Nonhealing ischemic ulcers are a common problem in the lower extremity. The etiology of nonhealing ulcers in the lower extremity is multifactorial, but systemic causes, such as diabetes mellitus and peripheral vascular disease, are commonly involved. Many treatment modalities have been attempted to heal these types of wounds. Invasive procedures, such as arterial bypasses, muscle flaps, and skin grafts, have been used with some success. However, noninvasive treatment modalities are severely limited. Further investigation is needed to explore noninvasive treatment options that could decrease the number of ischemic ulcers that lead to amputation.

Nitric oxide is an endogenous gas released by endothelial cells that induces vasodilatation and plays other important roles in the wound-healing process. Nitroglycerin preparations are liberators of nitric oxide. Podiatric physicians have used nitroglycerin paste and patches on patients in an attempt to increase perfusion to the foot. However, the drug’s efficacy seems to be largely anecdotal. A prospective, randomized, placebo-controlled, double-blind study was conducted to investigate the efficacy of a nitroglycerin patch in locally increasing perfusion to the foot. Twenty-two healthy subjects were randomly assigned to either a drug group (nitroglycerin patch, 0.2 mg/h) or a placebo group (adhesive patch without active ingredient). The patch was applied to the plantar arch of the foot. Objective and subjective measures were then used to detect changes in perfusion to the foot after a 2-hour experimental period. The objective measures, cutaneous thermometry and photoplethysmography, found no significant measurable difference in perfusion to the foot between the drug and placebo groups (P > .05). A subjective questionnaire used to assess changes in temperature or sensation detected by the subject yielded similar results. Thus a nitroglycerin patch dose of 0.2 mg/h showed no measurable ability to increase perfusion to the foot. Further research is needed to validate the indications for this therapy. (J Am Podiatr Med Assoc 96(4): 318–322, 2006)

Effect of a Nitroglycerin Patch on Perfusion to the Foot in Healthy Subjects

Paul Jeong Kim, DPM*
L. Clay Ballinger, DPM†
Donald Kushner, DPM‡

Nitric oxide is an endogenous gas released by endothelial cells that induces vasodilatation and plays other important roles in the wound-healing process. Nitroglycerin preparations are liberators of nitric oxide. Podiatric physicians have used nitroglycerin paste and patches on patients in an attempt to increase perfusion to the foot. However, the drug’s efficacy seems to be largely anecdotal. A prospective, randomized, placebo-controlled, double-blind study was conducted to investigate the efficacy of a nitroglycerin patch in locally increasing perfusion to the foot. Twenty-two healthy subjects were randomly assigned to either a drug group (nitroglycerin patch, 0.2 mg/h) or a placebo group (adhesive patch without active ingredient). The patch was applied to the plantar arch of the foot. Objective and subjective measures were then used to detect changes in perfusion to the foot after a 2-hour experimental period. The objective measures, cutaneous thermometry and photoplethysmography, found no significant measurable difference in perfusion to the foot between the drug and placebo groups (P > .05). A subjective questionnaire used to assess changes in temperature or sensation detected by the subject yielded similar results. Thus a nitroglycerin patch dose of 0.2 mg/h showed no measurable ability to increase perfusion to the foot. Further research is needed to validate the indications for this therapy. (J Am Podiatr Med Assoc 96(4): 318–322, 2006)
tremities. A study by Yuen et al\textsuperscript{11} demonstrated a significant decrease in pain experienced by patients with diabetic peripheral neuropathy. Nitroglycerin has also been used for the topical treatment of ischemic processes (eg, Raynaud’s phenomenon) in upper- and lower-extremity digits.\textsuperscript{12-14} Nitroglycerin paste has long been used by podiatric physicians in the lower extremity. Anecdotal evidence has suggested its use for increasing perfusion to the lower extremity. However, limited research supports the use of nitroglycerin for this purpose. A study by Francis et al\textsuperscript{15} demonstrated an increase in perfusion in the lower extremity with topically applied nitroglycerin paste. Jones et al\textsuperscript{16} presented two clinical cases showing good success using nitroglycerin ointment for the treatment of pressure ulcers. The clinical application of nitric oxide through various delivery systems would have great relevance in the treatment of diabetic wounds in the lower extremity.

