

# Thrombolytic Therapy Saves Frostbitten Limbs

BY MIRIAM E. TUCKER  
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WASHINGTON — Thrombolytic therapy has resulted in limb salvage among 18 patients with severe frostbite treated at one Minnesota hospital in the last few years.

Thrombolytic therapy has been available for management of frostbite for 10 years and has the potential to reduce the need for some of the amputations. However, use of this protocol has not extended to the rural northern areas where most cases of frostbite are treated.

Severe frostbite results in ischemia and blistering with subsequent demarcation and loss of tissue. Prostaglandins and other chemical mediators are released locally, resulting in intense spasm and blistering. Arterial thrombosis results from injury to endothelial cells that retract to expose subintimal collagen, subsequently triggering acute thrombosis after re-warming.

The worse scenario is a freeze-thaw-refreeze injury in which, upon refreeze, ice crystals form intracellularly and kill the cells, rather than extracellularly as occurs in the initial freeze injury, according to Dr. George R. Edmonson of St. Paul (Minn.) Radiology.

Traditional treatment for frostbite has simply been to rewarm the affected extremity, wait to see how much tissue recovers, then amputate the rest. But over the last couple of decades, investigators have been experimenting with intra-arterial infusion of various thrombolytic and vasodilating agents to dissolve clots and relieve arterial spasm, in attempts to preserve more tissue and salvage more limbs.

At the annual meeting of the Society of Interventional Radiology, Dr. Edmonson described the patient care process used at Regions Hospital, also in St. Paul. Patients are admitted from the emergency department to the burn unit, where surgeons assess the affected limb for severity of injury



Fingers with deep frostbite (left) can be saved from amputation with restored blood flow (right) after treatment with tenecteplase, papaverine, and heparin.



PHOTOS COURTESY DR. GEORGE R. EDMONSON

and blood flow. Diagnostic arteriography is done to assess small vessel occlusion and loss of “distal tuft blush” at the tips of digits. Catheters are positioned for simultaneous infusion of treatment drugs into each affected limb. Blisters and wounds are managed in the burn unit with debridement or amputation as appropriate.

Since the mid-1990s, Dr. Edmonson and his associates have been treating frostbite of the extremities with a variety of combined antithrombotic, antiplatelet, and vasodilating agents. Initially, they used urokinase along with heparin and papaverine, then switched to reteplase, and now have moved to using tenecteplase (TNK) because of its superior plasma stability and higher fibrin specificity compared with reteplase. Tenecteplase is degraded more slowly in the bloodstream during infusion, and binds more firmly to the clot at the target than do similar agents. Because it also affects the normal clotting proteins to a lesser degree, it may therefore reduce the risk of bleeding, he explained.

During three unusually mild Minnesota winters, six patients aged 18-65 years with severe frostbite who were at risk for amputation were treated for up to 72 hours with intra-arterial TNK infusions at 0.25 mg/hour per limb with coaxial papaverine at 30 mg/hour per limb and in-

travenous heparin at 500 mcg/hour. They were managed in the burn unit with arteriography during the infusion.

Of the six patients, three who had 16 involved digits responded well and required no amputations. The other three (six limbs, 30 digits) had incomplete angiographic responses. Of those, two (four limbs, 20 involved digits) improved noticeably following TNK infusion, but then developed infections and required partial amputations. One patient—who needed intubation for alcohol withdrawal—failed to respond and lost eight fingers, but his thumbs were saved. There were no major bleeds or other peri-procedural complications.

Those results were compared with data from 10 surviving patients (aged 14-77 years) of 12 who were treated with the same protocol using various doses of reteplase and papaverine over a 2-year period. Six of the patients recovered with no amputations, four had lost 31 digits at 45 days, and two had amputations but more distally than would have been anticipated without treatment.

More recently, six more frostbite patients were treated with TNK. Five of these patients had complete response and one had no response. To date, 8 out of 12 TNK-treated patients have been saved from amputation.

Response to TNK is more rapid than is response to reteplase, with arteries reopening within an average of 24 hours, compared with 36 for reteplase and 72 for urokinase. However, all of these agents are far better than the traditional wait-and-amputate treatment of the past, Dr. Edmonson said.

