Verrucae are small, benign, highly vascular epithelial neoplasms that occur singly or in a multiple presentation. Plantar verrucae are usually caused by infection with human papillomavirus types 1, 2, and 4. A clinical trial was conducted to assess the safety and efficacy of monochloroacetic acid and 10% formaldehyde versus 10% formaldehyde alone in the treatment of simple plantar verrucae. Of 57 patients enrolled in the study, 26 were in the monochloroacetic acid and 10% formaldehyde group and 31 were in the 10% formaldehyde alone group. The overall cure rate for this population was 61.4%. There was no statistically significant difference in the cure rate between treatment groups. (J Am Podiatr Med Assoc 96(1): 53-58, 2006)
other means whereby viral particles are either picked up or lie dormant and then are transported to the deeper cutaneous layers.7 The shoe environment (dark and often moist) allows the virus to survive.

The diagnosis is usually made clinically. The clinical signs include divergent skin lines, multiple small dark spots, and hyperkeratosis. After trimming, one sees multiple capillary tips perpendicular to the lesion’s surface. When deeply trimmed, the capillary tips will bleed. The differential diagnosis includes lichen planus, acrokeratitis verruciformis, epidermolytic hyperkeratosis, acrochordons, clavi or callus-lichen planus, acrokeratosis verruciformis, epithelium that could easily be scraped. In 1961, Vickers22 conducted a survey of 646 children that showed that 10% formaldehyde foot soaks for 15 to 20 min per night for 6 to 8 weeks cured 80% of all plantar warts up to 1 cm in diameter. Formaldehyde is thought to act as a skin sensitizer, and the irritant effect of the aldehyde causes the body to react in a manner similar to that seen in contact allergic dermatitis.33, 34 Formaldehyde-releasing preservatives are well-known allergens found in many topical preparations, including medication.33 More than 22% of 280 health-care workers with skin lesions were diagnosed as having an allergy to aldehydes, and most of the reactions were to formaldehyde.34 In vivo experiments have shown formaldehyde to have significantly higher eosinophil and basophil counts in sensitized guinea pigs.34

The original formulations of monochloroacetic acid and 10% formaldehyde used in the 1976 study by Dagnall20 and the 1943 study by Thompson,31 respectively, are no longer available. The current delivery systems for monochloroacetic acid (Monocete EZ Swabs; Pedinol Pharmacal Inc, Farmingdale, New York) and 10% formaldehyde (Lazerformalyde Solution; Pedinol Pharmacal Inc) have never been investigated. Therefore, the purpose of this clinical trial was to assess the safety and efficacy of monochloroacetic acid (Monocete EZ Swabs) and 10% formaldehyde (Lazerformalyde Solution) versus 10% formaldehyde (Lazerformalyde Solution) alone for the treatment of simple plantar verrucae.

### Materials and Methods

Assuming that the cure rate for the treatment group is 90%, a sample size of 60 (30 patients per arm) will give 80% power to detect a difference between groups of 35 percentage points using the \( \chi^2 \) test for proportions with 1 df. Patients were included in the study if they were older than 10 years but younger than 65 years and had simple, solitary plantar verrucae 5 mm in diameter or smaller. Patients were excluded if they were younger than 10 years or older than 65 years; had peripheral vascular disease; had used an over-the-counter acid preparation for wart removal.
in the past 2 weeks; had other dermatologic conditions, such as malignant melanoma, psoriasis, lichen planus, or mosaic verrucae; were unable or unwilling to apply the medication at home; or were unable or unwilling to sign an informed consent form (if >17 years of age) or an assent form (if ≤17 years of age).

The protocol and the informed consent forms (adult and child) were approved by the institutional review board of the New York College of Podiatric Medicine. At the baseline visit, after fulfilling the inclusion/exclusion criteria and completing the history and physical forms, the patient signed the written informed consent form. If the patient was a child (≤17 years old), the parent signed the informed consent form and the child signed the assent form. The history and physical forms included information on the history of the verrucae along with any previous treatment, with a concomitant medication form used as needed. Clinical assessments, including a visual analog scale for pain, were performed at all visits. A photograph was taken. The wart was debrided, and instructions on applying 10% formaldehyde treatment were given.

