Venous ulcers affect approximately 1% of the world’s population, increasing health care expenditures and decreasing quality of life. Several hypotheses may help explain their origin. Insufficient veins or valves (dysfunctional valves in the veins that allow backward blood recirculation due to incomplete valve closure) or impaired muscle function may lead to abnormal calf muscle pump function that can elevate ambulatory venous pressure. The aim of this study was to evaluate the efficacy of pentoxifylline in treating chronic venous ulcers.

Methods. From May 2009 to March 2010, 40 patients with chronic venous ulcers were randomly assigned to 2 groups: a standard treatment group that received compression therapy or an intervention group that received oral pentoxifylline (400 mg, 3 times daily) in addition to compression therapy. Time duration of wound healing, edema, pain, and ulcer size in the 2 groups were studied. For all tests, \( P < 0.05 \) was considered significant.

Results. The median duration of complete wound healing was 4 months in the intervention group and 6.25 months in the standard treatment group (\( P = 0.007 \)). Recovery from pain and edema was not statistically significant after 3 months’ follow-up in either group. After 3 months of treatment, ulcer size decreased more in the intervention group compared to the standard treatment group (\( P = 0.02 \)). Pentoxifylline in association with compression therapy decreases both time to complete wound healing and ulcer size.

Venous ulcers affect approximately 1% of the world’s population, increasing health care expenditures and decreasing quality of life. Several hypotheses may help explain their origin. Insufficient veins or valves (dysfunctional valves in the veins that allow backward blood recirculation due to incomplete valve closure) or impaired muscle function may lead to abnormal calf muscle pump function that can elevate ambulatory venous pressure (venous hypertension). This hypertension subsequently results in local venous dilatation and pooling, concomitantly trapping leukocytes that may release proteolytic enzymes that destroy tissue. Venous pooling also induces interendothelial pore widening and deposition of fibrin and other macromolecules that trap growth factors within them, rendering them unavailable for wound repair. Compression therapy,
the mainstay treatment, reduces edema, reverses venous hypertension, and improves calf muscle pump function. Several treatment options can be employed as adjuvants to compression, such as systemic therapy with pentoxifylline or aspirin, autologous grafts, tissue-engineered skin, growth factor therapy, and/or vein surgery.\textsuperscript{5}

Pentoxifylline is a xanthine derivative used in the treatment of peripheral vascular disease.\textsuperscript{6–8} Although it is often classified as a vasodilator, pentoxifylline’s primary action reduces blood viscosity, probably due to its effect on erythrocyte deformability, platelet adhesion, and aggregation.\textsuperscript{8–11} Pentoxifylline also inhibits production of cytokine tumor necrosis factor alpha (TNF-\(\alpha\)), a property currently under investigation in a number of diseases. The most common adverse effects are nausea, gastrointestinal disturbances, dizziness, and headache. Studies suggest that pentoxifylline may be effective in increasing the healing rate of chronic venous ulcers with or without compression therapy but at a higher dose than is used for treating claudication (400 mg, 3 times daily).\textsuperscript{12} In the present study, the authors evaluated the effect of pentoxifylline on the time to complete healing of chronic venous ulcers.

\textbf{Methods}

\textbf{Patients.} From May 2009 to March 2010, 40 patients diagnosed with chronic venous ulcers in the vascular clinic of Shahid Rajaii Hospital (Qazvin, Iran) were enrolled in this study after obtaining informed consent. Twenty patients were randomly allocated to compression therapy (standard group) and 20 to pentoxifylline with compression therapy (intervention group). Randomization was performed by means of sealed opaque envelopes containing computer-generated random numbers. The standard treatment group received only compression therapy and the intervention group received oral pentoxifylline (400 mg, 3 times daily) in addition to compression therapy. Mean age of patients was 37.5 ± 8.5 years in the intervention group and 36.9 ± 11 years in the standard treatment group. The exclusion criterion was arterial insufficiency that was ruled out by Doppler ultrasound imaging.

\textbf{Data collection and variable definition.} Pain was assessed by a numerical rating scale in which the patient was instructed to choose a number from 0 (no pain) to 20 (unbearable pain) that best described their current pain.\textsuperscript{13} To assess leg edema,\textsuperscript{14} the examiner pressed his fingertip against a bony prominence for 5 seconds, and then removed it. A residual indentation indicated pitting edema, which was graded on a scale of 1 (mild) to 4 (severe). Questionnaires were used to collect data. Patient’s pain, edema, and ulcer size were recorded at their first clinic visit, as well as 1 and 3 months after treatment. Patients were instructed to refer to the vascular clinic monthly, and time duration of complete wound healing was recorded.