This prospective, double-blind, randomized, placebo-controlled study investigated whether nitroglycerin can induce measurable increases in perfusion to the foot in healthy subjects. To our knowledge, no study has thoroughly examined the clinical efficacy of the application of nitroglycerin patches in the foot. A logical first step in the investigation is to measure, objectively and subjectively, the effects of nitroglycerin in healthy subjects. We decided to use a transdermal nitroglycerin patch (Minitran [Nitroglycerin] Transdermal Delivery System; 3M Pharmaceuticals, St Paul, Minnesota). We believe that a transdermal nitroglycerin patch is superior to nitroglycerin paste in many ways.\textsuperscript{17, 18} First, the patch can deliver a known amount of the drug in a given period. Second, the patch comes in standardized doses, which allows for more accurate dosing schedules. Third, the patient is less likely to have difficulty applying the patch than in using the paste. Furthermore, the 0.2-mg/h dose was chosen because there are no reported antianginal effects at this dose (G Gabangerter, 3M Pharmaceuticals, oral communication, July 1999). We desired a dose that would have limited systemic effects, thereby alleviating fears of drug effects on the heart and coronary vessels. Objective and subjective measures were used to detect any changes in peripheral circulation to the foot. The objective measures included cutaneous thermometry and photoplethysmography.\textsuperscript{19,23} A subjective questionnaire was also used to assess any changes in temperature or sensation detected by the subject.

Methods

Before the onset of this study, the rationale, the methods, and the participation of human subjects were approved by the Ohio College of Podiatric Medicine Institutional Review Board/Research Committee. Twenty-two healthy podiatric medical students (15 men and 7 women) were paid to participate in the study. Their ages ranged from 23 to 33 years. The subjects were demographically further divided into 11 whites, 7 blacks, and 4 Asian Americans. Subjects were randomly assigned to either the placebo group (n = 11) or the drug group (n = 11) using the Microsoft Excel “Random Number Generator” (Microsoft Corp, Redmond, Washington). The placebo patch was constructed of adhesive material with dimensions similar to those of the transdermal nitroglycerin patch. The subjects were rotated through three stations. At station 1, the subjects were asked to take off their shoes and socks. Either the placebo or the drug patch was applied proximal to the navicular tuberosity on the right foot. A stockinette was used to cover both feet, with a segment of the stockinette overhanging the toes distally, and the stockinette was pulled over the ankle proximally. The stockinette served two functions. First, it prevented the subjects and the experimenters responsible for taking measurements from seeing whether the subjects had been assigned to the drug or placebo group. The second intended function of the stockinette was to shield the foot from ambient temperature changes.

At station 2, the hallux was exposed to allow for transcutaneous temperature measurement. The temperature was taken at the plantar distal aspect of the hallux using an infrared thermographic scanner (DermaTemp; Exergen Corp, Boston, Massachusetts). At station 3, pulsatile blood flow at the hallux was measured using a photoplethysmograph. All measurements were taken bilaterally. The subjects were then seated for 2 hours with their legs elevated horizontally to the ground. After 2 hours, the subjects were asked to complete a questionnaire describing any subjective sensations they had experienced. The subjects were asked to describe the sensation in the right and left feet (increased sensitivity, loss of sensation, nonspecific abnormal sensation, or no change in sensation), any change in temperature in the right and left feet (increase in temperature, no change in temperature, or decrease in temperature), and any systemic effects (lightheadedness, dizziness, headache, nausea, or other). The patches were removed at station 1, and measurements were again taken at stations 2 and 3.

Every attempt was made to conduct a “double-blind” study. The subjects did not know to which group they had been assigned. The experimenters who applied the patch did not take any measurements. The experimenters who took the perfusion measure-
ments did not know whether the subjects belonged to the drug or the placebo group.

