14), one should be cautious in interpreting the results. However, when the cure rates

of periungual warts separately analyzed, it was 39% in group 1 and 66% in group 2, a difference of 27% ( $p<0.05$ ;  $P=0.01$ ) (Figure 1). This means a double freeze is beneficial for warts on this site.

Hypopigmentation was the commonest side effect noted in both groups followed by blister formation, pain and hyperpigmentation (Figure 2). Infection was the least common. However there was no significant difference in the rates of side effects between the two groups (Figure 2).

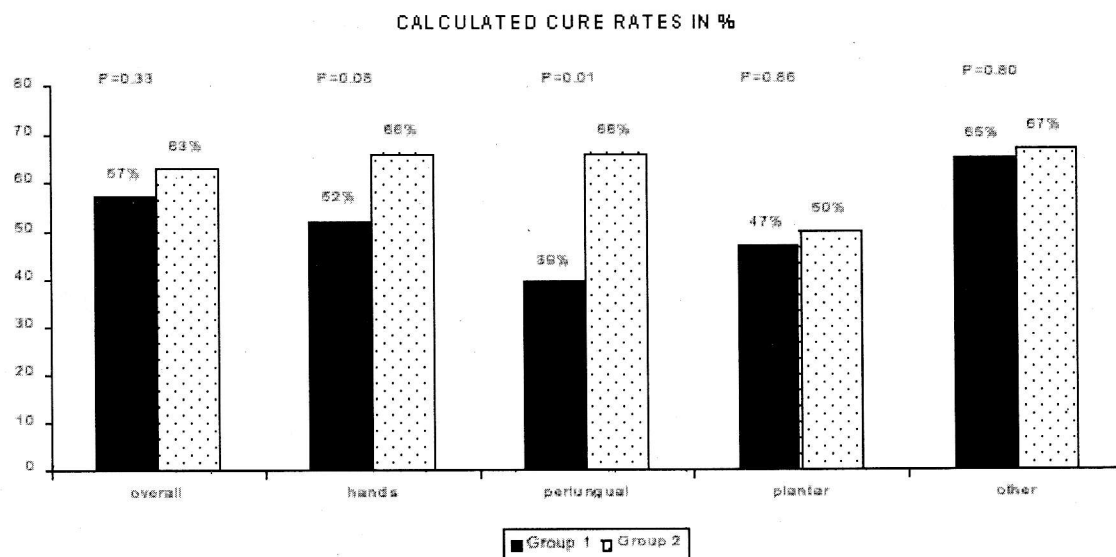


Figure 1.

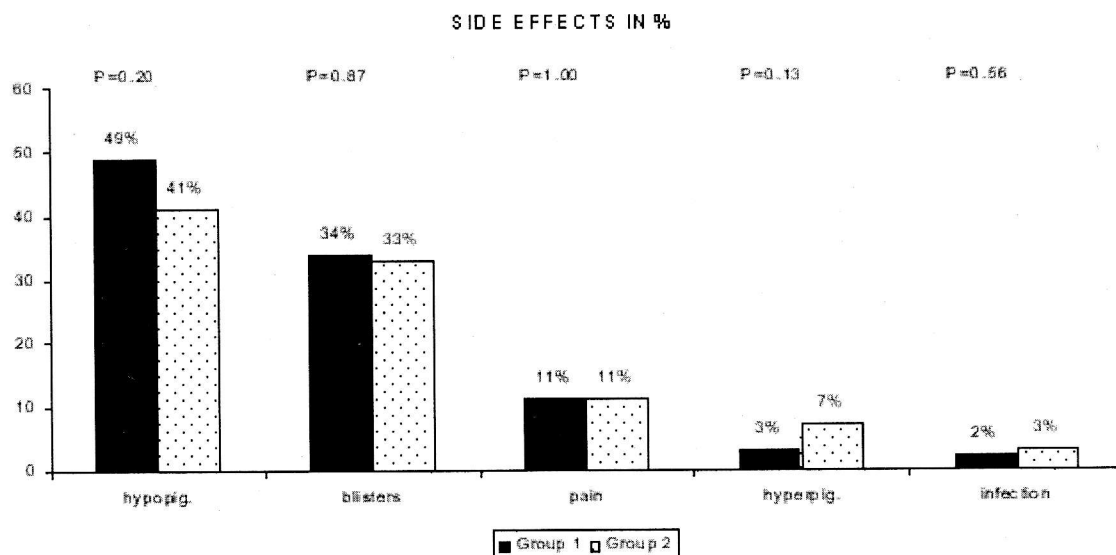


Figure 2.

## Discussion

LN<sub>2</sub> cryotherapy is a regularly used form of treatment for many benign and malignant dermatological conditions including cutaneous warts<sup>1</sup>. Nitrous oxide gas which has a boiling point of -196°C is applied directly to the lesion by means of a cotton bud or spray gun<sup>1,5</sup>. In addition to the local destruction, it is thought to stimulate an immune response<sup>1</sup>.

Several studies support the use of LN<sub>2</sub> as an effective treatment for common warts<sup>3,14</sup>. However, cure

rates vary depending on the treatment regime. Out of the very few studies that have been done worldwide about LN<sub>2</sub> cryotherapy, most of the work had been carried out to assess whether aggressive therapy gives a better cure rate<sup>6,7,8</sup>. In these studies treatment had been intensified by giving a second freeze-thaw cycle,<sup>6</sup> by advocating a sustained freeze<sup>7</sup> or by applying LN<sub>2</sub> more frequently<sup>8</sup>.

One such study showed aggressive therapy with a sustained freeze improved efficacy at all sites but carries a significant morbidity<sup>7</sup>. Berth Jones et al

compared single vs double freeze cycles and found out results somewhat similar to our study. That is, although aggressive therapy by giving a second freeze-thaw cycle has a better overall cure rate, the difference between the two groups falls short of statistical significance<sup>6</sup>. But in this particular study plantar warts seem to benefit from a second freeze<sup>6</sup>, although in our study this was not evident. Because the sample number was small in both groups in our study, this may have affected the outcome of the results of the plantar warts. Periungual warts were not separately analyzed in that study and side effects were not noted<sup>6</sup>. Therefore, we cannot compare the results of our study with the previous one in terms of the above.

There were several factors that could have had an effect on the outcome of our study. There was a possibility that a defaulter could be a subject with overall clearance of warts. The cure rates and the adverse effects were expressed only as a proportion to all subjects completing the study and not as a proportion to all subjects entering the study.

As LN<sub>2</sub> is a common procedure most dermatologists use, larger studies could be carried out to assess the efficacy of multiple freeze-thaw cycles to warts at certain special sites. However, by analyzing earlier studies<sup>6,7</sup> and our study we can recommend double freeze thaw cycles to improve cure rates at certain resistant sites like the periungual area. Since adverse effects were not noted in earlier studies comparing single vs double freeze cycles, this aspect should be further studied to give a definitive conclusion. There is also a need to focus on variables like age, sex, duration prior to treatment and number of warts in terms of the response rate.

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