Cryosurgical Treatment of Warts: Dimethyl Ether and Propane Versus Liquid Nitrogen — Case Report and Review of the Literature

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ABSTRACT

For years, dermatologists have relied on cryotherapy with liquid nitrogen as a safe and effective treatment for warts. More recently, several over-the-counter (OTC) wart-freezing therapies have become available. Manufacturers have substituted liquid nitrogen with dimethyl ether and propane (DMEP), and marketed these new preparations to be safe and effective alternatives to in-office cryotherapy with liquid nitrogen. However, data from in vitro studies and comparative studies in humans refute manufacturers' claims that these products reproduce in-office cryotherapy.

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INTRODUCTION

Viral warts are benign proliferations of skin and mucosa secondary to infection with human papillomavirus (HPV). To date, over 100 HPV genotypes have been identified. Collectively, these genotypes produce a wide spectrum of disease from the common wart (verruca vulgaris) to the genital wart (condyloma acuminatum).

In 1963, Massing and Epstein published the results of a two-year study which examined the natural history of warts. They found that 70 percent of individual warts studied resolved after two years without treatment. In light of this evidence, one might conclude that no treatment may be appropriate for those individuals who are able to stomach the wart's appearance. In point of fact, however, only 46 percent of these patients remained wart-free after two years.[1,2] Thus, the potential for autoinoculation, transmission, and disease recalcitrance demands that these warts be destroyed.

DISCUSSION

Mechanism of Cellular Injury

For years, dermatologists have relied on cryotherapy with liquid nitrogen as a safe and effective treatment for the common wart. The mechanisms by which cryotherapy results in cellular injury is based upon the rapid transfer of heat from the skin to liquid nitrogen, which has a boiling point of -196°C. Rapid cooling of tissue results in direct cellular injury via ice crystal formation and ischemic necrosis secondary to vascular changes. Viral destruction is contingent upon adequate keratinocyte necrosis. The probability of achieving an adequate level of necrosis for effective viral eradication increases with accelerated rates of temperature change during the cooling phase of cryotherapy.

As tissue temperatures fall to -5°C to -15°C, extracellular ice crystals begin to form. The formation of crystals not only mechanically disrupts cellular membranes, but also disturbs fluid homeostasis. During the freezing phase, the extracellular fluid becomes hypertonic. The result is cellular dehydration as water flows from the intracellular to the extracellular space via osmosis. When thawing occurs, the extracellular fluid becomes hypotonic and the rapid flow of water back into the cells may result in rupture of the plasma membrane and cell death. Below -40°C intracellular ice crystals form, further damaging the keratinocyte plasma membrane.[3] Vascular changes associated with circulatory failure become evident between the formation of extracellular and intracellular ice crystals, as tissue temperatures fall below -15°C. Microthrombi form within damaged vessels leading to ischemic necrosis.[4] Thus, the degree of keratinocyte necrosis is dependent upon both the rate of cooling and the minimum tissue temperature achieved.

An End to In-office Cryotherapy for Warts?

In recent years, several OTC wart-freezing therapies have become available. These products substitute liquid nitrogen with DMEP. Manufacturers market these preparations to be safe and

effective alternatives to in-office cryotherapy. One manufacturer went so far as to say their product is "the most successful method of wart removal used by physicians." We describe the case of a 25-year-old male with persistent post-inflammatory hyperpigmentation secondary to self-administered treatment with an OTC wart removal product containing DMEP.

Case

A 25-year-old male presents with a brown-grey macule following treatment with an OTC wart-freezing product. The patient sought treatment from his primary care physician four years earlier when he presented with a viral wart, and his physician recommended an OTC wart freezing product containing dimethyl ether and propane. The patient described the formation of a hemorrhagic blister and scab. When the scab fell off two to three weeks later, the wart remained. Treatment was repeated. Again a hemorrhagic blister formed over the frozen area, concealing a smaller wart which had not been eradicated. This time, however, a permanent brown-grey discoloration remained.

CONCLUSION

In a 1996 study, Caballero *et al.* demonstrated equal efficacy with physician-administered DMEP and liquid nitrogen cryotherapy in the treatment of verruca vulgaris. The authors concluded that no clinically relevant differences in efficacy, safety, and tolerability exist between the two agents.[5] Subsequent to these findings, DMEP-containing cryotherapy devices have become commonplace in the primary care setting. Manufacturers of OTC wart-freezing products have used this data to propel their products to the reach of the consumer. However, a careful evaluation of the study design brings the validity of the aforementioned conclusions into question.