The photoplethysmograph was used to measure changes in the degree of pulsatile flow to the distal aspect of the hallux. This blood flow is represented as a trace on a continuous strip of paper. The average increase in amplitude (measured in millimeters) for three consecutive positive inflections was used as the photoplethysmograph measurement. The temperature readings were read in degrees Fahrenheit. Preexperimental measurements were taken before the application, and postexperimental measurements were taken after the 2-hour period.

Results

Subjective Questionnaire

The results of the subjective questionnaire are as follows. Three subjects (two in the drug group and one in the placebo group) reported increased sensitivity in the right foot, two (both in the placebo group) reported nonspecific abnormal sensations in the right foot, and two (both in the drug group) reported increases in sensitivity in the left foot. Subjects with increased sensitivity or nonspecific abnormal sensation in the right foot were not the same subjects who reported increased sensitivity in the left foot. Five subjects (four in the drug group and one in the placebo group) reported an increase in temperature in the right foot, two (both in the drug group) reported increases in temperature in the left foot, and one (in the placebo group) experienced an increase in temperature in both feet and lightheadedness. One subject (in the drug group) reported “slight tingling in the right foot,” and one (in the drug group) reported an “intermittent tingling sensation in the right foot.” Overall, 6 of 11 subjects in the drug group and 3 of 11 subjects in the placebo group reported a change in sensation or temperature. No subjects reported bilateral sensation changes, and only one (in the drug group) reported bilateral temperature changes. Three subjects (two in the drug group and one in the placebo group) reported both sensation and temperature changes in the right foot.

Photoplethysmography

Average (SD) amplitudes were as follows: right foot of the drug group preexperimentally, 6.9 (6.3) mm; right foot of the drug group postexperimentally, 4.4 (3.4) mm; left foot of the drug group preexperimentally, 7.1 (6.8) mm; left foot of the drug group postexperimentally, 4.6 (5.4) mm; right foot of the placebo group preexperimentally, 4.9 (3.9) mm; right foot of the placebo group postexperimentally, 2.6 (1.0) mm; left foot of the placebo group preexperimentally, 4.9 (3.4) mm; and left foot of the placebo group postexperimentally, 2.5 (1.3) mm. A t-test revealed a significant difference between the preexperimental and postexperimental measurements for the drug group in the right foot (P = .068). There was also no significant difference in the right foot between the drug and placebo groups postexperimentally (P = .071) or in the drug group between the right and left feet postexperimentally (P = .390).

Discussion

According to the questionnaire, it seems that several subjects in both groups experienced changes in sensation and temperature in their feet. There were almost an equal number of subjects reporting sensation changes in the right foot in both groups. However, there were, however, more reported increases in temperature in the drug group. The only likely explanation for the placebo group reporting sensation and temperature changes is a psychological effect. Before the onset of the experiment, the potential positive effects and adverse effects, including sensation changes and increases in foot temperature, were disclosed. Because the subjects did not know which treatment group they were assigned to, they may have assumed that they were in the drug group. Numerous subjects at the completion of the experiment inquired about which
group they had been assigned to, and most assumed that they had been assigned to the drug group. It is possible that any subjective changes experienced by the drug group could also be attributed to a psychological effect. Differentiating between a psychological effect and a drug effect is extremely difficult and is beyond the scope of this study.

We recognize that there are inherent problems with the use of questionnaires. The subjective nature of questionnaires with their multiple variables makes interpretation difficult. However, taken together, there were more reports of subjective changes in the drug group than in the placebo group. Another interesting finding was that there were no reports of systemic effects in the drug group, whereas one subject in the placebo group reported lightheadedness. This is important in light of the fact that we believe that the 0.2-mg/h dose should not induce any systemic effects.

