Randomized Controlled Trial Study on the Clinical Efficacy of Liquid Nitrogen and Dimethyl Ether Cryotherapy for Viral Warts

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Abstract: To analyze the efficacy of liquid nitrogen and dimethyl ether cryotherapy for the treatment of viral warts, 480 patients with viral warts admitted to our hospital from March 2022 to June 2024 were selected. 228 patients were randomly assigned to the comparison group and treated with liquid nitrogen cryotherapy, while 252 patients were assigned to the observation group and treated with dimethyl ether cryotherapy. The clinical efficacy and adverse reactions of both treatments were observed and compared. The results showed that there were no significant differences in the cryotherapy efficacy between the two groups. The analysis suggests that both liquid nitrogen and dimethyl ether are equally effective for treating viral warts, with dimethyl ether showing lower adverse reaction rates and more tolerable pain levels, which offers higher clinical application value.

***Keywords*:** dimethyl ether, viral warts, liquid nitrogen, cryotherapy

1. Background Overview

Viral warts are a general term for skin diseases caused by human papilloma virus (HPV) infection, commonly seen in clinical practice as common warts, filiform warts, flat warts, plantar warts, etc. [1]. In recent years, the number of patients infected with viral warts has continued to increase, and this population has become quite large. In our hospital, the majority of viral wart patients are diagnosed with common warts and plantar warts. Treatment methods include surgical excision, physical cryotherapy, and chemical agents such as topical solutions [2,3].

Cryotherapy is one of the most common and mainstream methods for treating skin warts and other skin lesions. Liquid nitrogen, as the most widely used cryogen in clinical practice, has been the mainstay for cryotherapy applications. However, the pain caused by liquid nitrogen limits its use [4]. The application of dimethyl ether as a cryogen for treating viral warts and other skin lesions is relatively rare in China but has been widely used in foreign countries. Products that use dimethyl ether or dimethyl ether-propane mixtures as cryogens for wart removal not only come in various forms but also have high levels of commercialization. This study aims to compare the clinical efficacy and safety of liquid nitrogen and dimethyl ether cryotherapy for viral warts, analyze the application value of dimethyl ether as a cryogen, and explore new treatment methods for viral warts and other skin lesions, improving clinical treatment efficacy while reducing patient pain.

2. Cryotherapy Introduction

The principle of cryotherapy for treating viral warts is to destroy the wart tissue using low temperatures. For most wart tissues, the optimal freezing temperature is around -30°C. If the tissue is kept below -20°C, freezing at -20°C will significantly increase the rate of tissue destruction. When the tissue temperature rises above the freezing point, the slower the temperature increase, the more ice crystals form in the wart cells, causing more damage. Repeated freezing and thawing causes greater destruction to the wart tissue, although the exact interval for freezing and thawing cycles has not yet been determined.

Targeted spraying, using a handheld cryotherapy system, is another method of cryotherapy. There are many mature products available domestically and internationally, such as the WART FREEZE (FDA 510K Number K130599 ,China Medical Device Registration Import Number 20182092311), HISTOFREEZER WART REMOVAL SYSTEM (FDA 510K Number K023487),DR. SCHOLL'S FREEZE AWAY WART REMOVER (FDA 510K Number K031697), WARTIE WART REMOVER (FDA 510K Number K140314) and the Freeze’n Clear Skin Clinic Warts & Tags (FDA 510K Number K211099).

3. Research Materials and Methods

3.1 Clinical Data

A total of 480 patients with viral warts who were admitted to our hospital between March 2022 to June 2024 were

selected for this study. Inclusion criteria: Patients whose lesions meet the diagnostic criteria for viral warts. Exclusion criteria: Patients with other diseases that present lesions similar to viral warts; patients who have received other treatments for the lesions; patients who may experience interruption of wart treatment or other uncertain factors within 60 days; patients with leukopenia or those who have undergone antiviral treatment within 14 days prior to treatment.

Among the 480 patients, 228 patients were randomly divided into the liquid nitrogen cryotherapy comparison group (112 males, 116 females, aged 15-60 years, average 32.5±5.0 years), including 108 cases of common warts and 120 cases of other types of warts. Another 252 patients were divided into the dimethyl ether cryotherapy observation group (132 males, 120 females, aged 16-52 years, average 35.3±5.0 years), including 120 cases of common warts and 132 cases of other types of warts. There was no statistically significant difference between the two groups in terms of gender, age, condition, medical history, etc. (P>0.05), and they can be compared.

3.2 Information Collection

Data was collected through a statistical form distributed at the outpatient clinic. The information recorded included the patient's name, age, type of wart, location of the wart, duration of the wart, presence of any comorbidities, allergy history, previous treatment experiences, and so on. After receiving an explanation from the physician and giving informed consent, patients chose their treatment plan.

3.3 Methods

For the comparison group, cryotherapy was performed using liquid nitrogen. A cotton swab was dipped in liquid nitrogen, removed, and pressed against the wart tissue, causing the wart tissue to start forming ice crystals. This process took about 5-20 seconds, until the ice crystals covered the outer 1-2 mm of the wart tissue. Two freeze-thaw cycles were applied. After one week, the lesions were observed, and if not healed, the treatment was repeated up to a maximum of four times.

For the observation group, the wart-freezing spray system (National Medical Device Registration 20182092311) was used following the prescribed operation procedure. The device uses dimethyl ether as the cryogen and is a relatively newer cryotherapy device. It is widely used in Europe and the United States for treating various types of viral warts and has obtained European Union IIa CE certification and U.S. FDA 510K certification. It has been imported and registered in China for several years.

