

Reduction of the Incidence of Amputation in Frostbite Injury With Thrombolytic Therapy

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Hypothesis: Thrombolytic therapy will decrease the incidence of amputation when administered within 24 hours of exposure.

Design: Single institution retrospective review of clinical outcomes and resource use.

Setting: Burn unit of a tertiary academic referral center.

Patients: From 2001 to 2006, patients with severe frostbite admitted within 48 hours of injury underwent digital angiography and treatment with intra-arterial tissue plasminogen activator (tPA) if abnormal perfusion was demonstrated. These patients were compared with those treated from 1995 to 2006 who did not receive tPA.

Interventions: Tissue plasminogen activator vs traditional management of frostbite injury.

Main Outcome Measures: Number and type of surgery were recorded, along with amputations of digits (fin-

gers or toes) and more proximal (ray, transmetatarsal, or below-knee) amputations. Resource utilization including length of stay, total costs, cost per involved digit, and cost per saved digit were analyzed.

Results: Thirty-two patients with digital involvement (hands, 19%; feet, 62%; both, 19%) were identified. Seven patients received tPA, 6 within 24 hours of injury. The incidence of digital amputation in patients who did not receive tPA was 41%. In those patients who received tPA within 24 hours of injury, the incidence of amputation was reduced to 10% ($P < .05$).

Conclusions: Tissue plasminogen activator improved tissue perfusion and reduced amputations when administered within 24 hours of injury. This modality represents the first clinically significant advancement in the treatment of frostbite in more than 25 years.

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THE TREATMENT OF FROSTBITE has remained essentially unchanged for the last 25 years. Today, traditional therapy consists of tissue rewarming, prolonged watchful waiting, and often delayed amputation.¹ While many other areas of burns, trauma, and critical care have advanced significantly in their treatment modalities, the saying "Frostbite in January, amputate in July" is still relevant today.² A variety of maneuvers aimed at advancing the care of patients with frostbite have been attempted, including hyperbaric oxygen,³⁻⁷ surgical and medical sympathectomy,⁸⁻²⁰ pharmaceutical agents,²¹⁻²⁵ and anticoagulation.²⁶⁻³⁶ None of these have resulted in alterations in the management of this disorder.

Recent reports have described the use of thrombolytic therapy using urokinase or tissue plasminogen activator (tPA) as a potential therapy for frostbite.³⁷⁻⁴⁰ Beginning

in 2001, we employed thrombolytic therapy for severe cases of frostbite at our regional burn referral center. We hypothesized that our experience would demonstrate that thrombolytic therapy decreased the incidence of amputation when administered within 24 hours of exposure.

METHODS

PATIENT POPULATION

The University of Utah Medical Center is a 425-bed tertiary care teaching facility. The Burn Center is an American College of Surgeons- and American Burn Association-verified regional facility dedicated to the care of patients with burn trauma. The 12-bed unit is staffed by 3 full-time burn surgeons and provides care for a wide range of burn, soft tissue, and traumatic injuries, including frostbite. Beginning in 2001, we instituted a protocol in which patients with evidence of clinically significant

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frostbite underwent assessment of extremity perfusion using ⁹⁹Tc-scintigraphy or digital angiography. Patients who demonstrated perfusion defects were given a course of intra-arterial tPA (Alteplase; Genentech Inc, San Francisco, Calif). We reviewed all patients treated with this protocol from 2001 to 2006. Outcomes of patients who received tPA were compared with a control group consisting of all patients with varying degrees of injury severity who were not treated with thrombolytic therapy from 1995 to 2006.

STUDY DESIGN

This retrospective study was approved by the institutional review board of the University of Utah Health Science Center. Patients with frostbite were identified by searching our Trauma Registry, American College of Surgeons/American Burn Association (TRACS/ABA) database. Data were extracted from patient medical records. Admission history was used to identify exposure circumstance and duration. Physical examination data were obtained from standardized burn diagrams and documented soft tissue and vascular assessments. The number of digits and proximal extremities involved were recorded. Time to admission, tPA therapy, and duration of tPA treatment was determined from documentation included in patient medical records.

