Combination of Essential Oil of *Melaleuca alternifolia* and Iodine in the Treatment of Molluscum Contagiosum in Children

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ABSTRACT

Molluscum contagiosum is a common childhood viral skin condition and is increasingly found as a sexually transmitted disease in adults. Current treatment options are invasive, requiring tissue destruction and attendant discomfort. Fifty-three children (mean age 6.3+5.1 years) with the diagnosis of molluscum contagiosum were treated with twice daily topical application of either essential oil of *Melaleuca alternifolia* (TTO), a combination of TTO and organically bound iodine (TTO-I), or iodine alone. At the end of 30 days, 48 children were available for follow up. A greater than 90% reduction in the number of lesions was observed in 16 of 19 children treated with TTO-I, while 1 of 16 and 3 of 18 children met the same criteria for improvement in the iodine and TTO groups ($P<0.01$, ANOVA) respectively by intention-to-treat analysis. No child discontinued treatment due to adverse events. The combination of essential oil of *M. alternifolia* with organically bound iodine offers a safe therapeutic alternative in the treatment of childhood molluscum. Clinical Trial Registry ACTRN12610000984099.

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INTRODUCTION

Molluscum contagiosum (MC) is a common and benign contagious viral skin condition of childhood occurring worldwide. It was first described by Bateman in the beginning of the nineteenth century.[1] MC currently accounts for approximately 1% of all diagnoses of skin disorders in the US[2,3] with an occurrence of up to 10% in the pediatric population under age 10.[4] The incidence of sexual transmission in the adult population is also rapidly increasing.[5,6] In addition, between 5% and 20% of patients with HIV have symptomatic MC.[7]

The molluscum contagiosum virus (MCV) is a doubled-stranded DNA poxvirus with no significant animal reservoir.[8-11] It is a cytoplasmically replicating virus and proliferates in the follicular epithelium.[12] In immunocompetent patients the illness is self-limited and MCV infection generally does not recur.[8] However, MCV exhibits an ability to avoid host defense mechanisms,[13,14] and it is not unusual for lesions to persist and spread. The lesion presentation may vary from small papules that may be mistaken for atopy but more often reveal the characteristic central umbilication permitting easy identification (Figure 1).

The general recommendation for treatment is expectant management,[3,12] with spontaneous resolution generally occurring in 12 to 30 months. However, lesions may spread to the face or cover extensive portions of the body, prompting the desire for treatment. Treatment options largely depend upon tissue destruction and include curettage, cryotherapy, laser, electrodessication, or application of caustics such as trichloroacetic acid, KOH, or cantharadin.[15-17] Recently, topical immune modulators such as imiquimod have been used with some success.[18] However, all current treatment options involve some degree of pain, discomfort, or irritation to the patient with accompanying distress to the parents of small children. In addition, treatments that rely on tissue destruction may increase the risk of infection and scarring.[3,12,19] Thus, the need exists for a safe, painless, effective, and rapid treatment option.

Our previous studies with Australian lemon myrtle (*Backhousia citriodora*) demonstrated clearance of lesions in less than 50% of children with MC.[20] However, there are more recent reports of cytotoxic effects with use of this oil.[21] In an attempt to improve both safety and efficacy, we evaluated other formulations.

The essential oil of *Melaleuca alternifolia* (tea tree oil [TTO]) has been used topically as an antiseptic for decades,[22] while chemical and therapeutic characterization of the essential oil (steam distillate) from *M. alternifolia* has a body of literature dating back to 1925,[23] demonstrating broad-spectrum antibacterial[24-29] and antifungal[30,31] action. Iodine has also been used topically for decades worldwide as a safe and effective topical antiseptic. The known antiseptic actions of iodine and tea tree oil, in conjunction with their long history of topical safety, prompted us to evaluate the combination of TTO and iodine as a topical treatment for MC.

We tested topical application of a tea tree oil: iodine preparation (TTO-I), TTO alone, and topical iodine alone as control in the

treatment of MC in 53 children in a randomized, placebo controlled, blinded protocol with intention-to-treat analysis. Forty eight children completed the study and were available for follow up. The results after 30 days of treatment showed a 90% or greater reduction in the number of visible molluscum lesions in 16 of 19 (84.2%) children treated with the TTO-I preparation versus 1 of 16 (6.2%) and 3 of 18 (16.7%) children treated with iodine or TTO alone, respectively. These results demonstrate the potential efficacy and safety of the combination of TTO and organically bound iodine as a therapeutic modality in treatment of MCV.