3.4 Statistical Analysis

The data in this study were analyzed using SPSS 17.0 statistical software. Continuous data are presented as means (± standard deviation), and comparisons were made using t-tests. Categorical data are presented as percentages, with comparisons made using chi-square tests. If the P-value was less than 0.05, it was considered that there was a significant difference with statistical meaning

3.5 Efficacy Assessment

The regression time of viral warts for both groups of patients was recorded, and adverse reactions were observed during the treatment. After the treatment, clinical efficacy was assessed according to the following criteria.Cured: The patient's lesions were completely resolved; Significant improvement: The diameter of the lesion shrank by 70% or more but less than 100%; Effective: The diameter of the lesion shrank by 30% or more but less than 70%;Ineffective: The diameter of the lesion shrank by less than 30%.Total efficacy rate = (Cured + Significant improvement + Effective) / Total cases × 100%.

4. Results

4.1 Clinical Efficacy Comparison

There was no significant difference in the total effective rate for the treatment of common warts and other warts between two groups (P>0.05), as shown in Table 1.

4.2 Lesion Regression Time Comparison

In the comparison group, the regression time for common warts was 1.59 ± 0.53 weeks, and for other warts, it was 2.21 ± 0.36 weeks. In the observation group, the regression time for common warts was 1.53 ± 0.52 weeks, and for other warts, it was 2.37 ± 0.41 weeks. The lesion regression time for common warts in the comparison group was similar between the two groups (P>0.05), while the regression time for other warts was similar between the two groups (P>0.05).

Table 1. Comparison of clinical efficacy between the two groups of patients

Groups		Number of cases	Cured	Significant Improvement	Effective	Ineffective	Total Effective Rate
Comparison Group	Common warts	108	40 (37.0%)	36 (33.3%)	24 (22.2%)	8 (7.4%)	100 (92.6%)
	Other warts	120	52 (43.3%)	32 (26.6%)	24 (20.0%)	12 (10.0%)	108 (90.0%)
Observation group	Common warts	120	48 (40.0%)	32 (26.6%)	32 (26.6%)	8 (10.0%)	112 (93.3%)
	Other warts	132	60 (45.4%)	40 (30.3%)	24 (18.2%)	8 (6.0%)	124 (93.9%)

4.3 Analysis of Adverse Reactions

The primary adverse reactions following treatment included pain, swelling, and blister formation. In the comparison group, 40 cases experienced adverse reactions, accounting for 17.5%, including 16 cases of blisters, 16 cases of swelling, and 8 cases of pain. In the observation group, 16 cases experienced adverse reactions, accounting for 6.3%, including 8 cases of blisters, 4 case of swelling, and 4 case of pain. Adverse reactions in both groups resolved within 1-2 weeks with symptomatic treatment. The incidence of adverse reactions was significantly lower in the observation group than in the comparison group ($P<0.05$). No patients from either group discontinued treatment due to discomfort.

4.4 Analysis of Tolerance

The tolerance of the two treatments was evaluated based on patient feedback, divided into three grades: good, average, and poor. Among the patients treated with dimethyl ether cryotherapy, for common warts, 60 cases (55.5%) reported good tolerance, 48 cases (44.6%) reported average tolerance, and none reported poor tolerance. For other viral warts, 72 cases (60.0%) reported good tolerance, 44 cases (36.7%) reported average tolerance, and 4 case (3.3%) reported poor tolerance. In comparison, among patients treated with liquid nitrogen cryotherapy, for common warts, 60 cases (50.0%) reported good tolerance, 60 cases (50.0%) reported average tolerance, and none reported poor tolerance.For other viral warts, 84 cases (63.6%) reported good tolerance, 40 cases (30.3%) reported average tolerance, and 8cases (6.1%) reported poor tolerance.

The results indicate that dimethyl ether and liquid nitrogen cryotherapy have comparable tolerance levels during wart treatment.

5. Discussion

Cryotherapy has a long history of application in dermatology. This method is simple, effective, and widely accepted by patients. Liquid nitrogen is commonly used as the cryogen for cryotherapy[5]. Clinical practice has shown that liquid nitrogen cryotherapy often causes intense pain.

A wart-freezing spray system is a newer cryotherapy device that has been used in various clinical treatments of warts in the U.S. and Europe. Its primary cryogen is dimethyl ether, with a treatment temperature of -25°C. Dimethyl ether cryotherapy is performed by tilting the spray can so the applicator head faces downward, pressing to release the cryogen, and gently applying the applicator head to the lesion for 10 seconds. This process freezes the target tissue.

Compared to traditional liquid nitrogen cryotherapy, dimethyl ether cryotherapy operates at a relatively higher temperature, causing less cellular damage and offering greater safety. Additionally, dimethyl ether cryotherapy causes less pain.

This study compared the treatments of liquid nitrogen and dimethyl ether cryotherapy and found no significant difference in the efficacy for common warts and other types of viral warts between the two groups. This indicates that, despite the higher freezing temperature of dimethyl ether compared to liquid nitrogen, it can still achieve comparable therapeutic effects. Since temperatures below -20°C are sufficient to cause cell death, dimethyl ether's much lower freezing temperature is adequate for destroying the targeted cells.[6]

6. Conclusion

This study observed the occurrence of adverse reactions during treatment in both groups. The incidence of adverse reactions was significantly lower in the observation group than in the comparison group, indicating that dimethyl ether cryotherapy poses a significantly lower risk of adverse reactions compared to liquid nitrogen cryotherapy. This difference is attributed to the temperature variations between the two treatment methods. Additionally, the wart-freezing spray system is easy to store, highly portable, and convenient to use, making it particularly suitable for regions or small hospitals where the use of liquid nitrogen is challenging. Furthermore, it causes fewer adverse reactions and offers better patient tolerance, suggesting that it could gradually replace liquid nitrogen as the preferred treatment method for viral warts.

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