EVALUATION AND TREATMENT REGIMEN

All patients were evaluated by an attending burn surgeon at the time of their admission. Initial therapy consisted of immediate rewarming and fluid resuscitation as appropriate. Vascular examination included assessment of Doppler pulses, capillary refill, and skin color. Patients who appeared to have circulatory compromise, as evidenced by absence of pulses or black/deep purple discoloration of digits, then underwent perfusion evaluation by digital angiography. Patients with a history of concurrent trauma, neurological impairment, recent surgery or hemorrhage, or bleeding diathesis were excluded. If significant perfusion defects were demonstrated, tPA was administered at an initial rate of 0.5 to 1.0 mg/h into the extremity via the femoral or brachial arterial catheter sheath. Heparin was also administered at 500 U/h into the intra-arterial catheter. Repeat angiograms were obtained every 8 to 12 hours to evaluate response to therapy. Tissue plasminogen activator was discontinued when perfusion was restored to distal vessels or at an absolute limit of 48 hours.

Patients' affected areas were then managed with local wound care, which was identical to patients not treated with tPA. Following admission and initial evaluation, extremities were washed gently. Intact blisters were left in place; ruptured blisters were carefully debrided, and the underlying wounds were evaluated for evidence of perfusion. Extremities with intact blisters were dressed with dry gauze padding, which was changed daily. Extremities that required debridement were dressed with antibiotic ointment, nonadherent gauze (Adaptic; Johnson & Johnson, New Brunswick, NJ), and dry gauze wraps, all of which were changed twice daily. All involved extremities were elevated, and patients were assisted with gentle range of motion therapy twice daily.

Injured extremities were maintained using local wound care until 1 of 2 end points was reached. Amputation was performed if areas of obvious necrosis or mummification developed. Otherwise, wounds that appeared to be healing were continued in dressings until complete re-epithelialization occurred or skin grafting was deemed necessary. Often treatment was completed on an outpatient basis.

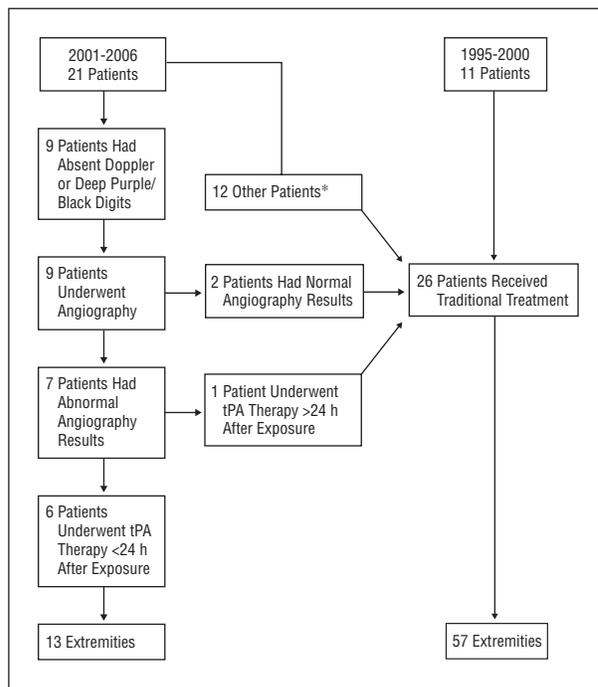


Figure 1. Evaluation and treatment groups of all patients with frostbite at the University of Utah admitted from 1995 to 2006. Asterisk indicates present Doppler/clinical findings were limited to bullae without significant discoloration or a delay in presentation. tPA indicates tissue plasminogen activator.

ANALYSIS

Primary end points were the number of digital amputations (fingers or toes) and more proximal amputations (ray, transmetatarsal, or below the knee). Secondary end points included cumulative length of stay (which included readmissions for surgery or rehabilitation), total costs, cost per involved digit, and cost per saved digits. Cost per involved digit was calculated by dividing the total cost per individual patient by the number of involved digits for each. Similarly, cost per saved digit was calculated by dividing the total costs per individual patient by the number of digits that did not require amputation. Statistical analysis was performed using SPSS software, version 14.0 (SPSS Inc, Chicago, Ill). A *P* value < .05 using the Mann-Whitney *U* test was considered significant.

RESULTS

From 1995 to 2006, 32 patients were treated for frostbite injury at our regional burn center (**Figure 1**). Seven patients received tPA therapy, 6 of whom received therapy within 24 hours of exposure. The seventh patient received tPA after 48 hours of tissue thawing and was therefore included in the control group. Patient characteristics are listed in **Table 1** and **Table 2**. The majority of patients were men and presented with lower extremity involvement. Study patients had a high incidence of substance abuse, mental illness, and homelessness. Vehicle breakdown was also a prominent risk factor for frostbite injury, found in 8 of the 32 cases.