"We tested topical application of a tea tree oil: iodine preparation (TTO-I), TTO alone, and topical iodine alone as control in the treatment of MC in 53 children in a randomized, placebo controlled, blinded protocol with intention-to-treat analysis."

Study Protocol

Fifty-three children (mean age 6.3+5.1 years) with MC were enrolled (Table 1). Children were otherwise healthy without major disease, at or above the 50th percentile for height and weight, and met all age-appropriate developmental milestones. Mean length of time with the diagnosis of molluscum was 5.6+5.3 months. Detailed written informed consent was obtained from the parents, and the study protocol was in conformity with the Helsinki Accords regarding human subjects.

The TTO-I preparation contained 75% (v/v) essential oil of Australian *M alternifolia* (terpinene-4-ol content 40.1%, conforming to Standards Association of Australia, AS 2782-1985), high selenium canola oil, and organically bound iodine in a proprietary formulation (U.S. patent #7,311,928 generously provided by Naturopathix, Inc., Boise, ID) to yield a total iodine concentration in the formulation of 35 micromolar. The preparation contained no preservatives, additives, or solvents. The identical tea tree oil and canola oil were used in the TTO alone group. The iodine alone formulation contained the same organically bound iodine in a vehicle of high selenium canola oil to yield a total iodine concentration in the formulation of 35 micormolar.

Children were randomized to treatment group. Nineteen children were randomized to TTO-I, 18 children to TTO alone, and 16 to iodine alone. Treatment consisted of application of one 4 ul drop to each molluscum lesion twice daily. Treatment was continued for 30 days or until all lesions had resolved if this required less than 30 days. Treatment was considered successful if lesions completely cleared or were reduced in number by greater than 90% by the end of day 30. Parents and physicians were blinded to treatment protocol. Participants were seen every 10 days to monitor progress and assess for adverse events. A mild synthetic lemon fragrance not containing citral was added to scent the iodine olive oil preparation. This fragrance by itself had no therapeutic effect (data not shown).

RESULTS

Forty-eight children were available for follow-up at the end of 30 days. In the TTO-I treated group, 1 child was lost to follow-up; 2 had reductions in the number of lesions but did not meet the 90% criterion; 11 had total resolution of all palpable lesions; and 5 had reductions in the number of lesions greater than 90% at the end of 30 days for a total of 16 of 19 children meeting the study criteria for treatment success. In the TTO alone group, 5 children had some reduction in the number of lesions but did not meet the 90% criterion, and 4 children met the 90% reduction criterion. In the iodine treated group, 2 children withdrew as the parents perceived worsening of the molluscum and sought other treatment, 4 children had spontaneous reduction in the number of lesions but did not meet the 90% reduction criterion, and 1/16 met the 90% reduction criterion. There was variation in the number of molluscum lesions at the end of 30 days in the iodine and TTO groups, with some children having an increase and some a decrease in lesion number.

The treatment was well tolerated and often resulted in a dramatic clearing of visible molluscum lesions (Figures 2 and 3).

The mean number of lesions at enrollment was 22+19 (mean+sem) and did not differ between treatment groups. Lesion number for the entire study population ranged from a minimum of 7 to a maximum of 69, with a median value of 29.

Adverse effects were limited to a small amount of redness around the base of some lesions. Of the 48 children available for follow up, 4 mothers (1 TTO-I, 2 iodine, 1 TTO) reported areas of redness that were concerning to them on a total of 21 molluscum lesions. No area of redness was larger than the 3 mm radius, and no lesion showed signs of infection. No patient discontinued treatment due to adverse reactions. It was not uncommon for parents to report lesions themselves becoming reddened during course of treatment, but no parent reported pain or discomfort in the child from this redness. Parents of 3 children in the TTO-I group and 4 in the TTO group reported a transient sensation of warmth with application, which cleared in approximately 90 sec or less. The difference in incidence of reports of redness around lesions between TTO-I, TTO alone, or iodine was not statistically significant, but both treatment groups had a greater incidence of redness of lesions themselves than the iodine alone group. There was no blistering or other sign of gross cytotoxic effect from application of either TTO-I or TTO alone for the duration of the study. There was no

FIGURE 1. Typical umbilicated appearance of molluscum lesions **a)** on the thigh of a 7-year-old boy and, **b)** severe molluscum on leg of 4-year-old girl.

