Molluscum contagiosum effectively treated with a topical acidified nitrite, nitric oxide liberating cream

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Summary

A double-blind, group-sequential clinical trial of acidified nitrite was performed to demonstrate the efficacy of this nitric oxide donor in treating molluscum contagiosum. Subjects received either 5% sodium nitrite co-applied with 5% salicylic acid under occlusion, or identical cream with 5% salicylic acid, omitting sodium nitrite. Active and control treatment groups were well matched for the number and duration of lesions and made a similar number of applications. We found a 75% cure rate in the active treatment group and 21% cure with control treatment (P = 0.01). The mean time to cure was 1.83 months. Staining of the skin and irritation were frequent side-effects but did not prevent successful treatment.

Key words: acidified nitrite, antiviral, molluscum contagiosum, nitric oxide

Molluscum contagiosum 1 and 2 are related to ortho-pox and parapox viruses and share some homology with vaccinia. Nitric oxide (NO) has been shown to have antiviral effects in DNA, RNA, enveloped and encapsidated viruses. It reduces replication of herpes simplex type 1, vaccinia and the orthopox ectromelia virus, murine coronavirus and in vitro, but not in vivo, has antiviral properties for avian reovirus infection. Not all viruses are inhibited by NO, e.g. tick-borne encephalitis virus is resistant to its effects. We have previously described the use of acidified nitrite cream as an NO donor to treat dermatophyte infections and now show the effectiveness of this topical treatment in molluscum contagiosum.

Within keratinocytes, the molluscum virion colonies are isolated in a unique sac which provides an immunologically privileged environment for replication. Lesions lack a T-cell and killer cell infiltrate, reflecting absence of a host response. This may result from the expression of epitopes on the molluscum bodies mimicking those normally found on the surface of macrophages. Current therapies include physical destruction, manual extrusion, liquid nitrogen therapy and curettage, all of which are painful, although pain can be reduced by lidocaine/prilocaine (Emla) cream. The pain of these therapies is important, as most patients are under 10 years old. There are few well conducted clinical trials of therapy for molluscum, although povidone iodine and 50% salicylic acid was effective in one such trial and 5% podophyllotoxin in another. Interestingly, the latter trial showed only a 16% response rate over 3 months with placebo therapy, demonstrating the slow rate of spontaneous resolution. The infection can be severe in patients with human immunodeficiency virus (HIV)-induced immunosuppression, where disfiguring facial lesions are a therapeutic problem. In some such patients, resolution with the antiviral cidofovir has been noted when coincidentally given for cytomegalovirus infection.

Subjects and methods

As we could not estimate the size of the effect of this therapy, we chose a double-blind, group-sequential design in which subjects were randomized to receive either 5% sodium nitrite co-applied with 5% salicylic acid under occlusion, or identical cream with 5% salicylic acid but omitting sodium nitrite, as a control. Children under 1 year of age, pregnant or lactating women, an unco-operative child or mother, and those on immunosuppressive drugs or known to have HIV infection, were excluded. Lesions on the face were
excluded because of potential stinging or staining of the skin. Subjects were asked to apply the treatment to each individual lesion every night and record the treatment in a diary. Wherever possible, occlusion with cling film or light adhesive tape was suggested, but certain body sites and widely distributed lesions often precluded occlusion. Statistical analysis was on an intention-to-treat basis. Repeated $\chi^2$ analyses (Pearson’s, SPSS statistical package) were scheduled after 15, 20, 25, 30 and 35 patients completed, with a prospective stopping rule for $P < 0.003, 0.011, 0.016, 0.019$ and 0.031 on successive analyses. Completion was defined as 3 months, or when the patient was cured or dropped out, if sooner. At least 1 month of treatment was necessary to be valid for efficacy. The log rank test was used to assess differences in cure rate over time, with the last evaluable status carried forward for drop-outs.

Results
The median age of subjects was 6 years and interquartile range 4 years. Twenty-two were girls and eight boys. The infection had a mean ± SD duration of 8·23 ± 3·959 months. No significant difference was found between the active treatment and control groups in the number of lesions per patient or duration of these lesions (Table 1). Cure was significantly greater with NO treatment after 30 patients completed therapy, with 75% cure in the active treatment group and 21% cure with control treatment (Table 2) ($\chi^2$ with Yates’ correction $P = 0.01$, Fisher’s exact test $P < 0.01$), and the mean time to cure ± SD was 1·83 ± 0·91 months.

A Kaplan–Meier plot (Fig. 1) demonstrates the rate of cure over time and was analysed by the log rank test.

This showed a significant difference in the survival curves, with cure being greater in the active group ($P < 0.01$). Four of 16 patients stopped the active treatment because of irritation and lack of efficacy, and two further patients who cleared complained of significant irritation. Similar irritation occurred in four of the controls. Lack of efficacy was the primary reason for stopping treatment in 10 of 14 controls. Brown staining was recorded in six subjects with active treatment but not in controls. Patients were not disturbed by this, as there was improvement in the lesions.

Subjects dropped out of the study evenly in both active and control groups, including subjects that were cured. Five active and four control subjects dropped out after 1 month, six in each group dropped out after 2 months, and five active and four control subjects completed 3 months. The mean ± SD number of treatments in the active treatment group was 38 ± 20 compared with 49 ± 25 in the control group. This confirms that the control group did not fail to clear because of early withdrawal. Although instructed to apply the treatment nightly, on average it was only applied every second night. This was because treatment was fiddly and time-consuming or, where there was irritation, treatment was omitted for a few days. No other systemic or other adverse events were noted.

Discussion
Acidified nitrite cream is an effective therapy for this distressing condition and, unlike physical treatments,
Nitric oxide (NO) has specific antiviral effects at levels below those toxic to host cells, by inhibiting viral replication. It probably acts on several targets by inhibiting RNA synthesis, DNA replication, early and late viral protein synthesis, and by nitrosylating viral structural proteins. We have shown that higher concentrations of NO from nitrite and ascorbic acid are immunopotentiating. We showed that NO caused lymphocyte, macrophage, and neutrophil infiltration, expression of the adhesion molecules intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 and migration of antigen-presenting cells. We also showed an increase in p53. It is therefore possible that NO acts through DNA toxicity to infected cells, promoting apoptotic cell death. We have successfully treated genital lesions of molluscum contagiosum and extensive lesions in two subjects with HIV infection. The immunosuppressed patients took longer to clear, suggesting that immunopotentiation contributes to the successful clearance of the virus.

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