Twelve of the 21 patients seen from 2001 to 2006 were included in the traditional treatment group. Of these 12 patients, 9 had a delayed presentation to the University of Utah and were not deemed eligible for tPA treatment.

Table 1. Characteristics of Patients Treated With tPA vs All Other Patients

Characteristic	Patients Treated With tPA (n = 6)	All Other Patients (n = 26)
Age, mean (SD), y	32.3 (9.3)	37.4 (15.3)
Male sex, No. (%)	4 (67)	21 (81)
Extremity involvement, No. (%)		
Upper	1 (17)	6 (23)
Lower	4 (67)	13 (50)
Both	1 (17)	7 (27)
Mechanism of injury, No. (%)		
Snow	4 (67)	10 (39)
Exposure	2 (33)	15 (58)
Chemical	0	1 (4)

Abbreviation: tPA, tissue plasminogen activator.

Table 2. Situational Factors of Patients Treated With tPA vs All Other Patients*

Characteristic	Patients Treated With tPA (n = 6)	All Other Patients (n = 26)
Situation		
Work related	0	1 (4)
Drug/alcohol intoxication or acute psychosis	4 (67)	12 (46)
Trauma	0	3 (11.5)
Vehicle breakdown	2 (33)	6 (23)
Sports related	0	3 (11.5)
Other	0	1 (4)
Mental illness	3 (50)	7 (27)
Homeless	0	11 (42)
Referred	5 (83)	16 (62)

Abbreviation: tPA, tissue plasminogen activator.

*Values are presented as number (percentage).

Of the other 3, the first patient had a liquid nitrogen exposure and was seen within 2 hours of injury. The second was involved in a trauma and tPA was contraindicated. The third patient had only 1 digit involved. These 12 patients presented with a total of 120 involved digits. Forty-nine digits required amputation, for an amputation rate of 41%.

In patients treated with tPA, the dose varied in each patient, ranging from a constant infusion of 1.0 mg/h to a tapered infusion initiated at 1.0 mg/h and subsequently reduced to 0.25 mg/h. The starting dose was 0.5 mg/h per catheter in 4 of 6 patients with bilateral extremity involvement. The total duration of therapy varied with a mean \pm SD of 26 ± 11.9 hours (range, 8-42 hours). Duration of therapy was determined by improvement noted on repeat angiography. Therapy was continued until perfusion was restored or until the attending surgeon and interventional radiologist felt that therapy was not resulting in gains for the patient. In many cases, the improvement in perfusion with tPA was dramatic (**Figure 2**). In either circumstance, this sometimes required comparing 2 angiograms obtained 12 hours apart. Administration of intra-arterial tPA resulted in only 1 com-

plication; a female patient developed a retroperitoneal hematoma that was managed nonoperatively and resolved without consequence.

The number and type of amputations performed on patients receiving tPA compared with all other patients is presented in **Table 3**. The reduction in the number of distal extremity amputations in the tPA group is statistically significant ($P < .05$, Mann-Whitney *U* test). Patients in the tPA group required amputation of 6 of the 59 digits injured by frostbite, compared with 97 of 234 digits in the historical group ($P < .05$). In the control group, there were a total of 14 proximal amputations, including 2 ray, 6 transmetatarsal, 1 Syme, and 5 below the knee, whereas no patient treated with tPA required an amputation more proximal than the digits. In the patients who received tPA within 24 hours, the mean duration from end of exposure to administration of tPA was mean \pm SD 11.2 ± 7.5 hours (range, 2-23 hours). Average time from admission to initial angiography was 4.5 hours.

Two patients suspected of having vascular compromise who underwent angiographic evaluation were found to have normal perfusion. Of these, 1 patient had a perfusion defect initially identified on pyrophosphate scanning and therefore underwent angiography. In the 10 frostbitten digits identified clinically in these 2 patients, only amputation of the distal great toe of 1 patient was required. Neither of these patients received tPA and therefore are included in the traditional treatment group.

Length-of-stay data were available for all patients. There were no statistical differences in cumulative length of stay, index admission length of stay, number of readmissions, total costs, costs per involved digit, or cost per saved digit.

COMMENT

Despite attempts to improve the management of frostbite, definitive treatment has not changed in decades. As others have previously shown, we again found that frostbite is an entity that afflicts homeless individuals and those with mental illness, and is often associated with substance abuse.⁴¹ Classic management of frostbite injury includes resuscitation, rewarming, and watchful waiting.¹ The outcome is either tissue recovery or progressive gangrene leading to eventual amputation.