Subjects were randomized to receive cryotherapy with either liquid nitrogen or DMEP. Following treatment, patients were assessed at one-week and again at a 15-day end-of-trial appointment to determine efficacy. In selecting an end date that precludes the detection of disease recurrence, the study fails to provide an accurate measure of the efficacy of cryotherapy with DMEP. Furthermore, as evidenced by the presented case, tissue exposed to cryotherapy may form a hemorrhagic blister and eschar which may conceal underlying residual disease well beyond the 15-day end-of-trial appointment.

In a similar study, Erkens *et al.* extended the end-of-trial appointment date to 2.5 months. At 2.5 months, 58% (25/43) of patients treated with liquid nitrogen were cured versus 28% (14/50) of those patients treated with DMEP (P=0.01).[6] Thus, with adequate follow up, liquid nitrogen appears to demonstrate therapeutic superiority; however, additional studies are needed to validate these findings.

Prior to this report, Burkhart *et al.* conducted an in vitro study comparing OTC wart-freezing products to in-office cryotherapy with liquid nitrogen. The tip of a thermometer was placed in direct contact with both liquid nitrogen and DMEP expelled from OTC wart-freezing products. Liquid nitrogen produced a recorded temperature of -100°C, the instrument's lower limit of detection, in less than 15 seconds. Despite manufacturer claims that the DMEP mixture freezes warts at a temperature of -57°C, the lowest temperature recorded when the thermometer was placed in direct contact with the coolant was -20°C at 45 seconds. Interestingly, when the device was used as per the package insert and the thermometer was placed in direct contact with the device's foam applicator tip, the lowest temperature recorded was -9°C.[7] This study illustrates that cryotherapy with DMEP, if used as per package insert, is unlikely to produce tissue temperatures cold enough to generate intracellular ice crystal formation or ischemic necrosis, phenomena that are seen at temperatures less than -40°C and -15°C, respectively. This study also illustrates that liquid nitrogen produces a more rapid rate of tissue cooling, associated with a higher degree of cellular necrosis. Collectively, these findings cast doubt on manufacturers' claims that these OTC products reproduce in-office cryotherapy with liquid nitrogen.

It is also important to note that in previous studies, cryotherapy with DMEP was administered by trained health care professionals using a patented applicator device.[5] Conversely, OTC wart-freezing products are typically administered by untrained individuals, using a different applicator system. On this basis, conclusions made regarding the safety and efficacy of in-office DMEP cryotherapy may not be applicable to similar OTC products. Despite having been on the market for several years, published data attesting to the efficacy of OTC wart-freezing therapies containing DMEP appears to be nonexistent.

Nevertheless, OTC wart-freezing products are marketed to the general public as a safe treatment modality for adults and children at least four years of age. One manufacturer even makes it known that both dimethyl ether and propane are commonly used in hairspray products. Such statements are misleading and dangerous, as they suggest that these entities are completely benign. Two case series describing significant cold thermal burns resulting from use of these products suggest otherwise.[8,9] Furthermore, it is clear from the presented case that permanent post-inflammatory hyperpigmentation is another potential adverse effect.

Post-inflammatory hyperpigmentation can be seen in the setting of epidermal inflammation, where melanocytes are stimulated to increase the production of melanin. Disruption of the melanocytes in the stratum basalis may result in pigment incontinence as melanin becomes trapped by macrophages in the dermis. As evidenced by the presented case, the resulting dermal melanosis is often permanent. It is important to point out that melanocytes are much more delicate cells that keratinocytes. Thus, while OTC wart-freezing therapies may not achieve temperatures ad-

equate for keratinocyte necrosis, melanocytes may be destroyed at -5°C. Consequently, the potential for post-exposure hypopigmentation also exists, especially in dark skinned individuals. But perhaps the greatest morbidity is not the immediate burns or pigmentation changes, but, rather, the delay in proper treatment of a malignant lesion masquerading as a viral wart.

In summary, the above case clearly demonstrates a poor outcome following multiple treatments with an OTC wart-freezing device. But given the lack of prospective data comparing OTC wart-freezing cryotherapy to standard cryotherapy with liquid nitrogen, only tentative conclusions regarding the safety and efficacy of these OTC products should be made.

DISCLOSURES

The authors have no conflict of interest to declare.

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