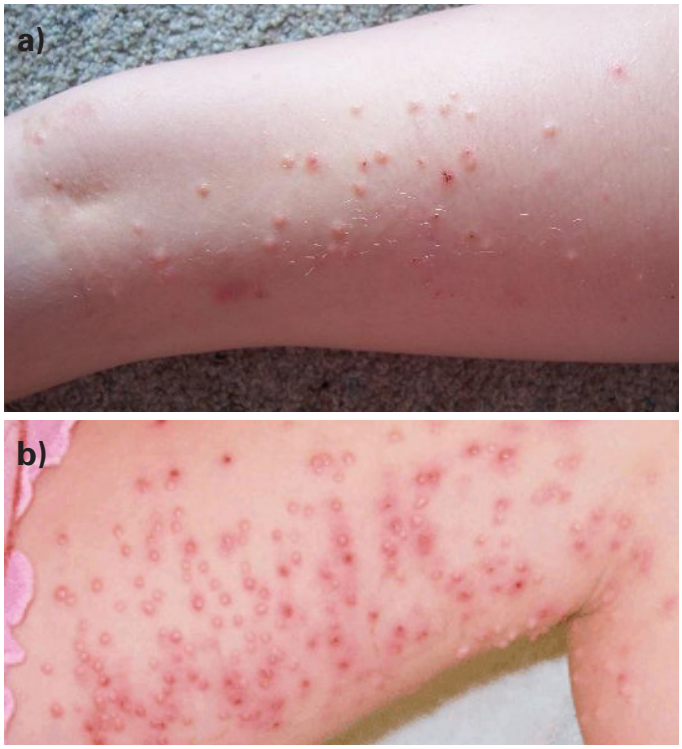


FIGURE 2. Molluscum on the thigh of 5-year-old girl before **a)** and the same girl **b)** on day 30 after treatment with TTO-I

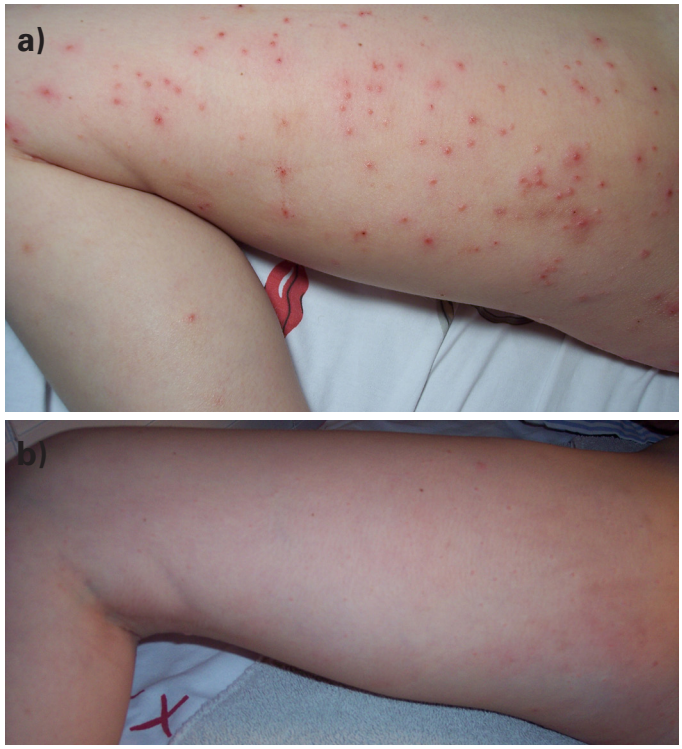
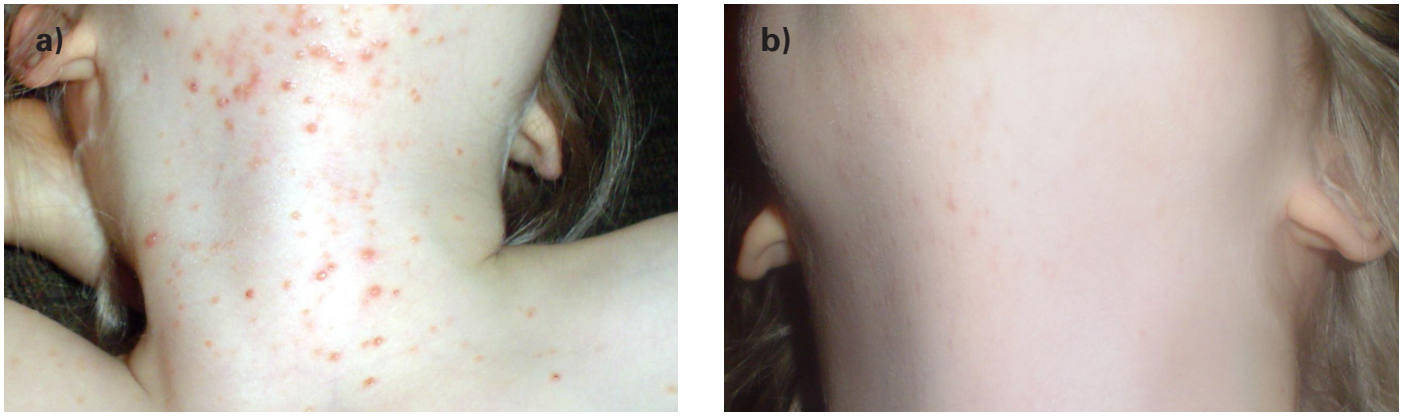