A number of treatment modalities to improve blood flow by addressing vessel thrombosis and vasodilatation have been considered in frostbite, although the majority of this research has been without adequate controls. Lange^{42,43} first described heparin sodium use in a rabbit model of frostbite in 1945, then subsequently used clinical volunteers to examine the role of heparin sodium in preventing tissue loss following cold exposure injury. Theis et al²⁷ followed with a series of 14 patients who received heparin sodium within 16 hours of admission, including one who eventually required amputation of a single digit. Dextran has been effective in a number of animal models of frostbite but has not been studied in a clinical setting to date.²⁸⁻³²

Surgical and medical sympathectomy showed promise in some preliminary studies.^{9,15,19} However, Bouwman et al²⁰ treated bilateral frostbitten extremities with intra-arterial reserpine, followed by sympathectomy 3 to

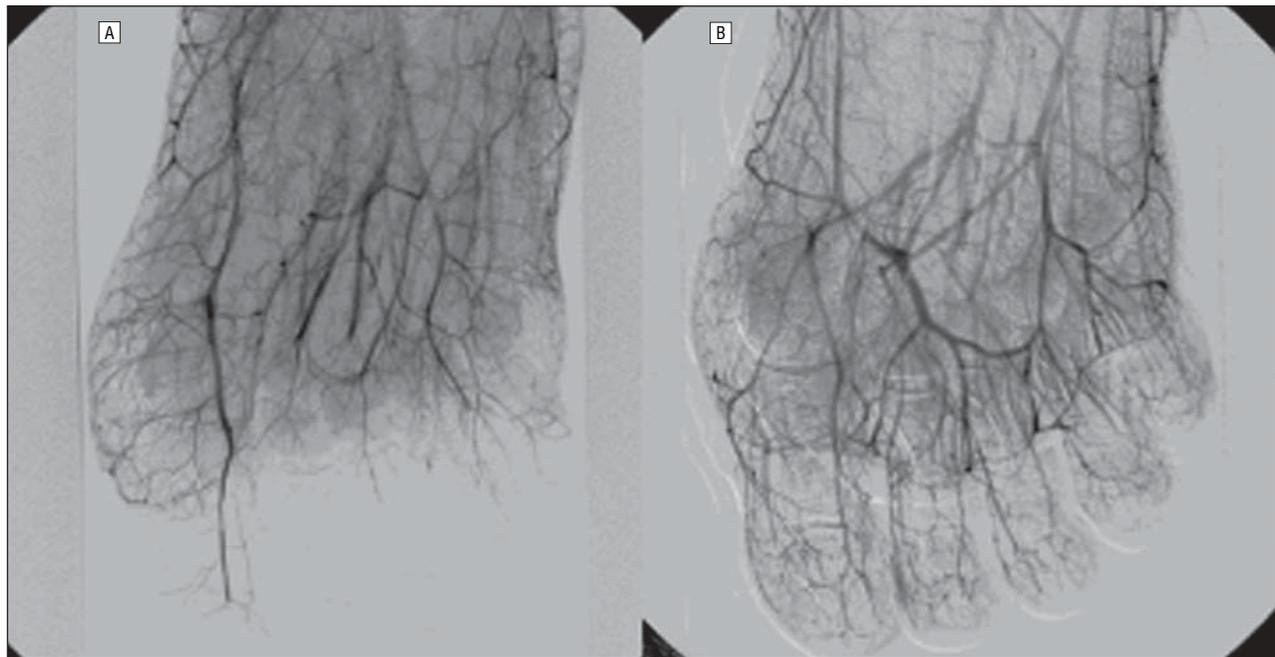


Figure 2. Digital angiography of a 19-year-old woman who sustained bilateral lower extremity frostbite following vehicle breakdown. A, The image demonstrates poor distal perfusion to the left toes. B, Following administration of tissue plasminogen activator via bilateral femoral catheters, angiography demonstrates return of perfusion. All 10 of her toes were saved.

Table 3. Amputation Outcomes of Patients Treated With tPA Compared With All Other Patients Injured by Frostbite

Agent	No. of Patients	No. of Involved Extremities	Extremities Requiring Amputation, No. (%)			No. of Digits Amputated/Total Digits Involved (%)
			None	Proximal	Digits Only	
No agent*	26	57	25 (45)	14 (25)	18 (29)	97/234 (41)
tPA administration, <24 h	6	13	10 (77)	0	3 (23)	6/59 (10)†
Total	32	70	35 (50)	14 (20)	21 (30)	103/293 (35)

Abbreviation: tPA, tissue plasminogen activator.