The patient returned in 2 weeks for visit 1 for clinical assessment and wart debridement. The patient returned in another 2 weeks for visit 2 (4 weeks of pretreatment with 10% formaldehyde). The wart was debrided, and a patch (swab with either the active monochloroacetic acid or dummy) treatment was applied by the investigator. An aperture pad was then applied. Patient instructions included leaving the aperture pad on for 48 hours, not getting the area wet, and then removing the aperture pad. The instructions were then to apply the 10% formaldehyde to the area once a day. Visit 3 (6 weeks of therapy), visit 4 (8 weeks of therapy), visit 5 (10 weeks of therapy), and visit 6 (12 weeks of therapy) included debridement (if necessary), acid/dummy treatment with aperture pad and 10% formaldehyde treatment (if necessary), patient education, and dispensing of both verrucae medicine and the rescue pain drug. A photograph was taken and a clinical examination performed at all of the visits. Compliance was measured by weighing the 10% formaldehyde (roll-on medication). An adverse-event form was completed, if necessary, at any visit before visit 6. All adverse-event forms were completed by the end of visit 6. After 12 weeks of therapy, a final summary assessed the treatment as cured, failed, or noncompliant (Table 1).16

**Results**

Of 57 patients entered into the study, 26 were in the treatment group and 31 were in the control group. Table 2 shows the demographics of the study population (age, sex, and race). Each patient was scheduled for seven visits (one baseline visit and six follow-up visits). Patients who were cured before the end of the study were not asked to attend subsequent follow-up visits. The average number of follow-up visits per patient was 5.1 (4.6 for the treatment group and 5.6 for the controls). Eleven patients were lost to follow-up and were considered to be noncompliers. Excluding noncompliers and patients who were not cured, the average number of follow-up visits was 3.8 for the treatment group and 4.8 for the control group.

Table 3 shows mean wart size by visit in the treatment and control groups. Regression analysis was used to determine whether treatment group was a predictor of wart size; because of attrition in the later

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**Table 1. Final Assessment of Treatment**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured*</td>
<td>Complete restoration of the skin lines in the area of the wart on examination with a magnifying glass</td>
</tr>
<tr>
<td>Failed</td>
<td>Complications or persistent pain; persistent clinical signs of warts</td>
</tr>
<tr>
<td>Noncompliant</td>
<td>Patient failed to attend follow-up visits</td>
</tr>
</tbody>
</table>

*If the patient was cured before the end of the study, he or she was evaluated at the end of the treatment visit.

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**Table 2. Demographic Characteristics of the Study Population**

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group (N = 26)</th>
<th>Control Group (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean [SD]) (years)</td>
<td>37.6 (20.6)</td>
<td>35.6 (19.4)</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>46.2</td>
<td>58.1</td>
</tr>
<tr>
<td>White race (%)</td>
<td>88.0</td>
<td>83.9</td>
</tr>
</tbody>
</table>

**Table 3. Wart Size by Visit in the Treatment and Control Groups**

<table>
<thead>
<tr>
<th></th>
<th>Wart Size (mean) (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment Group</td>
</tr>
<tr>
<td>Baseline</td>
<td>4.0</td>
</tr>
<tr>
<td>Visit 1</td>
<td>2.3</td>
</tr>
<tr>
<td>Visit 2</td>
<td>2.3</td>
</tr>
<tr>
<td>Visit 3</td>
<td>1.8</td>
</tr>
<tr>
<td>Visit 4</td>
<td>1.7</td>
</tr>
<tr>
<td>Visit 5</td>
<td>1.9</td>
</tr>
<tr>
<td>Visit 6</td>
<td>1.3</td>
</tr>
</tbody>
</table>
weeks, visit 3 was used controlling for baseline; no statistically significant difference was found ($P = .69$).