In an interview after the meeting, Dr. Edmonson explained that the difference between frostbite and typical peripheral vascular occlusion or thrombosis is that in frostbite, all of the small collateral vessels are thrombosed as well as the primary named arteries. The cut-off of flow is abrupt and complete, rather than an interruption with ischemia and some limited collaterals.

Moreover, the catheter system for drug infusion is proximal above the elbow or knee rather than directly into the clot as is the current standard approach to arterial thrombolysis.

Despite its use at several U.S. centers for the last decade, thrombolysis for frostbite has not yet become the standard of care because there have been no published results until recently, and thus far those have mostly consisted of anecdotal reviews of outcomes with wide-ranging dosages and treatment variations.

“That is why in 2003 I decided to initiate [a Food and Drug Administration–approved] prospective trial with rigid guidelines for treatment. The hope was that more scientific results might encourage others to use this type of treatment. The problem is the disease tends to occur away from the major academic centers on the coasts,” he said.

Future considerations include possibly increasing the heparin dose to reduce rethrombosis (since no bleeding problems have been seen), adding antiplatelet drugs to reduce clot formation, and a possible randomized trial comparing intravenous and intra-arterial administration of the drugs. Two sites have reported some success with high-dose intravenous administration. ■

## Postburn Outcomes Significantly Worse in Regular Smokers

BY PATRICE WENDLING  
Chicago Bureau

CHICAGO — Burn victims who are regular smokers prior to their injuries have poorer outcomes than do nonsmokers, data presented at the annual meeting of the American Burn Association suggest.

In a retrospective analysis of 240 patients, smokers had significantly more surgical procedures than did nonsmokers (1.3 vs. 0.8) and significantly longer hospital stays (13 vs. 9.5 days).

Additionally, smokers had an 85% increased risk of infection during inpatient treatment, said lead investigator Neal Doran, Ph.D., of the University of California, San Diego. The infection rate was 51% in smokers and 36% in nonsmokers, a significant difference.

The study included 80 patients, mean age 35 years, who smoked at least weekly, and 160 nonsmokers, mean age 37 years. The total body surface area burned was similar between smokers (average 7%, range 0.5%-35%) and nonsmokers (average 6%, range 0.3%-36%). The source of burns was flame in roughly 50% of cases, scald in 20%,

contact burns in 10%, and chemical, tar, steam, and sunburns in the remainder.

Impaired wound healing, defined as skin graft failure, was not significantly different between smokers and nonsmokers (10% vs. 3%), Dr. Doran said.

Impaired wound healing likely was not statistically different between groups because of the relatively few graft failures in either group, and also because graft failure—as a measure of wound healing—represents the extreme negative end of the healing continuum, Dr. Doran explained in an interview. Still, smokers were almost four times as likely to have graft failure, compared with nonsmokers (odds ratio 3.95).

Previous studies have shown that smoking is a significant impediment to wound healing because of the effects of the various chemical components of cigarette smoke such as nicotine, carbon monoxide, and hydrogen cyanide—all of which inhibit oxygen delivery to the wound site.

Because of the longer hospital stays, the cost of treatment was about \$3,150 more per smoker, not including the cost of surgeries.

Dr. Doran said burn injuries provide clinicians with a teachable moment for their patients who smoke. Burn patients are three times more likely to smoke than is the general population.

“When someone has had a health scare, it is an ideal time to provide a motivational intervention intended to change [that person’s] behavior,” he said.

During the question-and-answer session, an audience member observed that 55% of smokers had flame burns and that this uncommon burn pattern results in deeper tissue injuries that may account for the longer healing times reported among smokers. Dr. Doran responded that the rate of flame burns was not significantly different between the two groups, with 46% of nonsmokers also having flame burns.

Limitations of the study, conducted by Dr. Doran and his associates, Arpi Minassian, Ph.D., and Dr. Bruce Potenza, include the lack of information on the exact number of cigarettes smoked prior to burn injury and the patients’ smoking status during hospitalization.

Postdischarge outcomes in both groups are currently being analyzed. ■