*Includes 1 patient who received tPA starting 48 hours after exposure.

† $P < .05$ using Mann-Whitney U Test.

10 days later on one side, the other side serving as a control. They found no difference in tissue loss between treated and control limbs. Hyperbaric oxygen represents another recently studied modality for treatment of frostbite injury, though the literature has been limited to case studies in late clinical presentations.^{6,7} In short, none of these therapies have successfully demonstrated a clinically significant improvement in outcomes.

Recent experience using tPA as the primary therapy for severe frostbite injury has been reported.⁴⁰ Rationale for this therapy is based on the understanding that tissue injury in frostbite occurs from 2 distinct components. Initially, tissue freezing and crystal formation occurs and then is improved with tissue rewarming. The more significant cause of tissue injury occurs after thawing, and it is the robust local tissue inflammation and coagulation that stimulates microvascular thrombosis and progressive cell death.⁴⁴ By reversing local microvascular thrombosis, tPA has been postulated to restore perfusion before irreversible ischemia and necrosis.

Evidence supporting the use of tPA in frostbite injury has been steadily accumulating. Experimental stud-

ies using antithrombotic agents in animal models were reported in the mid-1980s.^{37,38} An initial report of tPA in clinical practice was published in 1992.³⁹ This review of 24 patients with severe frostbite included 4 patients with severe extremity frostbite who received tPA. Three of these 4 patients did not require any amputations. The fourth patient had digital involvement on multiple extremities, and amputation of 3 of the patient's fingers was ultimately necessary.

A recent series by Twomey et al⁴⁰ reports on 19 patients treated during the last decade, 6 of whom received intra-arterial tPA and 13 of whom received intravenous tPA. Thirty-three (19%) of 174 digits identified as at risk were amputated. One patient who had 10 digits amputated reportedly had prolonged exposure and experienced repeated freeze-thaw cycles. This patient is similar to the one in our series who presented 48 hours after exposure, received tPA, and failed to improve blood flow after 37 hours of therapy. He ultimately required amputation of all 6 involved digits. Expedient institution of tPA infusion therefore appears to be prerequisite for the salvaging of ischemic tissues. Both our series and that of

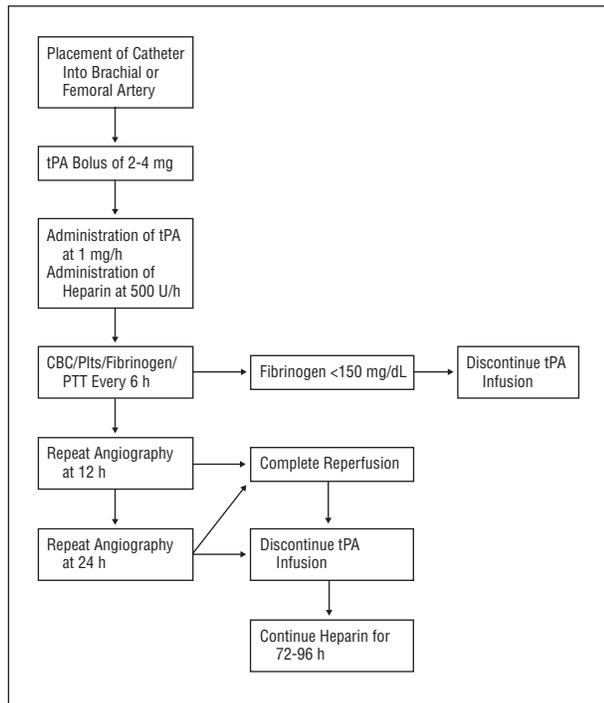


Figure 3. The University of Utah frostbite treatment algorithm. CBC indicates complete blood cell count; Plts, platelets; PTT, partial thromboplastin time; and tPA, tissue plasminogen activator.

Twomey et al⁴⁰ show that early administration of tPA can result in complete avoidance of proximal amputation, and digital salvage rates of 85% to 90% can be expected.

The study by Twomey et al⁴⁰ also found both intra-arterial and intravenous techniques to be equally effective. Two patients in that series had their agent stopped because of bleeding complications. In our series, 1 patient developed a retroperitoneal hematoma that resolved without intervention. The intravenous technique has the advantage of avoiding arterial puncture and catheter placement, both of which may result in iatrogenic complications. Our institutional protocol using intra-arterial infusion of tPA requires that patients are placed in an intensive care unit setting for monitoring during the time of the tPA infusion and while an intra-arterial sheath is present. The need for intensive care unit treatment might be obviated by intravenous administration of tPA. When combined with pyrophosphate scanning instead of diagnostic angiography, intravenous administration likely requires fewer resources overall and provides a potentially attractive approach to the management of acute frostbite injury.