Tenderness was assessed at baseline and at each follow-up visit by the patient and the physician. Of 202 joint assessments, physicians and patients agreed on tenderness 277 times, for a concordance rate of 94.9%. Physicians and patients disagreed only 15 times on assessment of tenderness. The proportion of tenderness assessments with a zero score, ie, absence of tenderness, rose in the treatment group from 30% at baseline to 100% at visit 6; in the control group, the proportions at baseline and at visit 6 were 35% and 100%, respectively. The proportion of zero scores for tenderness by visit is shown in Figure 1.

In the treatment group, the proportion of zero scores on the visual analog scale rose from 27% at baseline to 100% at the last follow-up visit. In the control group, the proportion of zero scores at baseline and last follow-up were 22% and 100%, respectively. Figure 2 shows the percentage of zero scores in the treatment and control groups across time.

The overall cure rate for this population was 61.4%. The cure rate for the treatment group (65.4%) exceeded that of the control group (58.1%), but this difference did not attain statistical significance ($\chi^2_1 = 0.32; P = .57$). The overall cure rate of 61.4% includes all 57 patients enrolled at the baseline visit. These patients (26 in the treatment group and 31 in the control group), from a statistical standpoint, are known as the “intent-to-treat” group and are included in the final statistical analysis that produces the overall cure rate of 61.4%. When excluding the 11 patients in the intent-to-treat group who were lost to follow-up and considered to be noncompliers, the cure rate changes. Excluding patients who were not assessed at visit 1 (the first follow-up visit) and were lost to follow-up, the cure rates were 76.5% and 75.9% for the treatment and control groups, respectively.

In the treatment group, 50% of the patients were cured by week 10, compared with 38.7% in the control group (10% formaldehyde only). This difference did not attain statistical significance ($\chi^2_1 = 0.73; P = .39$). Time to cure (in weeks) for the treatment and control groups is shown in Figure 3 using the Kaplan-Meier estimate (likelihood ratio test $P = .32$).

During the trial, one patient had an allergic reaction to the medication and one patient developed a skin infection. Both patients were treated conservatively with appropriate medication and completely recovered.

Figure 4 shows a patient randomized to the control group before and after 8 weeks of treatment with 10% formaldehyde alone. Figure 5 shows a patient...
randomized to the treatment group before and after 4 weeks of treatment with 10% formaldehyde alone and 6 weeks of treatment with monochloroacetic acid and 10% formaldehyde.

Discussion

Verrucae are small, benign, highly vascular epithelial neoplasms that occur singly or in a multiple presentation. Various therapies are currently available to treat verrucae, including chemical techniques, surgical procedures, immunotherapy, and other modalities (such as cryotherapy and antimetabolite injections). The purpose of this clinical trial was to assess the safety and efficacy of currently available delivery systems of monochloroacetic acid and 10% formaldehyde versus 10% formaldehyde alone for the treatment of simple plantar verrucae. All 57 enrolled patients were pretreated with 4 weeks of 10% formaldehyde and then were randomized to either the treatment...
group, with up to five applications of monochloroacetic acid every other week plus 10% formaldehyde, or the control group, continuing with 10% formaldehyde treatment for up to 12 weeks. The overall cure rate for this population was 61.4%. The cure rate for the 10% formaldehyde and monochloroacetic acid group (65.4%) exceeded that of the 10% formaldehyde alone group (58.1%), but this difference did not attain statistical significance. The cure rate changes when intent-to-treat patients who were noncompliant and not assessed at the initial follow-up visit are excluded from the analysis. When excluding patients lost to follow-up, the cure rates were 76.5% and 75.9% for the treatment and control groups, respectively.

The results of this clinical trial suggest that 10% formaldehyde is a safe and efficacious therapy for the treatment of simple plantar verrucae. Podiatric physicians are fully aware of the difficulty in treating verrucae. The current modalities can be time-consuming and frustrating for the physician, the patient, and the parents. The podiatric physician can now consider adding 10% formaldehyde as a single therapy or in conjunction with other known therapies for the treatment of simple plantar verrucae.

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References