FIGURE 3. Molluscum on the neck of 6-year-old girl at start **a)** and the same girl **b)** after 20 days of treatment with TTO-I.



correlation between the number of lesions present on a child at the beginning of the study and treatment effect.

DISCUSSION

Molluscum contagiosum virus is a cytoplasmically replicating, double stranded DNA virus possessing a complex genome encoding approximately 182 proteins[8] and exhibits genetic heterogeneity with four types, MCV-1 to MCV-4 and their variants.[32,33] In small children, the majority of infections are caused by MCV-1; whereas, in patients infected with HIV, MCV-2 causes the majority (60 %) of infections.[34] The genetic makeup of the MCV in this present study is unknown. Furthermore, it is unclear if genetic heterogeneity contributed to the differential effects observed, with some strains being sensitive to TTO-I application while others were not.

Clinically, MC is frequently seen on the face, neck, axillae, arms, and abdomen but may occur anywhere on the body except the palms and soles.[5,12,19] It occurs predominantly in pre-adolescent children, but also occurs in sexually active adults as an STD,

TABLE 1.

Effect of TTO, TTO-I, and I Alone on Visible MolluscumLesion Number After 30 Days

	Number Enrolled	Children with > 90% Reduction	Mean # Lesions at Study Entry (+sem)	Mean # Lesions at Study Conclusion (+sem)	Lost to F/U
Iodine	16	1	21+29	24+19	2
TTO	18	3	19+23	18+22	2
TTO-I	19	16*^	24+19	3+4*^#	1

*P<0.01 (One Way ANOVA) compared to iodine alone.
^P<0.01 (One Way ANOVA) compared to TTO alone.
#P<0.01 (One Way ANOVA) compared to day 1.

Fifty-three children (mean age 6.3+5.1 yrs) with molluscum contagiosum were enrolled. Treatment consisted of application of one 4 ul drop with a glass applicator rod to each molluscum lesion twice daily. Treatment was continued for 30 days or until all lesions had resolved if this required less than 30 days. Treatment was considered successful if lesions completely cleared or were reduced in number by greater than 90% by the end of day 30. The mean number of lesions at enrollment was 22+19 (mean+sem) and did not differ between treatment groups. At study conclusion, after 30 days of treatment with TTO-I, 2 children had reductions in the number of lesions but did not meet the 90% criterion, 11 had total resolution of all palpable lesions, and 5 had reductions in the number of lesions greater than 90% for a total of 16 of 19 (84.2%) children treated with the TTO-I combination having a 90% or greater reduction in the number of visible molluscum lesions.

participants in sports with skin-to-skin contact, and in those with impaired cellular immunity such as HIV-positive individuals.[19] Onset of lesions caused by MCV is usually gradual, beginning as a group of minute papules in one or two areas. Individual lesions are discrete, smooth, and may be inflamed but more typically appear as characteristic pearly, flesh-colored, dome-shaped papules with central umbilication[12] (see Figure 1). Variation in appearance is common, and the condition may be mistaken for eczema when the lesions are small.