Since 2001, we have used angiography followed by intra-arterial tPA infusion in patients with clinical and radiographic evidence of severe frostbite. Our current tPA protocol is shown in **Figure 3**. Compared with the historical control group, the incidence of digital amputation using tPA was reduced from 41% to 10%. Moreover, no proximal amputations were required in the patients who received tPA within 24 hours in our series. The control group underwent 14 proximal amputations, including 5 below the knee. The preservation of limbs, which maximizes patient functional outcome, is perhaps the greatest benefit conferred by use of tPA in frostbite injury.

There are several limitations to this study. First, because this is a small series and retrospective review, we were unable to compare equal groups based on severity. We did not have a historical control group with angiographic evidence of absence of blood flow, so we cannot demonstrate that the groups suffered injuries of equivalent objective severity. Most admitted patients had significant injuries with evidence of partial or full thickness tissue loss. The high incidence of proximal amputation in the control patients attests to the similarity in the spectrum of frostbite seen at our center during the study period.

Second, we do not have any data on functional outcomes. As this was a retrospective study, we only know whether patients healed or required amputation. Follow-up in these patients is difficult, as many of them have substance abuse problems or are mentally ill. We therefore cannot comment on the incidence of Raynaud syndrome, chronic pain, or sensation deficits.

Third, the possibility exists that patients who received tPA might have improved on their own without thrombolytic therapy. However, this limitation might be expected to favor controls, because their injuries were of variable severity, while all patients in the tPA group had clinically and radiographically documented severe injury. Two patients who had no evidence of extremity ischemia were evaluated but not treated; their favorable results are included among the control patients. Significant improvement was therefore demonstrated only among patients with objective evidence of compromised perfusion on presentation. A randomized multicenter trial would be the only definitive way to address these limitations. Owing to the remarkable results experienced at our institution and reported by others, we anticipate that such a trial is not forthcoming.

Candidates for this therapy are patients who present with severe frostbite as suggested by full-thickness tissue involvement, hemorrhagic blisters, and abnormal perfusion on either angiogram or pyrophosphate scanning. Initiation of therapy with 24 hours of rewarming also appears to be necessary. Exclusion criteria would include superficial frostbite, involvement of the tips of the distal phalanges, and contraindications to tPA, including concurrent trauma, neurological impairment, or recent surgery or hemorrhage.

Based on the dramatic improvements in perfusion and reduction in rates of amputations when tPA was administered within 24 hours of frostbite injury, we anticipate the continued use of tPA in patients who are admitted to our institution with acute frostbite. The protocol shown in **Figure 3** represents our group's current practice recommendation and is based on our clinical experience with tPA in frostbite injury. Additional studies are warranted to confirm our findings and to determine the best methods of assessing tissue damage and administering thrombolytics in terms of timing, duration, and route.

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Author Contributions: The principal investigator had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Bruen, Morris, and Saffle. *Acquisition of data:* Bruen, Ballard, and Saffle. *Analysis and interpretation of data:* Bruen, Cochran, Edelman, and Saffle. *Drafting of the manuscript:* Bruen, Ballard, Cochran, and Saffle. *Critical revision of the manuscript for important intellectual content:* Bruen, Ballard, Morris, Cochran, and Edelman. *Statistical analysis:* Cochran. *Obtained funding:* Saffle. *Administrative, technical, and material support:* Ballard, Morris, Cochran, and Edelman. *Study supervision:* Saffle.

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DISCUSSION

Thomas H. Cogbill, MD, LaCrosse, Wis: Although the treatment of severe frostbite may not seem particularly relevant in Cabos, Mexico, when I return to Wisconsin tomorrow I will prepare to treat our first frostbite patients with the opening of the deer hunting season this weekend. This well-presented paper and accompanying well-written manuscript is likely to immediately change my practice.

Drs Bruen and coauthors have demonstrated a dramatic reduction in the number of digits amputated and the avoidance of more proximal limb amputations in the group of severe frostbite victims treated with intra-arterial tPA infusion. The authors have critically analyzed their experience with this inno-

vative technique, which may indeed be “the first clinically significant advance in the treatment of frostbite over the last 25 years.” Several cautions are important to mention.