There was a decrease in temperatures in both feet in both groups postexperimentally, perhaps because the subjects were wearing their shoes and socks just before the preexperimental measurement; hence their feet would have been warmer at this point. It seems that the stockinettes could not maintain the same foot temperature throughout the experimental period. Furthermore, the subjects would have been more active before the experimental period, causing more blood to be pooled into the extremities, whereas the postexperimental measurements were taken after 2 hours of being sedentary. Because there was an overall cooling, it is difficult to comment on whether any actual change in temperature was induced by the drug. Statistically, there was no increase in temperature from the preexperimental point compared with the postexperimental point in the drug group bilaterally. Furthermore, there was no difference between the postexperimental drug and placebo groups. However, if the individual numbers are evaluated, an interesting trend is observed. On examination of the raw data, 5 of 11 subjects in the drug group actually had a measurable increase in temperature bilaterally. For the left foot, the average increase in temperature was 2.76° F (range, 1.1°–5.4° F). For the right foot, the average increase in temperature was 3.14° F (range, 0.8°–6.1° F). The bilateral increase in temperature suggests either that there was actually a systemic drug effect or that the subjects experienced an overall increase in body temperature during the experimental period independent of the drug. Three subjects in the placebo group also had a measurable average increase in temperature of 1.0° F (range, 0.8°–1.3° F). Only one of these subjects reported a bilateral increase in temperature. Taking these data into account, it seems that for subjects who experienced an increase in temperature, those in the drug group had a greater increase in temperature than those in the placebo group. It is also interesting to note that only one of the five subjects who subjectively reported an increase in temperature actually had a measurable increase in temperature. This subject was in the drug group.

The photoplethysmograph data displayed an overall decrease in amplitude for the drug and placebo groups bilaterally. Again, this could have been attributed to the subjects being sedentary for 2 hours before the final measurement was taken. Furthermore, the ambient room temperature may have influenced the measurement. It can be argued that the drug could not counteract the vasoconstriction of the vessels in the foot caused by the colder ambient temperature compared with the temperature of the foot in a shoe. The ambient temperature did not change appreciably during the experimental period. However, if the ambient temperature did have an influence, then we would not have seen an increase in temperature in five subjects. Three subjects in the drug group actually had increases in amplitude. However, these were small increases and were not bilateral. Interestingly, two of the three subjects were the same subjects who had measurable increases in temperature.

There was no statistically significant increase in perfusion, as measured by means of transcutaneous thermometry or photoplethysmography, in the drug group compared with the placebo group. The overall decreases in temperature and amplitude postexperimentally make interpretation difficult but suggest that environmental factors, specifically ambient temperature, may have played a role in the results. This role may have been so great that it obscured the measurable effects of nitroglycerin. By increasing the dose of nitroglycerin, the influence of ambient temperatures may be counteracted.

Although certain trends were discussed in the previous section, nothing truly indicates that nitroglycerin had any effect on locally vasodilating vessels. Furthermore, looking at the temperature data alone, it seems that if an effect was seen, it would be a systemic effect because it was seen in both feet. This would contradict our supposition that nitroglycerin is a “local” vasodilator. An argument can be made that there is no truly “locally” acting drug. Topical drugs rely on diffusion through the skin to have their effect. It is logical to conclude that a portion of the drug will be dispersed systemically through the capillary system, the venous system, and, eventually, the arterial system. Hence it is possible that the effect was diffused systemically, with little to no effect seen locally. Furthermore, limited systemic effects should be ex-
pected and should not be the primary reason to limit the use of a higher dose of nitroglycerin in the lower extremity. It is possible that at a dose of 0.2 mg/h, we have not reached the threshold necessary to measure an effect locally. If this threshold could be reached using a higher dose, we believe that we would see overall increases in temperature and amplitude for the drug group. We believe that the nitroglycerin patch, at a dose of 0.2 mg/h, had an effect on the vasculature to the foot. However, we believe that the effect was too minimal to be measured. Hence the logical next step in evaluating the potential use of nitroglycerin patches in increasing perfusion to the lower extremity is to examine a higher dose of the drug.

Conclusion

Nonhealing wounds have devastating consequences in the lives of patients and their families. Many ulcerations without early intervention progress to amputation. We believe that more research needs to be conducted in the field of wound care. Also, exploration of new treatment options should be supported. We believe that early intervention using noninvasive treatment modalities may reduce overall morbidity and mortality in patients with ischemic and neuropathic ulcerations.

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References