\textbf{Statistical Analysis}

Student’s \(t\)-test, chi-square, or Fisher’s exact test were used, where appropriate, for comparing clinical data between the 2 groups. \(P \leq 0.05\) was considered significant for all tests. All values were expressed as mean ± SD and were analyzed with SPSS 11.0 software.

\textbf{Results}

Mean time to complete wound healing in the intervention and standard treatment groups was 4 (SD 1.29) and 6 (SD 3.1) months, respectively (\(P = 0.007;\) Table 1), and was statistically significant. At 3 months’ follow-up, edema had subsided in 75% of patients in the intervention group and in 50% of patients in the standard treatment group.
tion group and in 50% of patients in the standard treatment group. Although the differences never reached statistical significance, recovery from edema was better in the pentoxifylline (intervention) group. Mean degree of pain at first clinic visit, 1 month, and 3 months after treatment was 14 (SD 3.5), 11 (SD 3.5), and 9 (SD 3.6), respectively, in the intervention group and 12 (SD 4.0), 9 (SD 4.8), and 8 (SD 5.8), respectively, in the standard group. Although mean degree of pain decreased more in the intervention group, it was not statistically significant (Table 2). Additionally, the mean ulcer size at the first clinic visit, 1 month, and 3 months after treatment was 8.69 (SD 3.72), 5.30 (SD 3.03), and 1.41 (SD 1.77), respectively, in the intervention group and 8.66 (SD 4.71), 6.15 (SD 4.30), and 3.78 (SD 3.78), respectively, in the standard treatment group, which was statistically significant ($P = 0.02$; Table 3).

**Discussion**

Treating venous ulcers represents a therapeutic challenge, the immediate goal of which is to restore epithelium. Compression dressings (bandages) are the mainstay treatment for chronic venous ulcers. The goal of compression is to increase venous ulcer healing by

### Table 1. Mean duration of complete wound healing.

<table>
<thead>
<tr>
<th>SD</th>
<th>Mean (month)</th>
<th>n</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.298</td>
<td>4.00</td>
<td>20</td>
<td>Intervention</td>
</tr>
<tr>
<td>3.143</td>
<td>6.25</td>
<td>20</td>
<td>Standard treatment</td>
</tr>
</tbody>
</table>

$P = 0.007$ (t-test)

### Table 2. Changes in pain after 3-month follow-up.

<table>
<thead>
<tr>
<th>Mean ± SD</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5.3 ± 2.7</td>
<td>Intervention</td>
</tr>
<tr>
<td>-3.9 ± 3.4</td>
<td>Standard treatment</td>
</tr>
</tbody>
</table>

$P = 0.16$ (t-test)

### Table 3. Changes in mean ulcer size.

<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
<th>n</th>
<th>Mean (cm²)</th>
<th>SD</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>Intervention</td>
<td>20</td>
<td>8.69</td>
<td>3.72</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>Standard treatment</td>
<td>20</td>
<td>8.66</td>
<td>4.71</td>
<td></td>
</tr>
<tr>
<td>1 month after</td>
<td>Intervention</td>
<td>20</td>
<td>5.30</td>
<td>3.03</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>Standard treatment</td>
<td>20</td>
<td>6.15</td>
<td>4.30</td>
<td></td>
</tr>
<tr>
<td>3 months after</td>
<td>Intervention</td>
<td>20</td>
<td>1.41</td>
<td>1.77</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Standard treatment</td>
<td>20</td>
<td>3.78</td>
<td>3.78</td>
<td></td>
</tr>
</tbody>
</table>

$t$ test
improving venous return and reducing edema of the lower extremities. Several systemic adjunctive treatments may be used in conjunction with compression therapy. Pentoxifylline has been shown to decrease white blood cell adhesion and activity, blood viscosity, platelet aggregation, and pro-coagulation and to increase fibrinolytic activity. Pentoxifylline is metabolized in liver and red blood cells to 7 active metabolites. Studies suggest it may be effective in treating venous ulcers. When pentoxifylline plus compression was compared to placebo plus compression therapy healing rates were 64% and 34%, respectively.

The results of the present study show that pentoxifylline plus compression therapy decreases the time to complete wound healing. In a 6-month randomized, placebo-controlled trial comparing pentoxifylline (400 mg, 3 times daily) with compression to placebo with compression in 172 patients, found that patients treated with pentoxifylline showed significantly greater healing (67% versus 30.7%, P <0.05).

Perhaps the fibrinolytic effect of pentoxifylline affects the pericapillary fibrin cuff and subsequently increases the healing rate of chronic venous ulcers. Further investigation is needed to determine the true mechanisms with which pentoxifylline acts on venous ulcers.

References