The experience of this busy burn unit is still rather small. Because of the retrospective, nonrandomized study design, we cannot assume that the experimental and control groups contain patients with comparable injuries. Based on the impressive differences in amputation rates, a randomized study of tPA thrombolysis vs traditional management may be ethically difficult to conduct. I have several questions for the authors:

1. Your initial screening evaluation to determine which patients went on to angiography consisted of clinical exam and assessment of pulses by Doppler. Those with evidence of circulatory compromise underwent angiography. Of 21 patients seen from 2001 to 2006, 9 had arteriograms and 12 were put directly into the traditional treatment arm. What was the outcome for those 12 patients? Did they have an amputation rate consonant with the others in the traditional treatment arm? If so, then perhaps all patients with severe frostbite should undergo screening angiography for optimal limb salvage.

2. Do you have enough experience to be able to predict outcomes based upon the level of arterial involvement seen on the initial angiogram? Can you state that digital vs metatarsal, tarsal, or plantar artery thrombosis is a predictor of success or failure with this technique? Would thrombosis of the proximal planar or tarsal vessels make an attempt at thrombolysis futile?

3. What were your angiographic end points of treatment? Did you wait for complete lysis of thrombus in the digital arteries or just improvement?

4. In 2005, Twomey and associates found that intra-arterial and intravenous administration of tPA were equally effective for the treatment of severe frostbite. Intravenous administration has several clear advantages in avoiding the potential complications of arterial catheters, especially in patients with involvement of multiple extremities. So, patients with hands and feet involvement might have 4 arterial catheters. Your current protocol calls for intra-arterial tPA administration. Do you plan to change your protocol to include intravenous administration?

I want to thank the authors for bringing this novel technique to our attention and the association for the privilege of discussing this paper.

Dr Cochran: I would like to thank Dr Cogbill for his insightful comments. I am delighted to know that you felt that this is something that will be of benefit to your patients and your practice.

In terms of the “other” patients, those 12 patients who did not undergo angiographic study, as Dr Bruen mentioned, that is a group that had a variety of different reasons for being placed into that group. In some patients, Doppler signals were present and therefore we felt that perfusion was adequate based upon that form of clinical examination. In addition, those are also patients who at times had clinical exams that did not involve discoloration or obvious early tissue necrosis, and therefore again it was felt that they had less severe disease. Most of those patients, as I recall, 8 of the 12, actually had a delayed presentation at 24 hours or greater from the end of their exposure period to cold. Based upon our prior experiences as well as those that Twomey documented in some of his earlier studies, the benefit of using tPA once you get past about 24 hours from the end of exposure seems to be less clear. Often those were patients who came to us 36, 48, sometimes even longer than that, hours after the end of their exposure, and therefore we did not deem it appropriate to expose them to the risks of arterial access as well as thrombolytics in the management of their disease.

Addressing the second question in terms of being able to predict the outcomes based upon the level of findings on the angiography. Most of our angiography actually demonstrated

that the disease was more distal. I don't remember any of the angios having, for example, a pedal level of demarcation. That is something that certainly would be of interest for us to continue to follow as we continue to accumulate more experience with this technique.

In terms of the threshold for when we stop therapy. Clinical resolution, that is complete clinical resolution, as you saw, for example, with the angiogram of the feet that Dr Bruen put up there, if that occurs prior to 24 hours, we will stop tPA at that point. If we reach 24 hours, even if we do not have complete resolution we will also stop at that point, as we have not encountered any clinical benefit extending the duration of thrombolytic therapy past the 24-hour time period.

Finally, in terms of our plans for consideration of the use of intravenous tPA. That is something that we are looking at, and I suspect that my partners and I will be trying this one during our management of some of our frostbite patients. Certainly it is advantageous in terms of considering patients with involvement of multiple extremities. I am not sure that it obviates the need for us to have arterial access. As Dr Bruen mentioned in his conclusions and in our conclusions, we aren't convinced, and there is nothing out there that clearly shows what the best study is to evaluate these patients. And there certainly has been good data showing that pyrophosphate scanning can demonstrate levels of amputation that are likely to occur. Our experience with pyrophosphate scanning has been somewhat limited. And what we have found was, in fact, that a patient with an abnormal pyrophosphate scan had a normal angiogram, and so they did not undergo tPA. We therefore have concerns that pyrophosphate scanning may in fact be a bit too sensitive and may not be the best study, and in light of that we are not convinced it would obviate the need for arterial access that we sometimes obtain in angiograms on these patients.