Like its viral relative, variola virus, MCV is specific to humans with no significant animal reservoir,[3] although rare isolated cases have been reported in a kangaroo and a horse.[10] Molluscum contagiosum virus is cytoplasmically replicating and proliferates within the follicular epithelium. Infected cells grow in size, while cellular organelles are dislocated and eventually obliterated by a large intracytoplasmic inclusion. Rupture and discharge of the virus-packed cells occurs, and debris and MCV accumulate in the central crater-like ostium[12] (see Figure 1). Infection is spread by skin-to-skin contact and by autoinoculation. In immunocompetent patients the illness is self-limited and MCV infection generally does not recur,[9] however, MCV exhibits an ability to avoid host immune defenses by a variety of complex mechanisms,[12] and it is not unusual for lesions to persist and spread, sometimes extensively (see Figure 1b). Diagnosis is based on the appearance of the lesions and can be confirmed by skin biopsy.

Iodine has been used for decades as a topical antiseptic. It is used by activated white blood cells as part of the killing mechanism directed against bacteria and viruses,[35,36] and has also been used clinically with limited success by topical application in the treatment of herpes simplex,[37] another virus with a large and complex genome. The U.S. Centers for Disease Control recommends iodine for topical antisepsis against MCV on surfaces,[39] however, since topically applied iodine does not penetrate the stratum corneum well it has little activity against MC when used alone on intact skin. Only very small quantities of iodine are absorbed through an intact skin,[37,38] thus posing little risk of systemic toxicity or effects on thyroid function when topically applied.

TeaTree Oil (essential oil of *Melaleuca alternifolia*; fam. Myrtaceae) is a small paper-barked tree indigenous to swampy regions along the north coast of New South Wales and Queensland, Australia. Leaves of the tree were first used medicinally by the Aborigines, and the tree became known by the common name of "tea tree" when Captain Cook and botanist Joseph Banks, investigating local flora (c. 1770), used the leaves of the tree to brew a spicy tea.[22] Steam distillation of the leaves yields an essential oil that came into use as a folk remedy as settlers colonized the indigenous portions of Australia, and in more modern times has found use in the cosmetic and perfume industries, as well as a food additive. Modern investigation of TTO properties began in 1925 when Penfold[23] extracted the oil and demonstrated antiseptic and anti-bacterial properties. The whole oil exhibits fungicidal activity against skin dermatomycoses[22,30,31] and bactericidal activity against a variety of pathogens including methicillin-resistant *Staphylococcus aureus*.[22,23,25] Known toxicity is low.[40,41,47] Tea tree oil TTO has been associated with skin sensitization, but at an incidence of less than 0.01%.[41]

Hausen et al[42] studied the influence of light, oxygen, and heat on TTO's ability to induce reaction in TTO-sensitive patients. Fifteen normal constituents or degradation products from TTO were patch tested in otherwise healthy volunteers. Fresh TTO was revealed to be a very weak sensitizing material whereas oxidized TTO was three times stronger. Oxidation and photodegradation of alpha-terpinene in the oil resulted in dramatic increases in the chief sensitizing agent, p-cymene. The authors conclude that the degradation products were the principal sensitizers, and proper handling and storage of the oil were able to minimize this effect.

MCV has not been successfully cultured, hampering in vitro studies. A few reports of antiviral activity of TTO have been reported.[43-45] Tea tree oil added at non-cytotoxic concentrations (0.003%) to African Green Monkey Kidney (RC-37) cell cultures inhibited propagation of Herpes Simplex Virus (HSV-I) by over 98% in a viral plaque reduction assay,[43] demonstrating strong inhibition of a complex enveloped virus in vitro. The authors conclude that free virus appeared to be very sensitive to the antiviral effects of TTO. The reduced infectivity of virus after incubation with TTO suggests that TTO may bind to virion envelope structures or may mask viral components necessary for adsorption or entry into host cells, but the exact mechanism is not known. It is unclear if these findings in culture relate in part or at all to the mechanism of action in this present clinical study. A clinical report of topical TTO against common hand warts caused by HPV has also appeared.[45]

The speed of action of TTO-I and a lack of generalized inflammation associated with its use suggested that the mixture was not acting as a generalized immune stimulant (e.g., Aldara), but rather may act more directly to inhibit viral propagation in some manner as discussed above. Furthermore, the apparent lack of a generalized toxicity to the skin in this study suggests that TTO-I was not acting by means of non-specific tissue destruction. The skin permeation effects of TTO are fairly limited,[48,49] however, there are components with significant lipophillicity.[46] The mechanism underlying the synergy between TTO and iodine demonstrated in this study is unclear. It may relate to enhanced penetration of iodine into superficial layers of skin by the TTO or some other as yet unidentified interaction.

The results of this study suggest that tea tree oil and organically bound iodine in combination are efficacious and safe in the topical treatment of MC in children.

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DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

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