Stephen G. Jolley, MD, Anchorage, Alaska: This is something I have a little bit of experience with. As a general surgeon in the Army stationed just outside of Fairbanks for 2 years, I saw over 100 cases of frostbite injuries because of the cold-weather exercises that we had, mainly from people coming from climates like this to Alaska to participate with shorts and flip-flops.

I think your paper is very important and has some important contributions to the treatment of frostbite. One of the things that I take from your paper is you are dealing primarily with fourth-degree frostbite injuries. In our population in Alaska, even with some education, most of the frostbite injuries are occurring in young individuals. And I think in your paper you have to define the age group that you are dealing with as well as the comorbidities.

In 2 years dealing with over 100 patients with frostbite, even with severe injuries to the hand and the feet, we had to do no amputations. Just simple rewarming and rehydration was sufficient. We would have skin sloughing like you have with severe burn injuries, and often have some altered sensation remaining. But I think that truly fourth-degree frostbite injuries have the highest risk of amputation and are uncommon in the younger population.

The question I have for you is how do you distinguish, using angiograms, between vaso-occlusion leading to amputation vs vasospasm that would recover with just rewarming and conservative therapy?

Dr Cochran: Your point is very well taken, and I do think our ability to look at this is definitely colored by our experience. I do believe that more minor cases of frostbite are often managed by outlying facilities in our region and are not managed by the burn surgeons. We certainly tend to see the worst of the worst. So that does definitely color our experience.

In terms of distinguishing on angiography vasospasm, that is a result of sludging and secondary consequences of the frostbite injury vs vasospasm, the simple vasospasm, I have on at

least one occasion seen our angiographers, either our vascular surgeons or our interventional radiologists, use papaverine to help establish that at time of study. Otherwise it does simply seem to be something that time tells the story on in terms of if the thrombolytic therapy produces any clinical benefit.

Obviously, giving the thrombolytics and giving it time if it is simple vasospasm is going to have the same effect as the thrombolytics hopefully will on someone who has sludging. But papaverine is really the only thing that I have seen them do in terms of trying to distinguish that. Typically our experience has been that on the initial angiography, if we find that there are findings consistent with poor perfusion, we will act on those.

John D. Corson, MD, Albuquerque, NM: I was a little confused about the technical aspects of doing this. Were you perfusing more than 1 limb at a time? If you were, what were you doing about adjusting the dosages of the drugs?

What was the timing between the amputation and the time of the original injury? Did you see any benefit in the thrombolytic group in terms of neurological outcomes?

Dr Cochran: Beginning with your question in terms of if there was greater than 1 limb involvement. As Dr Cogbill related, those were patients who would in fact have more than one catheter placed. Their total drug doses stayed the same and the amount of drug that was being perfused into each extremity was divided by however many extremities were involved. So, if it was supposed to be a dose of 0.1 and they had 2 involved extremities, then the rate would be 0.05 for each catheter.

The timing of injury vs amputation is something that we really struggled with finding a scientific way to describe for this paper and for the presentation because the bottom line is, it was attending preference. The 3 of us follow these people in clinic, look at them, and at some point when we either think it

is about to fall off or we think it looks so horrible that we can't stand it anymore, we think we have got adequate demarcation, we then go ahead and proceed with amputation. So, there is certainly a great deal of individual variability based on which of the 3 burn surgeons is looking at that. And there is not science in terms of at 6 weeks we are going to do it, there is no consensus between the 3 of us on that. Our practice patterns tend to be very similar, but there is no precise end point.

In terms of the benefit with neurologic outcomes, that is something that we haven't thoroughly examined. I can tell you from my experience seeing some of our frostbite patients in follow-up in our clinic that they do still tend to have a great deal of neuropathic pain. Now, one of the things that certainly becomes difficult to distinguish is that, as you saw from our data, a number of these patients have preexisting comorbidities in terms of substance abuse and psychosis/psychiatric history. So, one of the issues that you get into is, Are they having true neuropathic pain or is this more a consequence of their prior pre-existing substance abuse issues?

Roger G. Keith, MD, Saskatoon, Saskatchewan: One of my questions has been asked. And that is, the salvaged limb tends to have paresthesia and anesthesia. And I think you have addressed that.

The other, which we see frequently, particularly in our native population who work outdoors through the winter, is the tendency to reinjury, recold injury in these patients. Although your sample is small, have you seen any evidence that this has been reversed?

Dr Cochran: We actually did have one recidivistic patient in this group who was a prior cold injury patient who went out and got cold injured again, not learning adequately the first time that that was the case.

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